A mixed methods investigation of trial design for measuring glaucoma medication adherence

Heidi Cate MSc

Submitted for the degree of Doctor of Philosophy

University of East Anglia

School of Pharmacy

Submitted in June 2016

Abstract

Sub-optimal adherence to glaucoma therapy has negative health and financial implications. The Norwich Adherence Glaucoma Study (NAGS) adopted gold-standard methods including randomisation and objective outcome measurement to investigate an adherence intervention. Patients were randomised to standard care alone (control group) or additional glaucoma and medication related information provision using Behaviour Change Counselling. A Travalert Dosing Aid® (TDA) was used to collect 8 months of adherence data. For the 208 patients randomised, adherence was higher than expected in the control group and there was no significant difference in adherence between intervention and control.

Two qualitative studies collected user experiences from NAGS and established patient experiences of administering eye drops using the TDA. Potential NAGS experimental design errors were identified that might have inadvertently introduced changes in patient behaviour, causing bias in the observed study outcomes; a phenomenon known as a reactivity effect. Thus, the React study was designed to quantify the magnitude of reactivity effects on observed adherence behaviour, but the study required the use of a modified consent method. Focus groups informed the content of a questionnaire that was piloted using cognitive interviewing methods. The subsequent questionnaire was distributed to 400 members of the public attending an out-patient NHS hospital. From the 208 questionnaires returned, the majority of respondents felt that the proposed React study used an acceptable consent method in order to investigate reactivity effects.

Work continues with the React study to recruit the target sample size. Participants with lower measured adherence were less likely to participate and this self-selecting bias compromised estimates of the true magnitude of reactivity effects. However, the evidence collected to date confirmed the presence of reactivity effects.

This research suggests that objective measures coupled with modified consent procedures may be an appropriate methodological strategy to minimise reactivity effects in trials designed to change behaviour.

Contents

List of Figures

List of Tables

List of Appendices

Glossary

AGIS	Advanced Glaucoma Intervention Study
ALT	Argon Laser Trabeculoplasty
BECCI	Behavioural Change Counselling Index
BMQ	Brief medication questionnaire
CNTGS	Collaborative Normal Tension Glaucoma Study
FMD	Frequency of Missed Dose
GMAM	Glaucoma medication adherence model
GP	General Practitioner
GSA	Glaucoma Support Assistant
HAART	Highly Active Antiretroviral Therapy
HBM	Health Belief Model
HIV	Human Immunodeficiency Virus
IMD	Index of Multiple Deprivation
IOP	Intraocular pressure
IQR	Interquartile range
MEMS	Medication Event Monitoring System
MI	Motivational Interviewing
MISC	Motivational Interviewing Skill Code
MMAS	Morisky Medication Adherence Scale
MPR	Medication possession ratio
NAGS	Norwich Adherence Glaucoma Study
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NNUH	Norfolk and Norwich University Hospital
NRES	National Research Ethics Service
NTG	Normal tension glaucoma
OH	Ocular hypertension
OHTS	Ocular Hypertension Treatment Study
OR	Odds ratio
PACG	Primary angle closure glaucoma

POAG	Primary open angle glaucoma
PPIRes	Patient and Public Involvement in Research
QBE	Question-behaviour effect
QoL	Quality of Life
RCT	Randomised controlled trial
SCT	Social cognitive theory
SD	Standard deviation
SIMS	Satisfaction with Information about Medicines Scale
SPSS	Statistical Package for the Social Sciences
TDA	Travalert Dosing Aid
TPB	Theory of Planned Behaviour
TRA	Theory of Reasoned Action
VAS	Visual analogue scale
WHO	World Health Organisation

Acknowledgements

It is with immense gratitude that I acknowledge the support and help of my supervisors; Debi Bhattacharya, Allan Clark and David Broadway. Debi, you have given me the self-belief to embark on this journey. Allan, I am indebted to you for your support with the statistics. David, I consider it an honour to work with you; this thesis would not have been possible if you had not shared your passion and enthusiasm for research with me many years ago, for always having confidence in me and a vision for what was possible!

To my fellow students and friends I have met on this journey, I've learnt so much from you all and I shall never forget the experience. I owe special thanks to Claire Easthall; we've had some great adventures whilst studying together. Little did we know that kissing the Blarney Stone was just the start of the friendship and that all these years on you would continue to inspire me and fill my life with laughter. I've listened to your words of wisdom, some of which first manifested on the badminton court, and I hope you agree that "I've tried hard"!

To my lovely work colleagues, Sally Edmunds, Corinne Haynes, Karen LeGrys Amy Morley and Naomi Waller, you are an amazing team! NAGS and the React studies would just not have been possible without you all. You have given me space and time to study and most importantly, a fresh cup of coffee when I walked in the office door!

Thanks to Jenny Lacey who inspired me and was so involved with the preliminary work with NAGS and the Steering Committee. Thanks also to Richard Holland for being a valuable part of the NAGS Steering Committee along with our public representatives Barbara and Michael. Special thanks to Michael Twigg and Claire Easthall who ran the NAGS focus groups, Caitlin Notely who supported me with the qualitative analysis and John Losasso for his help in sourcing publications for me with such efficiency.

And finally, to my amazing family; Mum, Dad, Chris, Isaac, Emily, and Sarah who have all supported me and listened to me when I thought it would never be possible to complete the task ahead. You have all seen me through my journey of education, which I decided to start later in life, and I would never have made it without your unfailing support, continued love and care for me. Mum and Dad,

thank you for all you have done to care for my family whilst I've studied. Chris, not many married couples have shared (or endured) the demands that studying and forging a career brings, and I consider myself blessed that I've been able to share this with you, my very special husband. Isaac, it was a pleasure to show you my graphs, and Emily, thank you for sitting so still on my lap so I could both cuddle you and work at the same time, you were just two years old when I started my PhD! To both my children, thank you for being so patient with me and I hope this thesis will inspire you in your own journey of education; let it be a reminder that you really can do anything if you work hard!

To all those dear and special to me, I think you will be pleased to hear that I have finally finished. It has been like a roller-coaster ride, fun and exhilarating with some pretty scary parts too. I cannot promise not to get on another ride like this again as I appear to be a 'challenge junkie', but I don't think I'll choose a ride quite as gruelling as this again!

Section 1. Introduction

Publications developed from this section:

Broadway D C and Cate H. Pharmacotherapy and Adherence Issues in Treating Elderly Patients with Glaucoma. Drugs and Aging. 2015, 32:569–581

Chapter 1. Glaucoma and Adherence to Medication

1.1 Introduction to glaucoma

Glaucoma is the leading cause of irreversible blindness worldwide and the second cause of blind registration in the UK.[1, 2] There are an estimated 500,000 people with glaucoma in England and Wales alone and more than 70 million people are affected worldwide.[3] Sight loss resulting from glaucoma causes problems with restricted mobility,[4] motor vehicle accidents,[5] and other such problems that effect everyday activities and lifestyle, which can also have prominent psychological effects for those with the disease.[6, 7] Studies in western developed countries have shown that approximately half of the people with glaucoma remained undiagnosed.[8-10] Together with a rapidly aging population, the prevalence of glaucoma is set to rise.[3] Once diagnosed, patients with glaucoma require lifelong treatment and careful monitoring; the costs associated with the management of such a disease are therefore high and these increase as the disease worsens.[11] The Cost of Blindness Report in 2003 estimated that as a chronic illness, an individual lifetime cost for a patient with glaucoma was as high as £40,000 in the UK[12] and the direct cost estimates for approximately 2 million US citizens were $2.9 billion.[13] Glaucoma has thus been described as ‘an important global public health concern’.[14]

Glaucoma is a disease of the optic nerve, the most common forms of which are classified into two different types, each with specific risk factors and therapeutic treatments; primary open angle glaucoma (POAG) and primary angle closure glaucoma (PACG). In PACG the iris blocks the drainage angle in the eye preventing the fluid (aqueous) draining from the eye. The decrease of aqueous drainage in turn leads to increased intraocular pressure (IOP), potentially causing permanent damage to the optic nerve. Without medical intervention elevated IOP can lead to a chronic and slowly progressive disease. However, in some cases the drainage angle can become completely closed and during a period of a few hours can cause an acute elevation of IOP associated with severe pain and rapid visual loss requiring urgent medical attention. Conversely, POAG is always chronic and slowly progressive in nature with no warning signs of the permanent

loss of vision that can be occurring. The drainage angle remains grossly unaffected in POAG, but compromised drainage of aqueous within the drainage angle tissue (trabecular meshwork) causes a rise in outflow resistance, elevation in IOP and subsequent damage to the optic nerve. The issue relating to IOP is complicated by the fact that certain individuals develop elevation of IOP without optic nerve damage (Ocular Hypertension; OH) whereas others develop optic nerve damage in the apparent absence of IOP elevation (Normal Tension Glaucoma; NTG). Although much less common, there are many types of secondary glaucoma where other ocular disorders result in elevation of IOP.

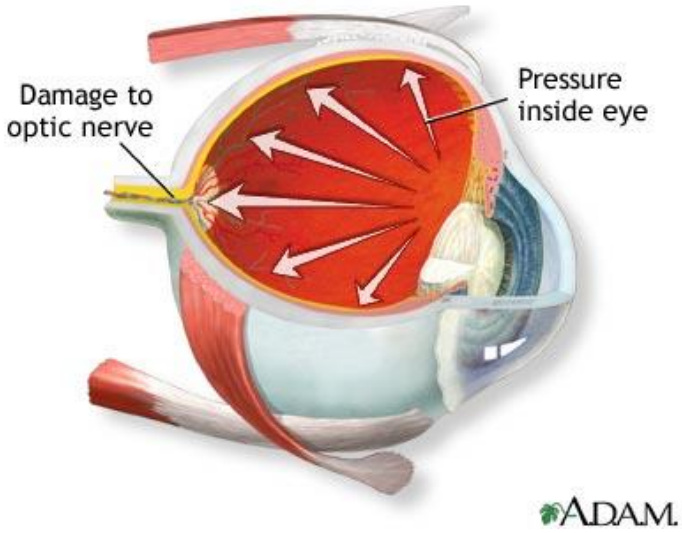
The main risk factor for all types of glaucomatous optic neuropathy is IOP and currently available treatment for glaucoma is aimed at reducing IOP, either by inhibiting the production and/or increasing drainage of aqueous.

There are fundamental risk factors that link race with the severity, prevalence and type of glaucoma. For example, the rate of blindness is higher in those of black race than white, and generally this is believed to be unrelated to socio-economic factors[15] (which are thought to exist when comparing black and white populations). Ethnic origin can play a role with respect to glaucoma risk and PACG, for example, it is relatively less common compared with POAG in European regions but is more prevalent in Asia where it is almost equal to that of POAG.[16] An anatomical precursor of PACG is a shallow anterior chamber, which can create a predisposition to PACG, this being more prevalent in Asia. Surveys also suggest that a greater proportion of people affected by PACG are bilaterally blind (10% for POAG and 25% for PACG).[17]

The most significant risk factor for glaucoma blindness is advanced loss of vision when the condition is first detected.[18] Thus, it is essential to detect glaucoma early to prevent significant sight loss. POAG is particularly difficult to detect and treat due to its slow progressive nature, lack of patient symptoms until significant damage has occurred, together with the lack of screening programmes. Thus, for all the types of glaucoma, POAG holds a particular challenge in terms of diagnosis, treatment and patient education.

1.1.1 Primary open angle glaucoma

Primary open angle glaucoma is characterised by progressive loss of retinal ganglion cells, reduction of retinal nerve fibre layer thickness and characteristic thinning of the neuroretinal rim at the optic nerve head (Figure 1.1 and 1.2).[19] No single factor has been identified to cause POAG. The damage done to the optic nerve is triggered in most cases by excessive pressure on the optic nerve that, over time, causes damage. The pressure is exerted by an increase of aqueous production (a watery liquid that fills the space between the lens and the cornea). POAG is usually bilateral, but often asymmetric. Although often asymptomatic at presentation, untreated POAG results in characteristic visual field loss (usually peripheral) and only later in the disease is central vision affected, this frequently being associated with symptoms. In the UK, total blindness from glaucoma is uncommon, but it remains the most common reason for an individual being registered blind in England and Wales, and the leading cause of irreversible, but preventable, blindness in the UK.[20]



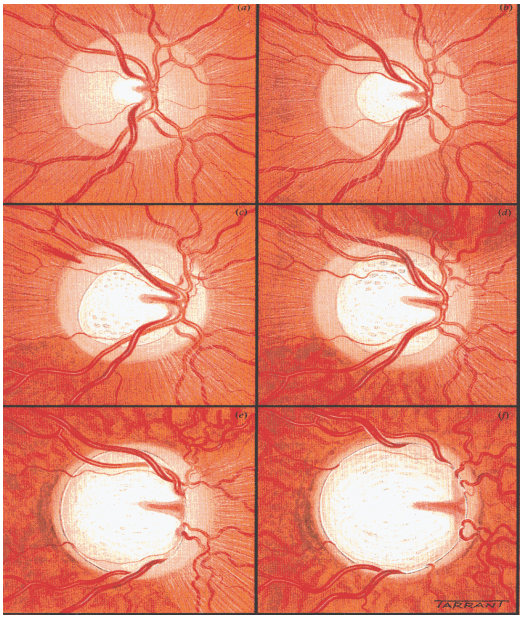
Adapted from A.D.A.M [21]

Figure 1.1 Cross section of the eye showing pressure on the optic nerve head

Normal optic nerve

Moderate glaucoma

Severe glaucoma

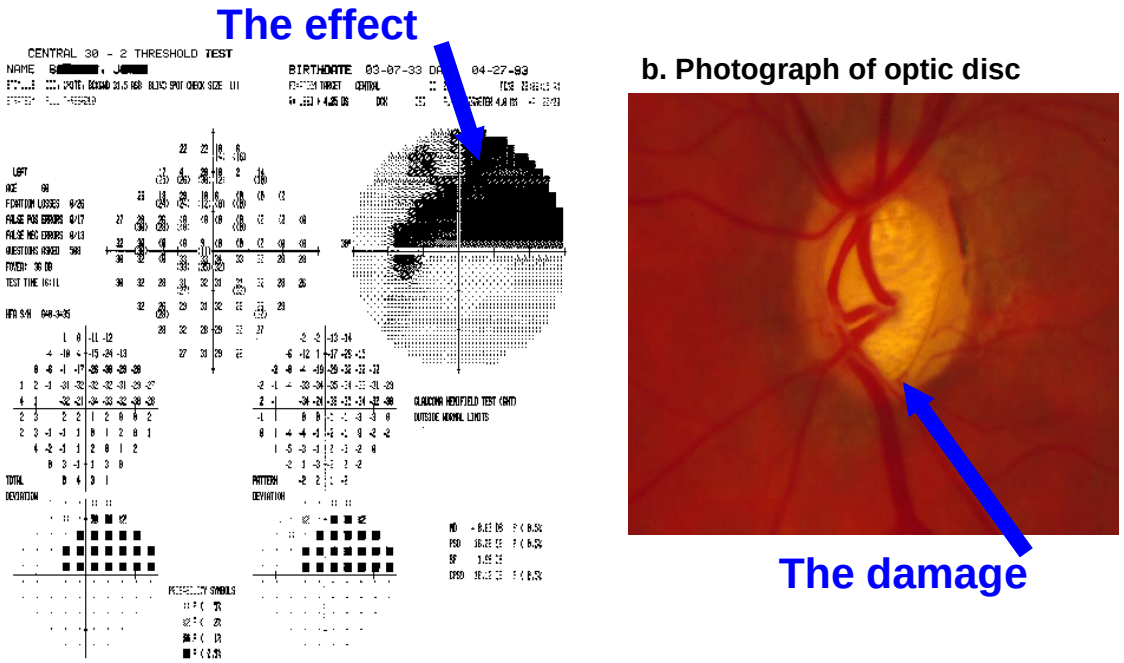


Artwork by Tarrant T.R.[22]

Figure 1.2 Front view of optic nerve head showing progressive glaucomatous damage

1.1.2 Diagnosis and follow-up care

The visual field test remains the most important functional test for assessing glaucoma. Visual field testing is aimed at detecting any loss of visual field (peripheral and central) and provides a map of that loss which is helpful in the diagnosis and future monitoring of disease progression. With automated Humphrey visual field analyses, the darker areas or black areas of the visual field print-outs indicate the areas of vision that have lost sensitivity to light relative to age-matched normal control eyes. An example of a Humphrey visual field print-out can be seen in figure 1.3a. Figure 1.3b shows how damage to the optic nerve seen by slit-lamp examination directly correlates to a loss of visual field shown on a visual field test as a black 'arc'. However, not all optic nerve damage will be detected using a visual field test and thus optic nerve assessment using slit-lamp biomicroscopy or imaging is essential, particularly in the earlier stages of the disease.



a. Visual field test results

Figure 1.3 An illustration of nerve damage and corresponding visual field loss for the left eye of a patient with POAG
a. Visual field test results showing the visual field loss 'arc' and b. photograph of the optic nerve head showing the point of maximum nerve damage.

The relative risk for POAG appears to rise continuously with the level of IOP and there is no evidence of a threshold IOP for the onset of the condition.[23] Despite previous beliefs, elevated pressure is not always apparent in eyes with manifest glaucoma and thus an eye with an IOP lower than the mean for the population (16 mmHg) may still show evidence of glaucomatous damage.

POAG has been subdivided into high pressure and normal pressure categories to reflect the fact that elevation of IOP is not always a feature of POAG. The benefits of lowering IOP, even if the pressure is within normal limits at the time of diagnosis, have been proven.[24] The main risk factors for POAG are, level of IOP, age, African descent and family history.[15, 25] It has also been suggested that diabetes, hypertension and migraine are associated risk factors.[26]

Normal tension glaucoma (NTG) is now considered to be a sub-group of POAG. Glaucomatous damage is detected whilst the mean diurnal IOP remains within the normal range (rarely above 21 mmHg, taken to be the statistical upper limit of the

normal range),[27] thus making elevated IOP a significant risk factor, but not the only causal factor of glaucoma. Fluctuation of IOP could also play an important role in the progression of optic neuropathy.[28] Drance[29] was one of the first to study diurnal IOP variation in patients with glaucoma. Drance pointed out that a single pressure reading on a patient may not necessarily be representative of what the pressure is most of the time, and certainly not indicative of highest value during the day.[30] However, finding the true diurnal and nocturnal IOP variation is problematic, the influence of body position on IOP over a 24-hour period and practicalities for the patient, all hindering assessment. Furthermore, the Early Manifest Glaucoma Treatment Study[23] found that IOP fluctuation was not an independent factor of glaucomatous progression. Thus, the available evidence for the role of IOP fluctuation in the progression of glaucoma is controversial[28] and as various IOP independent risk factors have been identified, it is assumed that these play a more significant role in the NTG sub-type of POAG.

For the purposes of further discussion, glaucoma refers to both POAG and NTG. Although glaucoma is not currently curable, with early detection and appropriate therapy the majority of glaucoma damage is preventable and those diagnosed early can expect to retain vision for the duration of their lives.

1.1.3 Ocular hypertension

Patients with an elevated IOP without detectable glaucomatous damage on standard clinical tests have ocular hypertension (OH). The decision as to whether or not to treat OH is problematic, since although a risk factor for glaucoma, only a minority of patients from this group will actually develop glaucomatous damage. Patients with mild/moderate OH can be left without treatment until the detection of early glaucomatous damage occurs.[25] It is reasoned that observation still allows timely intervention if damage begins before visual loss of consequence to the patient occurs. Conversely, it is argued that up to 20-50% of optic nerve fibres may be lost focally before damage is recognised by conventional perimetry and that once damage occurs this makes the remaining optic nerve fibres more susceptible to further damage.[25] The current recommendation from the National Institute for Health and Care Excellence (NICE) is to ensure that patients with significant risk of developing POAG should have treatment initiated before visual

loss occurs, whilst patients with low risk of developing POAG should not be given unnecessary long-term therapy.[27] Much research and debate continues in unravelling the complexity of detecting and treating glaucoma and its risk factors appropriately.

1.1.4 Long-term management of glaucoma and ocular hypertension

The European Glaucoma Society Guidelines[31] and The NICE Glaucoma Guidelines[27] sets out clear standards for the diagnosis and treatment of patients. A typical care pathway in the UK involves referral to a specialist glaucoma clinic for diagnosis by standard glaucoma examination followed by long-term monitoring, with treatment if indicated, according to risk of disease progression. Currently, provision of information for patients, carers and family members is usually provided by the diagnosing clinician.

In spite of treatment, most glaucoma will continue to progress,[27] albeit in a minor way when IOP is adequately controlled. Measures of progression are essential to ensure that the treatment reduced IOP is achieving the goal of reducing damage to the optic nerve. Progression may be considered to have occurred when there is evidence that visual field or optic disc damage has worsened.[27] As more technology becomes available, more sensitive and measurable progression markers have been established to assess optic disc appearance and visual field sensitivity.

There have been several large scale glaucoma studies investigating the efficacy of medical treatment in delaying or preventing the onset of POAG. The Ocular Hypertension Treatment Study (OHTS; n=1636) randomised patients with OH (with no evidence of glaucomatous damage) to either observation or treatment (topical ocular anti-hypertensive medication). The primary outcome of OHTS was the development of a visual field defect or optic disc deterioration attributed to conversion from OH to POAG. The OHTS study demonstrated that the probability of developing glaucoma over a 6-year period was reduced from 9.5% to 4.4% with medication (hazard ratio, 0.4; 95% confidence interval, 0.27-0.59; $p<0.0001$). The study concluded that maintaining IOP at a desirable range was effective in delaying the onset of POAG in patients with elevated IOP and thus an effective means of reducing glaucomatous progression.[32]

The Collaborative Normal Tension Glaucoma Study (CNTGS) found that in patients with NTG, a reduction in IOP from 16 mmHg to 11 mmHg resulted in a reduction risk of progression from 60% to 20%.[33] In the Advanced Glaucoma Intervention Study (AGIS), patients with POAG and moderate to severe visual field loss with low IOP below 18 mmHg, had no net progression of visual field loss detected during 8 years of follow-up.[34] The results of the OHTS, CNTGS and AGIS studies have demonstrated the importance of long-term follow-up of glaucoma and OH patients to ensure that target IOP is maintained and this pressure has controlled the progression of optic nerve damage and/or visual field defects. Although the correct diagnosis is an essential component in the management of glaucoma appropriate treatment is of equal importance.

1.1.5 Treatment goals for glaucoma and ocular hypertension

Treatment in its many forms, aims to decrease aqueous production and/or increase aqueous outflow to lower IOP and settle the fluctuations in IOP over a 24-hour period. The general therapeutic goal is a reduction in IOP by 20% - 30% from the initial pressure at which damage occurs and below 21 mmHg for cases of OH.[24, 27] Studies have shown that treatment regimens that achieve this IOP reduction may play a role in halting the progression of visual field loss in glaucoma.[23, 35, 36] The Early Manifest Glaucoma Treatment Study randomised POAG patients (n=255) to treatment (argon laser trabeculoplasty plus topical betaxolol; n=129) or no treatment (controls, n=126) and these patients were followed-up every 3 months for 6 years. The magnitude of initial IOP reduction was a major factor that influenced outcome, but each 1mmHg rise of IOP at follow-up was associated with an approximate 10% increased risk of progression.[23] More recently, the UK Glaucoma Treatment Study used a masked treatment allocation randomised controlled trial (RCT) to compare latanoprost (n=231) to a placebo (n=230). After 24 months, the mean reduction in IOP was 3.8 mmHg (SD 4.0) in the latanoprost group compared with 0.9 mmHg (3.8) in the placebo group and the preservation of the visual field with latanoprost was significantly longer than the placebo group (HR 0.44, 95% CI, 0.28-0.69; p=0.003).[36]

In addition to this, consideration to the reduction of IOP fluctuation must be given particularly in the case of patients with NTG. Case studies have shown where a

30% reduction from peak IOP has been achieved, but the magnitude of fluctuation has remained unchanged, glaucomatous progression has been detected.[28] However, disease progression is difficult to predict and can still be difficult to detect when mild.[37]

Choice of treatment is made on an individual patient basis. Consideration is given to the perceived threat to sight during lifetime, status of the fellow eye, likelihood of using treatment as directed, likelihood of surgical success and patient preferences regarding treatment options.[38]

Target IOP is an estimate of the IOP below which the IOP should be maintained to prevent progressive loss of vision. Numerous factors are considered in making the estimate of target IOP, including initial peak/mean IOP, degree of visual field loss, amount of optic nerve damage, age, gender past/present medical history and predicted life expectancy.[38] Frequent follow-up is required to ensure that target IOP is maintained and the risk of progressive field loss minimised. At follow-up visits patients need assessment of IOP, visual fields and their optic nerves. If the target IOP is achieved but progression continues, further pressure lowering intervention is warranted and a new target IOP should be set.[28]

1.1.6 Treatment options

Topical ocular hypotensive medications are recommended by the NICE glaucoma guidelines[27] for initial treatment; there are various types, which can be used alone or in combination. Other options include laser and filtration surgery procedures that can be employed to lower IOP by increasing aqueous outflow or reducing aqueous production. Currently, lowering IOP is the only proven form of management for preserving vision in eyes with glaucoma, although there is current interest in developing neuroprotective agents and drugs that improve ocular blood flow, which may aid the preservation of optic nerve function.[26]

1.1.6.1 Medical therapy

There are many factors to consider when prescribing eye drops. There are several medical contraindications to the use of certain medications such as beta-

blockers (eg. broncho-pulmonary disease or cardiac arrhythmia) since systemic absorption of beta-blocker drugs may cause adverse effects. Further aspects include cost and quality of life balance and whether the patient has the manual dexterity required to administer the drops to one or both eyes.[39] All topical medications carry a risk of local ocular side effects such as irritation, lacrimation, hyperaemia, dry eye, toxic or allergic conjunctivitis and/or keratopathy[39] and thus for asymptomatic patients, the side effects of topical therapy could be worse than the perceived effects of glaucoma itself.

There is a wide choice of topical agents available for treating glaucoma. Current ocular hypotensive agents in common use include prostaglandin analogues, beta-blockers, alpha-agonists, and carbonic anhydrase inhibitors. Prostaglandin analogues are often used as first line therapy and if only partly efficacious additional therapies are added to the therapeutic regimen. When initial or additional therapies are ineffective or side effects are experienced, alternative medications can be tried. Effective therapy regimens are pursued until the 'target pressure' is reached and the rate of progression is under control. Thereafter, patients are reviewed, often on an annual basis, for the duration of their lives to ensure the 'target pressure' is minimising progression with review of the treatment regimen at each follow-up visit.[38]

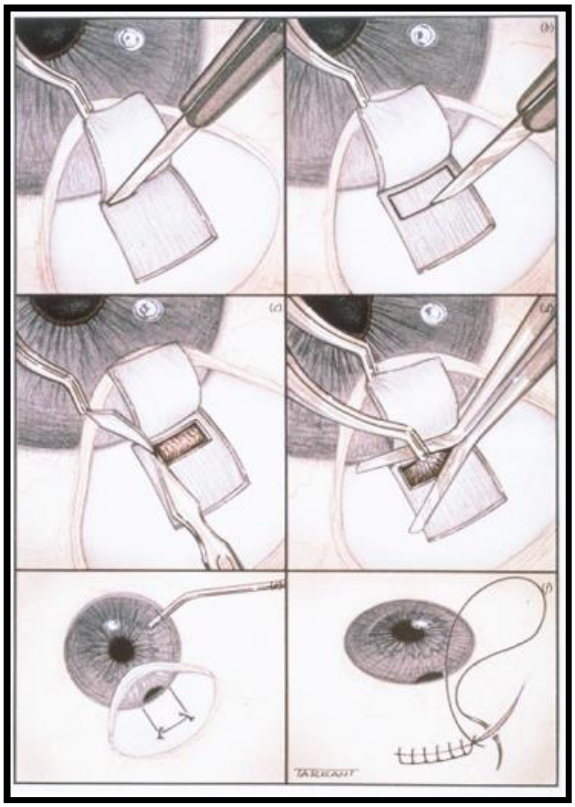
1.1.6.2 Laser therapy

When there is a failure of medical therapy either due to sub-optimal effect or use of eye drops, laser or surgical management may be indicated. Occasionally laser or surgical management is utilised as a primary option. There are several types of laser therapy, including Argon Laser Trabeculoplasty (ALT), Selective Laser Trabeculoplasty (SLT) and cyclodiode laser therapy. ALT improves the drainage of the aqueous fluid although the exact mode of action remaining unknown. SLT is a relatively new technology that uses laser to target specific cells within the trabecular meshwork as in ALT but it creates less thermal damage than ALT. As a new therapy the long-term outcomes of SLT have not yet been determined but efficacy studies are currently in progress. However, it is thought that since SLT uses low power and causes less damage to the trabecular meshwork than ALT, the former is safer to repeat than the latter, should the effects of the original

treatment begin to wear off.[40] Cyclodiode laser reduces the production of the aqueous fluid by partial destruction of the ciliary processes that produce aqueous humour. Cyclodiode laser, because of its destructive nature, is generally reserved for treatment of severe glaucoma where all other therapies have failed, although the threshold for using cyclodiode laser is falling as clinicians become more familiar with it. Cyclodiode laser is often used when an eye has become blind but because of elevated pressure remains painful.

1.1.6.3 Surgical therapy

The generally accepted gold standard surgical technique used in the management of POAG is a form of glaucoma filtration surgery called trabeculectomy. Trabeculectomy is generally very effective in achieving low IOPs but, as with all surgery, carries the risk of complications, failure and potentially total loss of vision should there be significant haemorrhage or infection associated with the surgery. Figure 1.4 shows a simplified step-by-step diagram of the procedure. The procedure site is just above the iris through the sclera as shown in Figure 1.4. A partial thickness scleral flap is formed, which is sewn loosely back in place overlying a small penetration into the anterior chamber. In successful cases, the fistula between the anterior chamber and the sub-conjunctival space allows continual outflow of aqueous through the created opening. In the early days following surgery, by using releasable sutures, the flap can be adjusted to achieve the right amount of aqueous outflow to try and achieve optimal IOP. Post-operatively the continual effectiveness of the procedure must be monitored to ensure that the IOP remains low and the features of glaucoma stable. Supplementary eye drops can be used to lower IOP further if IOP starts to rise or progression of the glaucoma occurs and the surgery appears to be only a partial success. Other surgical procedures can be performed to lower IOP and these include non-penetrating filtration surgery or the insertion of drainage tube devices.



Artwork by Tarrant T.R. [41]

Figure 1.4 Diagram of a trabeculectomy procedure

1.2 Adherence to glaucoma medication

Although current standard glaucoma treatments range from the use of topical medications, laser procedures to surgery, use of medication remains the most accessible, viable and effective option for the majority of patients with glaucoma. However, correct use of topical medication is still a major obstacle[42] and not all glaucoma patients use their therapy all of the time. Appropriate treatment is, however, of equal if not greater importance in the management of glaucoma than the diagnosis itself; the results from AGIS suggest that greater long-term fluctuation in IOP, determined by variation in IOP measures at each follow-up clinic visit, may be associated with greater visual field loss over time.[34] Several other studies have also noted that the rate and extent of visual field loss are worse with higher mean and peak IOP measures.[43, 44] The growing evidence suggests that worse control of IOP, greater fluctuations in IOP and worsening of visual field defects correlates with failure of use of medical therapy as directed.[45-48] A study carried out by Stewart *et al*. in patients with advanced POAG (n=72) found a significantly lower mean (15.4 ± 2.7mmHg) and peak (24.5 ± 6.9mmHg) IOP in patients whose vision remained stable for five years compared to higher mean (21.3 ± 3.2) and peak (39.2 ± 11.0mmHg) IOP, for those with decreased vision($p<0.001$). Furthermore, patients who lost visual function were significantly less likely to use medical and surgical intervention as recommended in comparison with patients whose vision remained stable ($p<0.001$).[45] Glaucomatous progression was seen in 50% of all patients noted to have poor use of medication and remained stable in 90% of patients who did use medication as directed; however, the method for assessing adherence was not described by Stewart *et al*. [45]

There is a wealth of literature which has attempted to measure and explain the complex phenomenon of medication-taking behaviour. The terminology used to describe medication-taking behaviour has evolved over time and has been controversial, many different terms are still used interchangeably, and no 'official' definition exists.[49] Each term has a different connotation and subtleties that need further explanation.

Traditionally practitioners have used the term 'compliance' to describe the extent of conformity to prescribed treatment regimens and patients' actual dosing

history.[50] More recently, ‘compliance’ has become less widely used since it implies a negative relationship between the prescriber as ‘the instructor’ and patient as a passive follower of doctors’ orders. Thus, ‘adherence’ is preferred since it accepts that there is an alliance between the patient and provider; the patient has the freedom to decide whether or not to adhere to the providers recommendations and therefore, adherence is a factual statement and is non-judgemental.[51, 52] The term ‘concordance’ is used to describe the interaction between the healthcare professional and patient at the point of prescribing to reach agreement on the therapeutic options even when there may be conflicting views.[51] Whereas, ‘adherence’ refers to the extent of conforming to the recommendations in terms of timing, dosage and frequency, the term ‘persistence’ is used to describe the duration of medication use from initiation to discontinuation.[53]

The therapeutic benefit from glaucoma medication is only maximized when administered correctly. In short, medication will not be effective if not administered. Yet, effective adherence is a health behaviour that involves a complex set of actions with four basic steps: obtain the medication, successfully instil the drop into the eye, use of the medication at the right time and remember to do so each day.[54]

In order to investigate the issues that are central to the topic of adherence with glaucoma medication, a review of previous research and existing opinions and theories was necessary. Personal knowledge gained from research undertaken in 2008 to understand the barriers that prevent good adherence[42] formed the basis of the initial literature review. Topics such as the magnitude of non-adherence, predictive factors, economic burden of non-adherence and how to measure adherence was largely informed by the body of work undertaken by Olthoff et al.[55] in which the evidence of non-compliance with ocular hypotensive treatment was published in 2005. Subsequent to Olthoff and Lacey’s work on non-adherence with glaucoma medication, in 2008 Haynes et al.[56] published a Cochrane review of interventions to enhance medication adherence. Although Haynes et al. included a range of both oral and inhaled drugs in their review, adherence to eye drops specifically were not included. Thus in 2009, Gray et al.[57] reviewed the interventions for improving adherence to ocular hypotensive therapy which was later updated by Waterman et al. in 2013.[58] Collectively the four reviews by

Olthoff, Haynes, and Gray were essential in informing the breadth of the topic and identifying the published literature which expands on these topics. Literature searches were also performed using Pubmed (from 1949), conference presentations and relevant RSS feeds to keep up to date with new and emerging work on the relevant topic areas.

1.2.1 Magnitude of non-adherence to medication

In 2003, The World Health Organisation (WHO) adherence project group found that poor adherence to treatment regimens was a commonly reported problem with an estimated 50% adherence rate for long term treatment of chronic illnesses in developed countries.[59] A meta-analysis of studies from 1948 to 1998 reporting adherence to medical treatment was published in 2004 by DiMatteo *et al*. with reported adherence being highest in Human Immunodeficiency Virus (HIV) disease, arthritis, gastrointestinal disorders or cancer and lowest in pulmonary disease, diabetes or sleep. The average non-adherence rate was only 24.8%.[60]

Studies specific to glaucoma treatment report similar high rates of non-adherence; a systematic review of glaucoma studies found that percentages of patients who deviated from their prescribed medication regimen ranged from 5 - 80%,[55] the disparity in reported adherence due to the varying definitions of non-adherence and assessments methods used. Studies using the Travalert Dosing Aid® an electronic eye drop monitoring device for use with travoprost (a prostaglandin analogue requiring once daily dosing), have reported adherence rates in the order of 75%.[61]

1.2.2 Barriers to use of glaucoma medication

Adherence to the use of medication is a multi-faceted process with numerous stages where a patient might deviate from their agreed regimen with more than 200 variables described over the years.[62] Various qualitative studies have also examined adherence behaviours among patients with glaucoma one of these being the study by Tsai *et al.* in which a four category classification of 71 identified barriers of significant obstacles to adherence with glaucoma medication were

created; regimen factors, individual patient factors, medical provider factors and situational (i.e. social/environmental) factors.[63]

More recently Newman-Casey and co-workers evaluated 11 commonly cited reasons for poor glaucoma medication adherence; scepticism that glaucoma medications are effective, poor knowledge about glaucoma, poor self-efficacy, forgetfulness, cost, difficulties with the medication schedule, side effects, difficulty with eye drop administration, mistrust in the physician, and perceived life stress.[64] Of these 11 reasons, poor self-efficacy, forgetfulness and difficulty with drop administration and the medication schedule were found to be the most significant barriers associated with poor adherence, when measured by patient self-report of medication use.[64]

1.2.2.1 Successful installation

The application of eye drops is a significant barrier to adherence for some patients with glaucoma.[65, 66] Eye drops are difficult to self-administer and require co-ordination, manual dexterity and good central vision.[67] Most patients with glaucoma are older adults who can be challenged by taking any medications; reasons include hearing difficulty, low health literacy, physical or cognitive disability and limited social and financial resources.[68] Research has shown that even when patients do adhere to their medication regimen, drop application technique can be poor. Only 60% of patients instilled the correct number of drops in a study observing 140 experienced patients with glaucoma.[65] In a cross sectional observational study of patients with glaucoma, nine out of ten glaucoma patients were not able to correctly instil eye drops into the eye.[69] Problems encountered included the wrong number of drops squeezed out from the bottle, eye drops falling on eyelids or cheek, the dropper tip touching the eye.[69] A questionnaire survey given to 253 consecutive patients with glaucoma in order to evaluate techniques for instillation of eye drops found that 25% of patients who self-administered their drops reported touching the dropper tip on their eye; furthermore, 17% relied on others to administer their drops for them.[70] In a study of 324 patients the most commonly self-reported problems with administration of eye drops included difficulty with: drop administration (44%), reading the print on the bottle (18%), side effects (16%), bottle squeezing (14%), seal removal (14%) and remembering to take medication (12%).[71]

1.2.2.2 Dosing regimens

As previously discussed, if fluctuation in IOP is harmful, then patients missing doses of medication for treatment of glaucoma, cause gaps in therapy that could increase fluctuation in IOP and varying adherence is thus an essential consideration. Furthermore, some glaucoma medication has a short half-life, thus successful adherence to therapy is not just dependent on administering eye drops on a daily basis but also at the correct time of day.[54] A study using an electronic monitoring device to measure time of administration of eye drops found that whilst all patients stated they were adherent, they did not take their medication at the correct time of day.[72]

Complex dosing regimens involve both the number of drugs prescribed, and the number of doses that have to be administered each day. In a qualitative study using 100 interviews with patients using eye drops for glaucoma, dose timing and frequency was listed as the third most common reason for non-adherence, the number of missed doses increasing with the number of doses required per day.[73] A study in the USA using a retrospective review of patient records found that the addition of a second drug in 1784 participants using latanoprost showed an increase in the time between renewed prescriptions by a mean of 6.7+/-25.6 days and 23% of study participants increased the interval by more than 2 weeks ($p < 0.0001$) compared with 3146 participants who continued on monotherapy.[74]

Whilst the evidence suggests that people on simpler drug regimens are more likely to adhere and persist with their ocular hypertensive therapy, the systematic review conducted by Waterman et al. found the evidence was weak as studies were of variable quality and only short term.[58]

1.2.2.3 Remembering to administer doses

Diabetes and hypertension are similar to glaucoma in their asymptomatic nature in the early stages and as such, can be associated with increased levels of non-adherence.[75] When patients are without symptoms they may not understand the importance of daily adherence[76] in contrast with diseases where patients are symptomatic if non-adherent with their medication, such as those used for pain relief or allergies. Forgetfulness is one of the most widely reported reasons for

non-adherence.[55, 63] However, it could be argued that forgetfulness is reported more often because it is considered to be a more socially acceptable barrier and easier for patients to say that they forgot to take their medication than discuss the real issues.[64] An internet survey of patients enrolled in the 'Medicare' social insurance programme in the USA (n=1220), found that patients who had multiple concerns about their medication were more likely to report forgetting to take their medications.[77] Thus, 'forgetfulness' may disguise other underlying reasons which may not be disclosed to health professionals or researchers, such as concerns about whether the medication is helping their condition.

Feedback from patients suggests that when using tablets from a 'blister pack', the empty 'blister' can act as a visual reminder that the intended dose has been administered. To overcome memory issues, tablets can be transferred into dosing boxes, which can be an important resource for elderly patients.[78] Visual cues from blister packs or dosing boxes and other similar practical reminders are not so easily possible with a bottle of drops.[79] Administering eye drops from a bottle may not only be difficult for patients to achieve but also restricts the use of the packaging as a reminder to use drops. Memory problems have the potential to result in either under-dosing or overdosing of therapy, the latter being important with respect to potential adverse side effects.

1.2.2.4 Disease severity

Non-adherence to follow-up visit schedules has been significantly associated with less severe disease; patients diagnosed as 'glaucoma suspect' had greater non-compliance to follow-up than those with manifest glaucoma.[80] In a retrospective cohort study of health insurance claims data, newly treated patients diagnosed with glaucoma (n=3623) were compared to patients diagnosed with suspected glaucoma (n=1677). Persistence with medication was marginally higher in those diagnosed with glaucoma than those with suspected glaucoma (RR 1.11; 95% confidence interval, 1.05-1.18).[81] A focused summary of the available literature by Tsai *et al*. also advocated that adherence could be proportional to disease severity.[82]

1.2.2.5 Access to medication

The cost of medication may be an important factor for some patients. However determining if this is a consistent barrier which significantly affects adherence with glaucoma medication is difficult to establish due to the different healthcare structures and payment practices between countries for the provision of care and medication. In a cross-sectional survey in the USA in 2006 (n=324), where individuals are responsible for their own cost of care via healthcare insurance providers, 41% of patients with glaucoma found that they had difficulty in paying for their medications.[71] However, in a previous interview study in the USA (1995, n=100), of individuals who paid fully for their medications only 11.5% stated that the expense of the medication on occasion had prevented them from obtaining their prescription.[73] Thus, comparing data over different time periods or data extraction methods could prevent the comparison of available data. However, both studies suggested that patients who have to meet full/partial medication costs personally may face restricted access to medication. Such a theory could be relevant to UK residents under the age of 60 and who do not meet the National Health Service (NHS) exemption criteria, who must pay a fixed prescription cost per item, although this hypothesis has not been systematically investigated. Further consideration also needs to be given to the fact that cost of medication as a barrier to adherence is likely to be under reported; in a survey of older adults with chronic illness, 66% of respondents did not inform their clinician that they intended not to buy their medication.[83]

Failure to reorder drops, or problems in obtaining new bottles can also lead to periods of missed doses.[42, 84] Unlike tablets in a 'blister pack' where the number of remaining pills can be counted and diarised collection of new prescription calculated, bottles containing liquid cannot easily be examined to determine how many doses remain; often the view of the liquid is either obstructed because the plastic bottle is too opaque or labels cover the majority of the small bottle.[39]

1.2.3 Predictive factors

Identifying predictors of adherence is an important consideration as a tool to improve patient long-term care and has the potential to reduce healthcare expenditure by identifying specific causes of non-adherence or distinguishing 'at-risk' patients, to enable specific 'targeting strategies'. Several studies have identified race and socioeconomic status as risk factors for non-adherence to eye drops;[85-88] African descent, lower income and increased number of eye diseases were found to be predictive of partial treatment adherence[85] as was age less than 50 or more than 80 years, African-American race and lower income[88] and non-white patients.[86] At present, there is no consistent evidence to suggest that other variables such as gender, time since diagnosis, number of medications used, health status, vision, education attainment, or living alone have any significant effect on adherence to medication.[58, 64]

However, a review of the literature which classified determinants into four different demographic aspects, knowledge, duration and severity of disease and complexity of treatment regimen, have failed to identify any consistent variables.[55]

1.2.4 The economic burden of non-adherence

Non-adherence increases the burden of healthcare required and increases the cost of healthcare. In a study describing the patterns and economics of glaucoma treatment, published by Denis *et al.*, 88 ophthalmologists examined 5 years of the medical item consumption data of 337 patients with OH and POAG.[89] Lower costs were positively associated in patients with less visual field defects. Higher expenses were always related to a greater severity of optic nerve damage and additional costs were always seen as the disease worsened. Although Denis *et al.* did not carry out a cost analysis of poor adherence, the number of medical

therapies tried contributed independently, in an additive way, to the total cost of glaucoma treatment in their study.[89] Furthermore, non-adherence can be mistaken for low medical efficacy of treatment. If a patient fails to respond to therapy, a change in therapy is often tried or additional topical agents added; this may only lead to further problems since adherence with therapy appears to decline with increasingly complex regimens.[66] Winfield *et al*. found that, even if asked, 69% of patients taking glaucoma medication would not tell their clinician that they were having problems with adherence and approximately 50% of the individuals started on glaucoma medications reported to discontinue them within 6 months.[66] Thus, non-adherence can lead to unnecessary additional prescribing, wastage of unfinished pharmaceutical supplies, more frequent hospital appointments and/or diagnostic tests, this leading to increased healthcare expenditure. If surgical treatment is required because all avenues of medical treatment have been explored, this not only increases the cost of glaucoma care significantly, but adds surgical risk to the patient.[89]

1.2.5 Measuring adherence

The method of measuring adherence utilised usually determines how adherence is reported; adherence can either be expressed as the percentage of doses taken by an individual or as the percentage of non-adherent subjects,[90] although this assumes that the definition of adherence has first been established. By convention, an 80% adherence rate is widely recognised as 'acceptable'.[91] But, an 'adherence rate' is just an arbitrary figure if it has no relevance to the effect on clinical outcome. Thus, classification of 'adherent' and 'non-adherent' parameters should be established in relation to the disease specific target at which a beneficial clinical outcome would expect to be achieved.[55] The desired 'adherence rate' for topical ocular hypotensive medication used in the management of glaucoma has yet to be quantified. Failure to establish a desired 'adherence rate' for ocular hypotensive medication has resulted from the inconsistency between patients in achieving their target IOP measure, the variance of drop efficacy between patients and the different treatment regimens used to control glaucoma on an individual basis. Without supporting evidence to suggest otherwise and due to the adverse consequences of non-administration ophthalmologists at the Norfolk & Norwich University Hospital aim for 100% adherence, this being supported by the Royal

Manchester Eye Hospital opinion.[92] Knowing that ocular hypotensive medication not only lowers mean IOP, but also minimises IOP fluctuations, strengthens the perceived requirement for 100% adherence. As already discussed, patients who stop and start treatment on a regular basis are thought to increase IOP fluctuation; on adherent days the IOP will be lower, on non-adherent days the IOP will be higher, causing peaks and troughs in IOP. Thus, although no conclusive evidence exists, the non-adherent patient may inadvertently increase the risk of developing progressive glaucomatous visual loss. Unfortunately, the complexity and ethical implications associated with such a theory prevents the collection of empirical evidence.

In addition to the nuances of defining adherence, the numerous methods of measuring adherence and reporting outcomes can also be problematic with respect to gathering good scientific evidence for studies of adherence.[58]

Subjective measures such as patient self-report are generally cheap and easy to administer but in comparison with objective measures, can yield higher adherence estimates.[93, 94] Whilst objective measures remain the gold standard of clinical trials they have several drawbacks.

1.2.6 Objective measures of adherence to medication

1.2.6.1 Electronic monitoring systems

Studies using electronic monitoring methods have become increasingly more common in recent years. The Medication Event Monitoring System (MEMS) contains a microelectronic circuit that registers the exact date and time of medication events, such as 'Track Caps' which record each time the bottle is opened to retrieve medication from within the bottle. Such a method can provide more detailed information about the timing of doses than can be obtained through most other methods and is considered to be an accurate method for assessing adherence. However use of the MEMS with eye drops would entail the user to unscrew the MEMS cap to retrieve the bottle of eye drops, subsequently unscrewing the eye drop cap before administering the dose. Thus, a "bottle within a bottle" method requires multiple extra steps that deviates from the usual administration procedure. Currently, no RCT has reported using the MEMS to

measure adherence to ocular hypertensive medication.[58] Electronic drug monitoring is a particularly attractive method employed to measure adherence with eye drops for glaucoma treatment, firstly because 'pill counting methods' cannot be employed when dealing with liquids and electronic monitors that can report the time that patients use their treatment is an important factor for glaucoma patients who must maintain a constant time of drop administration to avoid peaks and troughs in IOP.[72] Electronic dosing monitors may also be useful in identifying dosing habits and may give a better understanding of actual medication-adherence behaviour which cannot be derived by calculation of an 'adherence rate'.[79, 94-96] The studies by Norell and Granstrom were the first to use electronic monitors to obtain an objective measure of adherence with topical ocular hypotensive medication.[97, 98] More recently, Alcon® has introduced the Travatan Dosing Aid (Travalert®,TDA) which electronically stores data on the time, date and number of drops administered. The TDA can only be used in conjunction with Travatan® (travoprost) and Duotrav® (travoprost/timolol combination) eye drops due to the TDA's aperture size restricting other shaped bottles from fitting the device. Three studies using the TDA have reported that it accurately records drop administration.[93, 99, 100]

However, there is a potential drawback to the use of electronic devices because the monitoring device can be so obvious to the user that adherence behaviour is consequently modified.[94, 101] When research assessment prepares people to be more receptive to the study intervention or causes a modification in expected behaviour, a reactivity bias can occur which may either strengthen or weaken the true intervention effect size.[102, 103] When they occur, the effects of a reactivity bias can threaten the validity of any conclusions that are drawn from research studies and are therefore important to eradicate from studies. Electronic bottle monitoring, pill counting or bottle weighing may suggest to patients that they are not being trusted, resulting in resentment and a possible reduction in adherence or an undermining of any intervention that may be the object of the study using this measure of adherence.[104] However, a pilot study established that the TDA had no demonstrable impact on modifying adherence behaviour by emphasising the monitoring itself.[105] and a study carried out by Cramer *et al.* found that reactivity bias to medication monitoring devices was short lived and patients quickly returned to their self-medication behaviour patterns.[106]

Electronic devices are also expensive to fund, often more difficult to operate and cumbersome than the bottle itself, and their use thus leads to a predetermined selection of participants who would be able to operate such devices rather than being usable by the greater patient population. In addition, bottle openings do not always correspond to an applied dose.

The first studies reported by Norell and Granstrom.[97, 98] indicated that adherence could be improved significantly with an educational intervention, however, adherence was only monitored using the devices for a 20-day period following the educational intervention. As suggested by Cramer *et al*.[106], the 20-day period may not have been long enough to overcome the reactivity bias associated with the monitoring device itself and therefore longer term follow-up should have been used to allow patients to revert to their usual medication behaviour pattern. Longer term follow-up studies are needed to determine how long the effects of adherence interventions can persist.

1.2.6.2 Therapeutic outcome

In some diseases, objective observations can be made which are directly attributable to the use of medication such as hypertension where adherence can be assessed by taking blood pressure readings and diabetes by glucose or HbA1C monitoring which give an indication of the effectiveness of therapy. When the desired target of blood pressure/glucose/HbA1C control is reached, it can be considered that the patient is adherent to medication in order to have achieved therapeutic control. Due to the slow progressive damage to the optic nerve, determination of the effectiveness of therapy in patients with glaucoma, requires long term follow-up, possibly over many years, and or multiple repeat testing to establish true deterioration rather than fluctuation in test variation. An alternative would be to measure IOP control but as previously discussed, it is well documented that IOP is not constant and varies considerably throughout the day, particularly in eyes with glaucoma. Therefore, utilising IOP thresholds or IOP reduction by comparing one IOP measurement at a random time point against another is relatively futile with respect to assessing adherence. Likewise, whatever the target IOP, there is no guarantee that apparent achievement of that target IOP will halt progression of the glaucoma due to the variation of individual progression rates, often determined by other IOP independent risk factors such as

family history, co-morbidity and degree of glaucomatous damage already sustained.

Strategies to accommodate diurnal IOP fluctuations include the use of multiple daily readings to obtain peak and trough readings enabling calculation of a daily average or integrating IOP measures collected at several time points during the study period as utilised in the Ocular Hypertension Treatment Study.[32] However, the method of obtaining multiple IOP readings is time consuming, inconvenient and can also increase participant awareness that they are being monitored.

There have been six studies that have assessed non-adherence in relation to IOP or the progression of visual field loss.[107-112] A relationship would be expected because it is known that ocular hypotensive treatment is effective and adherence should result in a lower IOP. However, only the study by Konstas *et al.*[107] found non-adherent participants to have a higher mean IOP than adherent participants (n=100) (22.9 vs 18.5 mmHg; p>0.001). Adherence in this study was determined by participant self-report of missed doses per month and this correlated with level of IOP. However, this was a study of relatively small size and it relied upon participant self-report of adherence, which is known to underestimate adherence.

A failure to consistently demonstrate a relationship between adherence and IOP control,[55] could be explained by the lack of a quantified correlation or that the methodological quality of the studies performed has been poor, but more likely that the complexities of assessing the level of IOP due to individual differences, different types of glaucoma and effect of the diurnal variance lead to ‘noisy data’.

Furthermore, studies have demonstrated that adherence with medication improves in the five days before and after appointments with a clinician.[93, 113] Thus patients could be persistent with medication but not adherent to their treatment regimen and could inadvertently produce false positive clinical outcomes. In summary, with so many variables to control, assessing adherence rates based on rate of glaucomatous progression or IOP control is neither straightforward nor practicable. When adherence does not easily correlate with immediate clinical benefits ideally both adherence and clinical endpoints should be measured.[56]

1.2.6.3 Blood and serum samples

Many reviews have suggested that biologic assays are the most accurate measure of adherence.[114] Body fluid can be used for analysis to enable the concentration of the therapeutic drug to be measured. However, it is not always possible to detect the concentration of the therapeutic drug under investigation and therefore a marker drug, which has no therapeutic benefit other than its ability to be accurately measured, can be formulated and used to assess adherence with the medication. Such methodology, although objective, does have limitations. Some drug concentrations are highly variable due to individual variability of absorption and elimination. Development of pharmacokinetic models to support such methodology is costly and not always possible. Assessment of drug concentration has not yet been used to assess adherence with ocular hypotensive medications.

1.2.6.4 Prescription databases

Prescription databases provide prescribing data that can be used to estimate the level of adherence based on how many new prescriptions have been issued. However, while collection of a prescription suggests intention to use medication, it does not ensure its administration.[115]

Choo *et al.* in the United States, evaluated patient self-report, pharmacy dispensing records and pill counts using electronic monitoring as a validation standard for adherence with systemic antihypertensive treatment.[116] In the patients using an antihypertensive (n=286) it was revealed that refill prescription patterns were moderately correlated with electronic monitoring and it was suggested that pharmacy dispensing records could be used with predictive validity; by using gaps in the medication supply as indications of non-adherence.[116]

Prescription claim databases as described in the study by Choo *et al.*[116] are particularly common place in the US as their healthcare system relies heavily upon insurance claims for healthcare costs. Prescription claims data are particularly useful for identification of non-adherence due to discontinuation or changes in treatment. However, if patients do not collect prescriptions from the same source

each time or within the same pharmacy networks, the recording process can be unreliable.[117]

1.2.7 Subjective measures of adherence to medication

1.2.7.1 Physician estimated adherence

It has been reported that ophthalmologists do a poor job of detecting non-adherence in their patients.[118] In a study published in 1986, eye drop medication monitoring data were compared with ophthalmologist predictions of adherence[119] and it was found that ophthalmologists were unable to identify which of their patients were adhering correctly to prescribed therapy. More recently, in an observational cohort study (n= 196) using the TDA, virtually no correlation between physician predictions of adherence and electronic monitor recordings (r=0.09; 95% confidence interval, 0.00 – 0.19) was identified.[93]

Furthermore, another study found that 69% of patients when interviewed would not tell a doctor of their problems using eye drops; this was reflected in the lack of awareness among the medical staff of the problems experienced by these patients.[66] Thus, physician estimation of adherence does not appear to be a reliable measure of adherence.

1.2.7.2 Self-report of adherence

Patient self-report is used frequently as a measure of indirect adherence levels and involves questionnaires, diaries and/or interviews. Self-report tools are generally cheap and simple to carry out and specific to non-adherence. However, self-report measures can yield higher adherence estimates in comparison with objective measures.[93, 94] The discrepancy between self-report and objective measures of adherence is attributed both to the social desirability to be adherent to medication regimens as prescribed by clinicians and memory bias; if non-adherence is due to forgetfulness, how can a missed dose be remembered for the purposes of self-report? In addition, if patients have misinterpreted their prescribed regimen, they may not realise that they are not adhering and therefore self-reported adherence at a fixed point in time is not necessarily representative of adherence over a period of time.

Adherence is not a dichotomous variable, although it is usually described and presented in this way “are you adherent? Yes/no”. For the patient there may be many ‘shades of grey’ in the adherence pattern and a variety of factors that affect the use of medication on a given day. The visual analogue scale (VAS) is a commonly used picture-graphic tool used in questionnaires to assess subjective attitude to characteristics that cannot be measured, such as “how much pain do you feel”. As a measure of adherence, patients are asked to put a line on the scale indicating how much of the time they consider that they use their medication as directed. It has been proposed that VAS scales may be particularly useful in assessing medication adherence in lower-literacy populations.[120]

The missed-dose method for assessment of adherence is simple and involves asking patients to confirm whether they ever miss taking their medications and if so how often they do: once a day, once a week, once a month, rarely, never.[121] The missed-dose method can also be used in open-ended face-to-face interviews leaving the patient free to quantify their level of adherence if no suggested time has been given.

A recent glaucoma adherence study reported by Ajit *et al* [61] used the self-report of missed dose method to compare patient estimate of adherence with that of the TDA (n=34). Ajit *et al*. found that patient reported adherence was below that of the TDA in the majority of cases. In some cases, patients reported 100% adherence when their TDA indicated <40% adherence. Similar reports have been published by Okeke *et al.* [93] and Kass *et al.* [122] Therefore, relying on patient reports of adherence in glaucoma studies would appear to be prone to error.

- Brief Medication Questionnaire (BMQ)

Svarstad et al [123] developed the Brief Medication Questionnaire (BMQ), a self-report instrument for measuring and monitoring adherence from the patient perspective. The BMQ questionnaire has three parts; the regimen screen, belief screen, and recall screen, to increase the sensitivity and positive predictive value and specificity level of the questionnaire. The frequency of missed-dose screen uses neutral, open ended-questions and a short recall period of a week. The questionnaire was validated (n=20) using MEMS and the BMQ achieved a sensitivity level of 80-100% and accuracy of 95%.[123]

- The Morisky Medication Adherence Scale (MMAS)

The Morisky Medication Adherence Scale (MMAS) is a structured four-item self-report adherence measure validated for use in hypertensive patients. Results showed that 75% of the patients who scored high on the four-item scale at year 2 had their blood pressure under adequate control at year 5, compared with 47% under control at year 5 with a low score ($p<0.001$).[124] Although not validated for use in patients with glaucoma, MMAS has been used in hypertension studies which has a similar asymptomatic characteristic to that of glaucoma and thus has the potential to be useful for the latter condition.

Using questionnaires that attempt not only to measure adherence but also to provide information about medication behaviour helps to implement appropriate adherence interventions. There is a lack of literature comparing the different methods used to elicit which tools are preferred by patients, which take into account ease of use along with their reliability and usefulness as an adherence screening mechanism. It is interesting to find evidence of VAS specifically designed to function as an easily administered assessment tool suggesting that other tools are not accessible to all patients regardless of literacy, although this has not been described in the reviewed literature.

Clinicians and researchers struggle to determine the best way to measure adherence. Comparison of measurement techniques only add to the controversy as to whether measures really provide complementary information.

1.2.8 Further considerations when measuring adherence to glaucoma medication

It is plausible that the treatment options available for every different health condition will carry their own set of difficulties when measuring adherence. Measuring adherence in glaucoma patients has its own set of intricacies. Olthoff *et al*.[55] reviewed intervention protocols for glaucoma adherence studies and found the strictest definition of non-adherence to be taking less than 100% of prescribed eyed drops. Studies that reported patients who were not strictly compliant generally reported higher prevalence rates of non-adherence. In reality a number of definitions and cut offs are reported for each published study. Therefore, direct comparison of study results was not plausible or relevant.

Olthoff et al.[55] concluded that whilst all interventional studies reported a significant improvement in adherence the majority of studies had a poor research design. Only the studies of Norell and Granstrom[97, 98] were considered by Olthoff *et al.* to be demonstrative of acceptable trial design due to their use of an objective outcome measure: a medication monitor recording the day and time of opening the bottle. Other factors included a lack of adjustments made for confounding variables. The study by Konstas *et al*.[107] used a cross-sectional assessment of patients using various different eye drops for treatment of their glaucoma. No adjustment was made for patients who were required to use more complicated dosing regimens with multiple dosing of different medications a factor which has previously been reported to reduce adherence.[74] Length of the monitoring period, whether researchers were blind to the control and intervention groups, patients changing their adherence behaviour due to the fact they are being monitored (particularly just before clinic visits if IOP measure is the determinant of adherence), use of language in questionnaires which could introduce socially desirable answers and selection bias, are all areas for potential methodological failure.[55] Studies that lack a comprehensive methodological design have been compared under one umbrella when ideally, only comparisons of studies using the same methodology should be compared, particularly in a complex topic areas such as adherence; only then will we begin to understand true trends and adherence rates to guide future research.

Consideration of inter-country healthcare system differences are also required since elements of cultural disparity and structural diversity between healthcare systems can affect health beliefs and attitudes which, in turn, may affect adherence. Patients paying for medication may also be less likely to adhere when a condition is asymptomatic.[42]

Chapter 2. Improving adherence to glaucoma medication

Chapter 1 highlighted that medication non-adherence leads to poor clinical outcome for patients with glaucoma and increases the economic burden of healthcare costs. Estimating the magnitude of non-adherence and establishing the effectiveness of interventions designed to improve adherence is important for the advancement of ophthalmic care for patients with glaucoma. However, defining, measuring and reporting adherence is challenging. Chapter 2 looks at the health behaviour models that have underpinned our understanding of adherence behaviour. Knowledge, beliefs, motivation and planning abilities are the core explanatory frameworks from which interventions can be developed to improve the use of medication to ensure that patients with glaucoma receive the very best care in the future.

2.1 Behaviour change interventions

Behaviour change interventions aim to change behavior that is damaging to people's health. Interventions can range from a single intervention to high intensity interventions that can be delivered over a number of sessions. Behaviour change interventions are used in a wide range of health areas, such as alcohol misuse, eating disorders, lack of physical activity, unsafe sexual behavior and smoking. The common link is that the intervention aims to change behavior in order to improve an individual's health and wellbeing.[125]

Identifying facilitators and barriers to adherence as discussed in chapter 1.2.2 are helpful in isolating the practical assistance that patients require, but they cannot in themselves be used as preparatory work for developing behavior change interventions, since we must first understand the health education need.[92] There are many reasons for non-adherence to medical regimens and historically non-adherence has been categorised as being due to either intentional or unintentional forms of behaviour. Unintentional non-adherence is a passive process that

prevents use of medication, such as poor comprehension of dosing regimen, lack of education delivery by the clinician, or physical inability to self-administer medication. Intentional non-adherence has been described as a deliberate decision by the patient to deviate from the prescribed recommendations by not taking medication, reducing the dosing frequency or prematurely discontinuing the medication. However, the manifest behaviour is often an amalgam of a range of these factors and therefore the categories overlap.[126] Furthermore, forgetting is often categorised as unintentional behaviour, but forgetting use of drops can be influenced by intentional or motivational factors, such as lack of perceived need for treatment.[127] The overlap in categorisation of unintentional and intentional behaviour renders this inadequate as a framework to design adherence interventions.

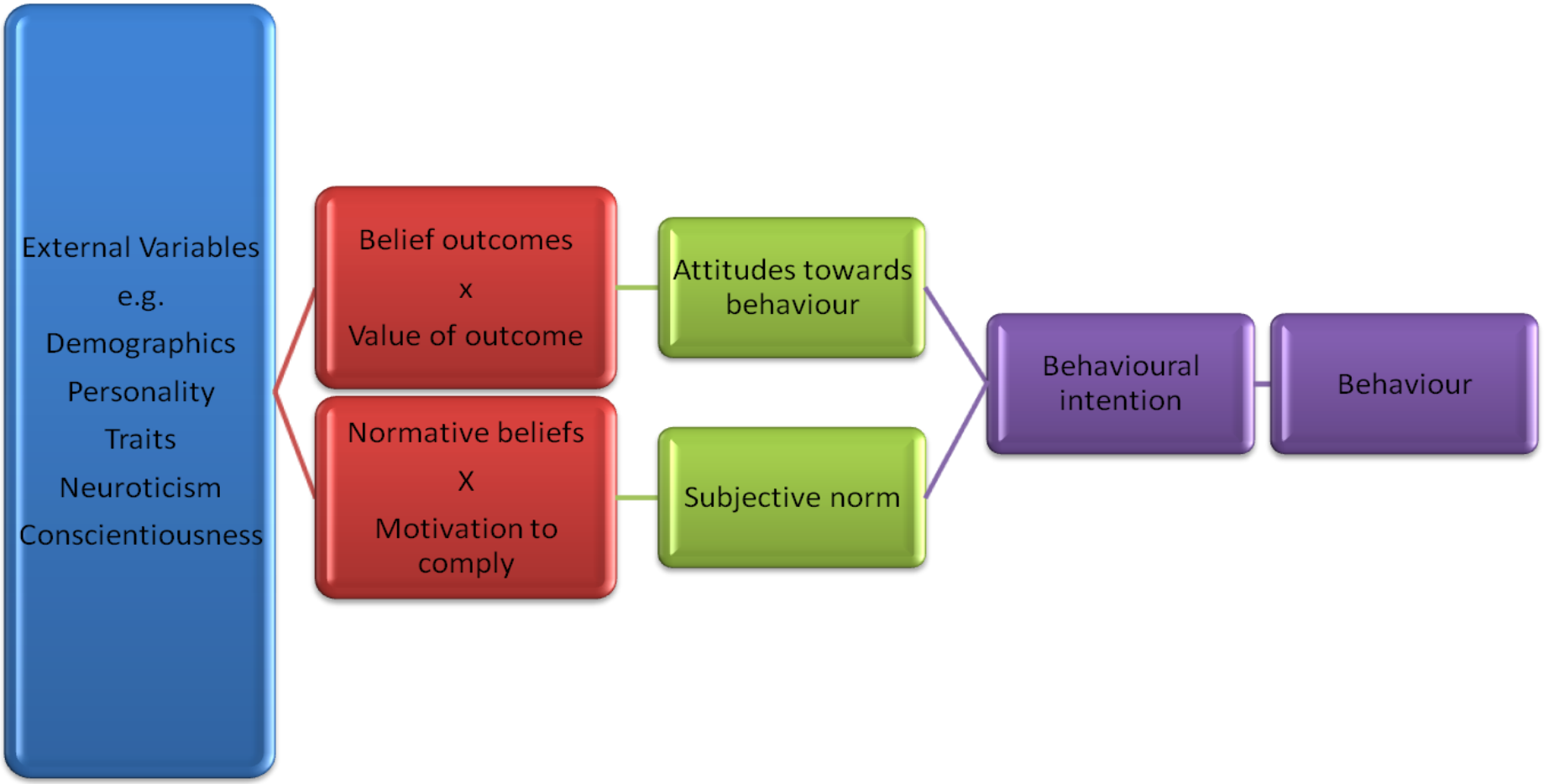
2.2 Behavioural models

There has been a move to maximise the impact that interventions have on adherence by using multi-component designs grounded in behaviour models. Thus, identification of the beliefs and cognitions that determine an individual's behaviour have become key in psychology and health-related disciplines. The Health Belief Model (HBM) was first described in 1966 by Rosenstock[128] and summarised by Dunbar *et al*. in 1979.[129] According to the HBM model, an individual will follow the directions given to them by their health practitioner providing they believe that they have a susceptibility to the illness, that the consequences of that illness are considered to be serious and the costs of the required action do not exceed the benefits; therefore the health practitioner's directions will be beneficial in reducing risk or severity of the disease. The application of health promotion is key in providing the individual with adequate knowledge of their condition to enable them to recognise the importance of these elements. However, whilst the HBM focuses on patient behaviour related to illness prevention, the model does not explore medication taking behaviour in relation to chronic illness.

The Theory of Reasoned Action (TRA) is a general model of behaviour, determining behaviour to be led by an individual's intention to perform a behaviour as described in Figure 2.1.[130-132] The intention is governed by two factors; firstly, attitude toward the behaviour is informed by beliefs about the outcomes of the behaviour combined with the perceived value of these outcomes and secondly, the influence of the social environment and subjective norm surrounding that person which is informed by the beliefs of what other people think and motivation to comply with the opinions of others. Thus, in a healthcare setting, TRA suggests that patients will evaluate the benefits, drawbacks or barriers of adhering to medication, before forming their own intention. Therefore, TRA predicts adherence behaviour is based upon pre-existing attitudes and intentions.

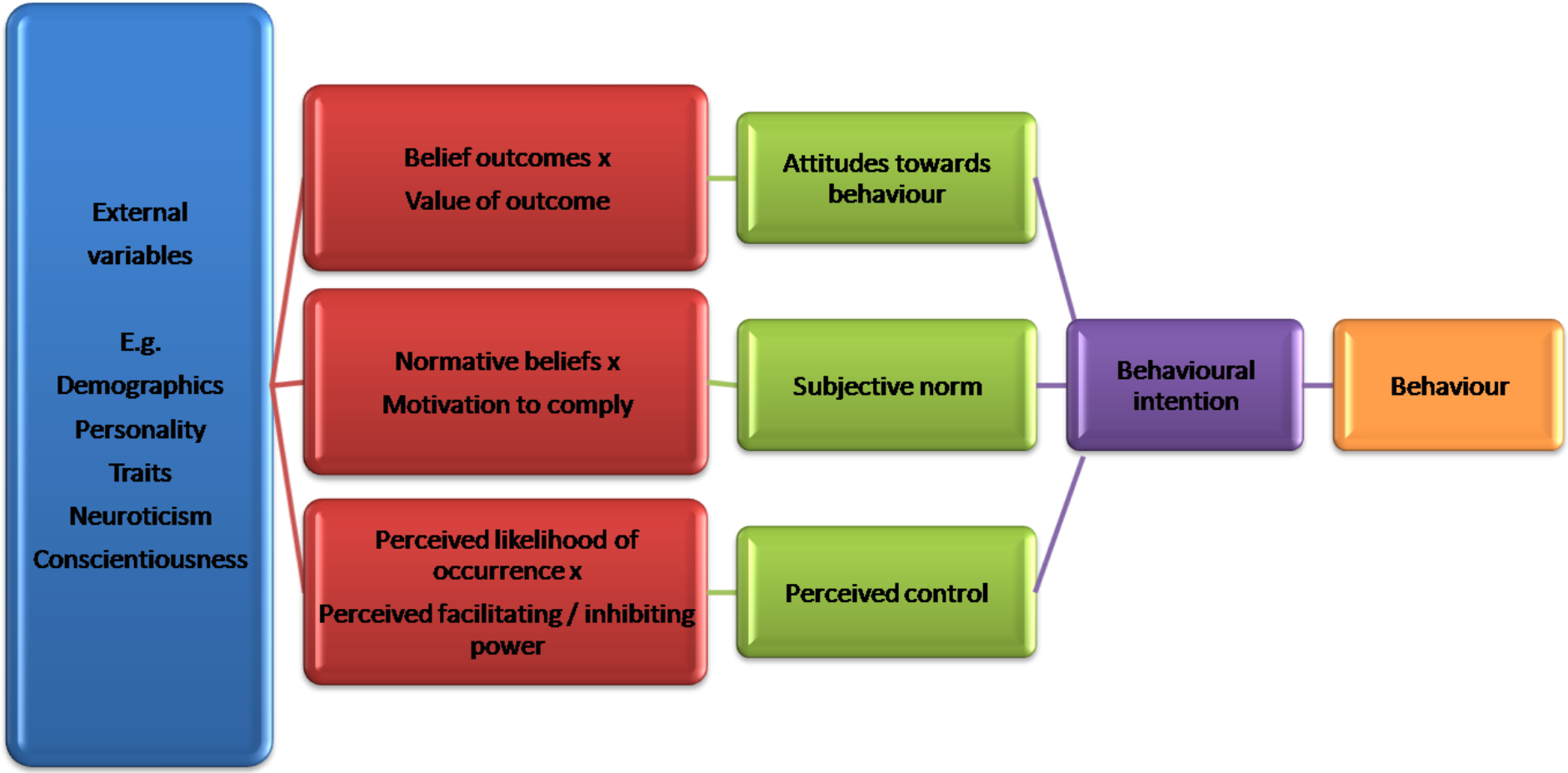
The Theory of Planned Behaviour (TPB) supplements the elements of the TRA by adding a third concept of perceived control as shown in Figure 2.2. If the individual believes they have control over their opportunities, resources and skills necessary to perform a particular behaviour they will be able to overcome the potential barriers.[131, 133] Thus, in a healthcare setting TPB expects that in addition,

the pressure of social norms the individual must feel able and confident to perform and control the behaviour required to remain adherent to medication.[134]



Adapted from Horne and Weinman [135]

Figure 2.1 Theory of Reasoned Action



Adapted from Horne and Weinman [135]

Figure 2.2 Theory of Planned Behaviour

Social Cognitive Theory (SCT) suggests that optimal adherence will be achieved if the individual believes in his or her capability to perform the appropriate behaviour, known as self-efficacy.[136] Thus, the behaviour outcome relates to whether the individual believes that certain behaviour will have a positive impact on their health condition and if they value the outcomes or consequences that will occur as a result of performing that specific behaviour or action. Self-efficacy can be improved by providing clear instructions and giving opportunities for training and modelling the desired behaviour.[131] Patients that have a stronger belief in the necessity for eye drops are more adherent[137] and studies that have targeted patient beliefs have been effective in improving adherence.[138, 139]

Unlike most other theoretical models, SCT has been applied to measure self-efficacy and outcome expectation scales in glaucoma patients using eye drops. Sleath *et al*. developed two specific instruments, one to measure self-efficacy and the other to measure outcome expectation.[140] To assess validity, two self-report measures of adherence (the MMAS [124] and a VAS measure) was distributed to 60 patients with glaucoma. The self-efficacy scales had a significant association with the patient self-report of adherence. Whilst patients with higher self-efficacy were significantly more likely to be adherent with their glaucoma medications, the outcome expectations scale did not correlate significantly with either adherence measure.[140] Such findings are important since they help to explain adherence behaviour and have the potential to be used in clinical practice. Patients could be screened to detect those who have low self-efficacy or confidence in using their glaucoma medications so that health providers can target education specifically for those individuals. However, more recent findings from a study using a different patient population with more patients newly prescribed treatment suggest that the self-efficacy questionnaire was not correlated with a MEMS adherence measure[94] and highlights the complexity of patient behaviour.

More recently, the methods that have been used to change different health-related behaviours have been brought together and integrated as part of an over-arching taxonomy of behaviour change techniques.[141, 142] The development of the taxonomy has led to new ways of conceptualising the factors which determine individual health-related behaviours. The COM-B[142] captures the range of mechanisms that may be involved with change by referencing the existing theories of behaviour. Interaction between three components: Capability, Opportunity and

Motivation (COM) cause the performance of Behaviour (B). The COM-B is recommended as a starting point to choose interventions that are most likely to be effective and address each identified component which can influence behaviour and is a useful new tool for research aimed at designing new interventions that involve behaviour change.

2.3 Intervention approaches

The findings from previous studies reveal that individuals often report more than one reason for non-adherence.[64] Thus, the causes of non-adherence are complex[42, 143] and a single intervention may not be enough to produce a sustained change in adherence behaviour.[144] A Cochrane review of adherence interventions concluded that effective adherence interventions were complex in nature and labour intensive with those using personal contact remaining the most effective.[145] Studies using multifaceted intervention components including education and discussing strategies for incorporating medication administration into their daily activities have detected a significant improvement in adherence.[97, 146]

A study designed to improve adherence to glaucoma medication using a 30 minute education and tailoring program (n=73), found a positive, significant improvement in adherence.[97] Norell's educational component was similar to other reported studies, however, the additional 'one to one' tailoring program allowed the patient to consider and discuss strategies for incorporating the medication administration into daily activities.

However, the evidence to support interventions to improve adherence with glaucoma medications remains weak.[57, 145] A systematic review of adherence intervention studies found that only 46% had enough power to detect clinically important effects to determine efficacy of the intervention.[145] Many studies have used self-report of adherence which is known to over-estimate adherence and thus may not adequately represent the differences between control and intervention groups. Thus, objective measures of adherence such as MEMS or pharmacy refill records should be employed.[57, 145]

2.3.1 Education

The NICE glaucoma treatment guidelines[27] launched in 2009 recommended that patient information should be improved to avoid the potential harm patients face due to uncertainty surrounding the disease. When information is withheld, this can lead to low adherence with medication and follow-up care which effects the positive clinical outcomes expected for patients with glaucoma and ocular hypertension and may also increase the anxiety felt by patients that may impact

upon quality of life. The HBM suggests that an individual with adequate knowledge of their condition is likely to acknowledge the importance of their diagnoses and act accordingly. However, whilst poor glaucoma education has been cited as an explanation for non-adherence to therapy,[42, 143, 147] the magnitude and nature of any association is unclear. Studies related to oral anti-hypertensives have found that education alone is ineffective in improving adherence[148, 149] and similar outcomes have been reported with glaucoma.[148, 150, 151]

The systematic review by waterman et al.[58] reported adherence interventions by Gray[139], Norell [97] and Okeke[146] which used education and/or patient education combined with other behavioural change interventions, all found improved adherence. However, four studies did not find any differences between their control and intervention groups. The semi-structured educational session reported by Sheppard *et al*.[150] identified an improvement in participant knowledge but no significant difference in adherence between intervention and control groups. Sheppard's findings may, in part, be attributable to the small sample size (n=73), short follow-up (12 weeks) and failure to ascertain the fidelity of intervention delivery by nurses.

Thus, the influence of both intentional and unintentional factors that lead to non-adherence and the complexity of human behaviour may explain the failure of purely educational interventions alone to achieve significant improvement in adherence to medication.

Traditionally, interventions have been delivered to single patients[58] but group-based educational interventions in patients with glaucoma have previously been investigated.[152] Group education has been found to be of equal value in comparison with individual education in diabetes.[153] There is only one previous glaucoma intervention study clearly set in a health education context which used a group based intervention using a health promotion approach investigated by Waterman *et al*.[154] The results from Waterman *et al.*[58] suggested that this approach would be appealing to certain individuals but not all patients and it still needs to be tested for equivalence to one-to-one delivery of education.

2.3.2 Patient-centred care

Patient-centred therapy was first developed by Carl Rogers in the 1950s and later introduced to the medical world by Michael Balint termed “patient-centred medicine”.[155] Evidence suggests that patient-centred medicine improves patient satisfaction with care received, reduces symptom severity, reduces health care costs and increases adherence to medication.[156, 157] Using patient-centred therapy in consultations to elicit a behaviour change is used in many health care settings to prevent and manage a wide range of conditions, for example, diabetes, asthma and heart disease.[158] Achieving greater adherence to medications uses communication that can engage the patient in shared decision making about medication in order to address the barriers to adherence.[159]

Thus, the goal of patient-centred communication in order to elicit a change in behaviour is to help the patient weigh up the perceived benefits of the change in behaviour with the perceived disadvantages. It has been illustrated as a seesaw reaction; when the perceived disadvantage is low and perceived benefit is high, then a decision and change in behaviour is easily achieved. However, when the costs outweigh the perceived benefits, the balance tips, and ambivalence to change occurs. Ambivalence in itself is a natural phase in the process of change, but ambivalence must be overcome in order to help a person move towards a change which is of benefit to them. As such, in some cases a brief intervention to explain the risks and benefits of a change in behaviour is enough to resolve the issues involved and for a change to be willingly accepted. However, where the benefits are unclear and the costs are high, a person may need additional help to move through their ambivalence and the magnitude of the help required to achieve this will be founded upon the type of behavioural change required, and resistance to change displayed by the patient.[160]

A qualitative study of factors influencing glaucoma treatment adherence reported that non-adherent participants were less likely to believe that the healthcare team devoted sufficient time to them, were less likely to ask questions and know of the benefits of the medication and were more likely to report problems with remembering to use their medication.[161] Clinical consultations are often didactic in nature[147] and thus providing a more relaxed environment to allow patients to discuss their concerns and ask questions may encourage better exchange of patient education and medication concerns.

2.3.3 Motivational interviewing and Behaviour Change Counselling

Motivational Interviewing (MI) has been suggested as an important area of research for use in interventions to improve adherence to glaucoma medication[147, 162] and more widely in other chronic conditions.[163-165] Motivational Interviewing and more recently Behaviour Change Counselling (BCC) have been developed in order to identify ambivalence and guide patients in adopting behavioural change[160] and is used today in many different health care related settings, such as smoking cessation, HIV prevention, management of disease, diet and physical activity and medication adherence, but its roots were first founded in addiction counselling. The theory and practice of MI differs when applied to both addictive or non-addictive behaviours and chronic diseases. For example, changing patient behaviour to adhere to medication does not have the same resistance and depth of psychological meaning as stopping alcohol, and thus non-addictive behaviours will need less time to overcome ambivalence.[163]

Miller and Rollnick (2002) define MI as *"a client-centred, directive method for enhancing intrinsic motivation to change by exploring and resolving ambivalence".*[166] In this sense, MI focuses on the concerns and perspectives of the individual and is wholly centred on the resolution of ambivalence in a particular direction of change. MI extracts the central motivation for change rather than imposing pressure, punishment or force. Thus, the interviewer prompts change talk and then responds to resistance by intending to diminish it. Miller and Rollnick, in particular advocate that MI is not a technique, rather a method of communication that evokes natural change.[167]

MI in its original format consists of multiple sessions of 30-60 minute duration. However, in a medical setting particularly in primary care, patient encounters typically range from 10-15 minutes and patients often do not see the same clinician at follow-up visits which limits the use of MI. When the duration and frequency of client contact is limited, it does not allow motivational interviewing to be used in its pure form as the depth of rapport is not present to maximise the effect. In addition, in medical and public health settings, there is often a multi-component approach to care such as the provision of educational materials and the communication of information.[163] Thus, BCC, an adaption of MI, is suitable for

brief consultations and was developed for use in healthcare settings by practitioners. Whereas MI uses open questions and reflective listening, often found in generic counselling,[168] BCC can be used to exchange information but also use listening skills to understand the patient perspective and then build motivation for change. BCC is often used as an opportunistic tool for patients rather than with clients deliberately seeking help and can be of brief duration or extended to a longer time if required, typically between 5-30 minutes.[169]

Training public health practitioners to use BCC can be problematic. Practitioners inherently learn a practitioner-centred technique since they deliver information to their patients in a prescriptive way. Thus changing to the motivational interviewing approach can be difficult. In addition the time frame for training practitioners tends to be limited.[163] However, the behaviour change counselling index (BECCI) was developed in order to evaluate the skills of practitioners using BCC and ensure that they meet the core skills required and can be used in research to evaluate practitioner competence using a BCC intervention in controlled trials.[158]

2.4 Conclusions

Improving adherence with anti-glaucoma therapy is an important objective in achieving adequate patient adherence with glaucoma medication since evidence suggests that any degree of non-adherence with glaucoma treatment could be a risk factor for the progression of glaucoma. It would appear that by increasing patient adherence there should be improvement in treatment effect and an associated reduction in overall health costs. Reduction in surgical management would be of particular benefit since any invasive eye surgery is both costly, carries a risk of failure, can lead to sight-threatening complications and is rarely a patient preference.

However, there is an ongoing challenge in the education and counselling of glaucoma patients, particularly in the area of disease awareness and the issues specific to non-adherence with topical medication. Due to the lack of quality evidence, governing bodies such as NICE are unable to provide clear evidence-based guidelines on how to improve knowledge and promote adherence. The NICE Guideline Development Group conclude by simply recommending that "patients are offered the opportunity to discuss their diagnosis, prognosis and treatment by providing relevant information in an accessible format at initial and subsequent visits… and that further research is required in order to make recommendations".[27]

The literature has revealed how an understanding of health behaviour models could be used to improve adherence. The NICE guidelines encourage the use of behaviour change interventions to encourage practitioners to help patients to adopt a healthier lifestyle.[125] Interventions should be prioritised based on the evidence of efficacy and cost-effectiveness, tailored to tackle individual attitudes, knowledge and skills associated with the target behaviour and can specify the theoretical link between the intervention and the outcome.

Previous multi-component interventions used to improve adherence to glaucoma medication have lacked grounding in approaches and models that focus on patients' beliefs, motivation and planning abilities, resulting in ineffective components. It was therefore proposed necessary to develop and trial an intervention that targets the factors elucidated in theoretical models to determine their impact on adherence. As such a BCC intervention as discussed in section

2.3.3 offered all the elements required of a reasonable and cost-effective intervention and would influence the body of work undertaken to achieve a successful intervention which is described in Chapter 3.

Understanding the methodological principles of measuring adherence also needed further development, the literature reviewed revealing where past research studies had failed. A discreet and effective way of measuring adherence and impact of an intervention was required.

Self-report methodology is easy to administer and analyse and is used frequently in adherence studies. Discerning the agreement between self-report measures and an objective measure of adherence will help our understanding for the use of these methodologies. It has been well documented that the effects of monitoring individuals to assess their level of adherence will affect their level of self-reported adherence but the degree of this effect remains unknown.

Clear predictors of non-adherence or reduced adherence have not yet been established for patients prescribed topical ocular hypotensive medications. Sociodemographic variables have been investigated previously but have not been shown to be accurate enough to ensure that patients at risk can be selected without the possibility of missing at-risk individuals. In addition, the evidence suggests that different degrees of non-adherence will lead to varying degrees of glaucoma progression. With tools that measure adherence with an adequate degree of accuracy, reliability and repeatability, then high quality studies can be performed to determine interventions that can improve adherence.

Section 2. Helping Adherence with Glaucoma Therapy; the Norwich Adherence Glaucoma Study

This section presents independent research funded by the National Institute for Health Research (NIHR) under its Research for Patient Benefit (RfPB) Programme (Grant Reference Number PB-PG-1207-14119). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health. Neither the sponsor nor funding organization had any role in the design or conduct of this research.

Chief Investigator: **Professor David Broadway**

Co-applicants: **Mrs Heidi Cate, Trial Manager**

Dr D Bhattacharya, Project Advisor

Dr A Clark, Statistician

Dr R. Holland, Clinical Trialist

Dr R. Fordham, Health Economist

Heidi Cate was one of the co-applicants on the NIHR grant before becoming a PhD student. The NIHR granted permission for Heidi to use this study as an educational project for her PhD.

Heidi was integral to the planning and design of the study and was Vice-chair to David Broadway on the Steering Committee.

Heidi was trial manager for the project and was also one of the key Glaucoma Support Assistants delivering the intervention to participants.

Heidi undertook the analysis under the guidance of Allan Clark the Statistician also a co-applicant.

Publications resulting from this section:

Cate H, Bhattacharya D, Clark A, Fordham R, Holland R, Notley C and Broadway DC. Protocol for a randomised controlled trial to estimate the effects and costs of a patient centred educational intervention in glaucoma management. BMC Ophthalmol. 2012; 12: 57

Cate H, Bhattacharya D, Clark A, Fordham R, Holland R and Broadway DC. Improving adherence to glaucoma medication: a randomised controlled trial of a patient-centred intervention (The Norwich Adherence Glaucoma Study). BMC Ophthalmol. 2014; 14: 32.

Cate H, Bhattacharya D, Clark A, Fordham R, Holland R and Broadway DC. A comparison of measures used to describe adherence to glaucoma medication in a randomised controlled trial. Clin Trials. 2015 Dec;12(6):608-17. doi: 10.1177/1740774515592636. Epub 2015 Jul 16

Presentations resulting from this section:

Cate H, Bhattacharya D, Clark A, Fordham R, Holland R and Broadway DC. The extent of non-adherence in patients using travoporst eye drops for glaucoma (poster). Health Services Research and Pharmacy Practice Conference, Cork, 2012.

Cate H, Bhattacharya D, Clark A, Fordham R, Holland R and Broadway DC. Non-adherence tin glaucoma and its association with satisfaction of glaucoma and medication information (oral). The Assocation for Research in Vision and Ophthalmology, Seattle, USA, 2013.

Cate H, Broadway DC, and Bhattacharya D. User experiences of a behaviour change intervention study to improve adherence to glaucoma medication (oral). UK Society of Behavioural Medicine, Oxford, 2013.

Chapter 3. The Norwich Adherence Glaucoma Study

3.1 Introduction

As discussed in Section 1, the majority of glaucoma damage is preventable with appropriate therapy[23, 32, 45] and the mainstay of treatment involves the daily administration of topical medications to reduce IOP.[27] Non-adherence to therapeutic regimens is associated with a reduction in treatment benefit[170] resulting in additional health service costs through changes to prescribed medication requiring additional follow-up to assess efficacy, wastage of unfinished pharmaceutical supplies, or the costs of surgery that may have been unnecessary.[89] If surgical treatment is required, there is also the increased risk of associated adverse effects and the costs of managing these.

According to UK national guidance,[27] a typical care pathway involves referral to a specialist glaucoma clinic for diagnosis by standard glaucoma examination, followed by long-term monitoring, with treatment if indicated, according to risk of disease progression. Provision of information for patients, carers and family members is usually provided by the diagnosing clinician. However, previous research in a UK eye clinic found that there was unsatisfactory hospital-led education where “doctors appeared too busy clinically to have time to provide adequate education … and poor communication” which had become a barrier to good adherence with glaucoma medication.[42]

The aim of the Norwich Adherence Glaucoma Study (NAGS) was to determine whether an intervention designed to both target beliefs and provide tailored education using a similar approach to Norell *et al.*[97] described in Section 1 could be beneficial in improving adherence with topical therapy. There is little evidence to suggest that adherence interventions can consistently improve adherence with medication within the resources available in clinical settings. Interventions are generally led by research teams which cannot easily be translated into routine clinical practice.[56] Thus, the NAGS study was also specifically designed to be led by specialist nurses and technicians working within the local hospital to provide a more realistic consideration of use of the intervention at a local level.

3.2 Intervention development

A successful behaviour change intervention should be underpinned by relevant evidence and theory identified in the early stages of development.[171] Previous qualitative work undertaken by the researcher and the wider research team led to the creation of the Glaucoma Medication Adherence Model (GMAM), [42] which is Illustrated in Figure 3.1. The GMAM elicits the barriers that prevent adherence with eye drop therapy, identifying positive and negative influences and provides the evidence base for development of the intervention. Because the GMAM was drawn from data collected from participants attending the Norfolk and Norwich University Hospital (NNUH) (the same patient population whom the intervention was being developed) we were confident that the identified factors that affect adherence were relevant to our target study population.

There is evidence to suggest that delivery of an intervention should be early in the patients trajectory of care.[92] Specifically, at least two studies have reported that patients need support and education when first placed on treatment,[42, 172] a theory mirrored by the GMAM; initial education about glaucoma and the advantages of using eye drops to prevent progression of glaucoma is likely to encourage use of eye drops from the outset of diagnosis. Therefore, paramount to the design of the intervention was the feasibility of delivering the intervention at the point of treatment initiation incorporating information provision as one of the main goals.

Information provision was aimed to be manifold; information about glaucoma/OH, treatment/medication and drop taking techniques. Information provided to patients about their glaucoma/OH was guided by current literature and patient information leaflets, and expert opinion from a glaucoma consultant at NNUH. The chronic, asymptomatic and slowly progressive nature of glaucoma must be communicated to patients so they understand the need for long-term follow-up to establish a maintained therapeutic regimen. Gaining an appreciation of how treatment efficacy is obtained is also problematic for patients using anti-hypertensive therapy since the benefits of persisting with the prescribed medication cannot be perceived until IOP is measured at each clinic consultation. Research has shown that the requirement for information about medication to ensure that medicines are taken appropriately varies widely amongst individuals. Thus, the quality of the information given to patients needs to be measured in relation to the extent in

which an individuals perceived needs for information have been met.[173, 174] To that end, SIMS offers a valid and reliable method of assessing patient satisfaction with medication information[175] by way of a questionnaire comprising of 17 items derived from published recommendations of the Association of the British Pharmaceutical Industry to enable safe self-management of medication.[176] Thus, the SIMS scale was used to guide the selection of information provided to patients about their travoprost eye drops. For example, 'how does your medication work?', and 'can you drink alcohol whilst using your medication?' appear on the SIMS scale and therefore such information was included in the intervention.

When basic information about glaucoma and treatment have been imparted, the GMAM indicates that patients will become motivated to use their eye drops but will require information about techniques to help administer eye drops to promote confidence in their use. Those patients who lack confidence in eye drop application and efficacy may cease to be adherent. Thus, providing information about good and safe application techniques was also paramount to the information provision part of the intervention.

The next barrier highlighted by the GMAM was the problems patients have with remembering to use their medication. Whist patients can be aided by good routine and memory aids, it is important to remember that adherence is easily disrupted by broken routines, busy periods and complex dosing regimens. Equally, there may be patients who are extremely motivated to use their eye drops, but for practical reasons beyond their control cannot become or remain adherent; examples such as poor dexterity prohibiting correct use of eye drops, poor memory which cannot be aided by daily dosing boxes, poor mobility which prevents collection of medication from the pharmacy or residing in a rural location to name but a few. Of course, personal states do not remain static and any sudden or unforeseen change in social or medical circumstances can also bring about practical barriers to using medication. Accordingly, motivating patients' use of eye drops and assessing ambivalence to maintaining use of drops is important for the long-term attainability of adherent behaviour. Consequently, building self-efficacy[136] is key to obtaining ongoing motivation and the skills necessary to overcome barriers which arise to the use of eye drops. Whilst information provision was an important aspect of the intervention, using a combination of teaching skills to brainstorm solutions to perceived barriers and exploration of

resistance to change and motivation was also necessary. A Motivational Interviewing approach, as discussed in Section 1, Chapter 2.3.3 had the essential elements required for this intervention.

As the GMAM concludes its 6-item chain of potential barriers, long-term adherence requires continuous feedback and education from clinicians to maintain motivation to use eye drops. Furthermore, the model advises that individuals experience a range of difficulties in managing their medications and each patient has a unique profile of needs. As such, a standardised intervention may not accommodate for these variances and the design of the intervention must be responsive to the needs of the individual[175] and address the unique challenges that adherence with glaucoma medication requires using a tailored, patient centred approach.[82] An intervention that could be used within the existing hospital healthcare setting to successfully overcome ambivalence to use of glaucoma medication, provide education about glaucoma and use of eye drops was felt to be a reasonable foundation from which a tailored intervention to improve adherence to glaucoma medication could be developed. A Behaviour Change Counselling (BCC) intervention was ultimately chosen as this offered the flexibility of use as a 'brief intervention' and could be developed to enable the healthcare providers to support medication adherence in a patient-centred way whilst also incorporating practical assistance such as teaching eye drop installation technique. In order to standardise the delivery of the information, the 'Behaviour Change Counselling Template' demonstrated in Figure 3.2 was used as the main structure of the BCC intervention.

At the time of designing this intervention for the NAGS study, the COM-B[142] discussed in Section 1, Chapter 2.2, had not been described as a new tool for designing interventions involving behaviour change and there was limited previous high quality research in medication adherence on which to build our novel intervention.

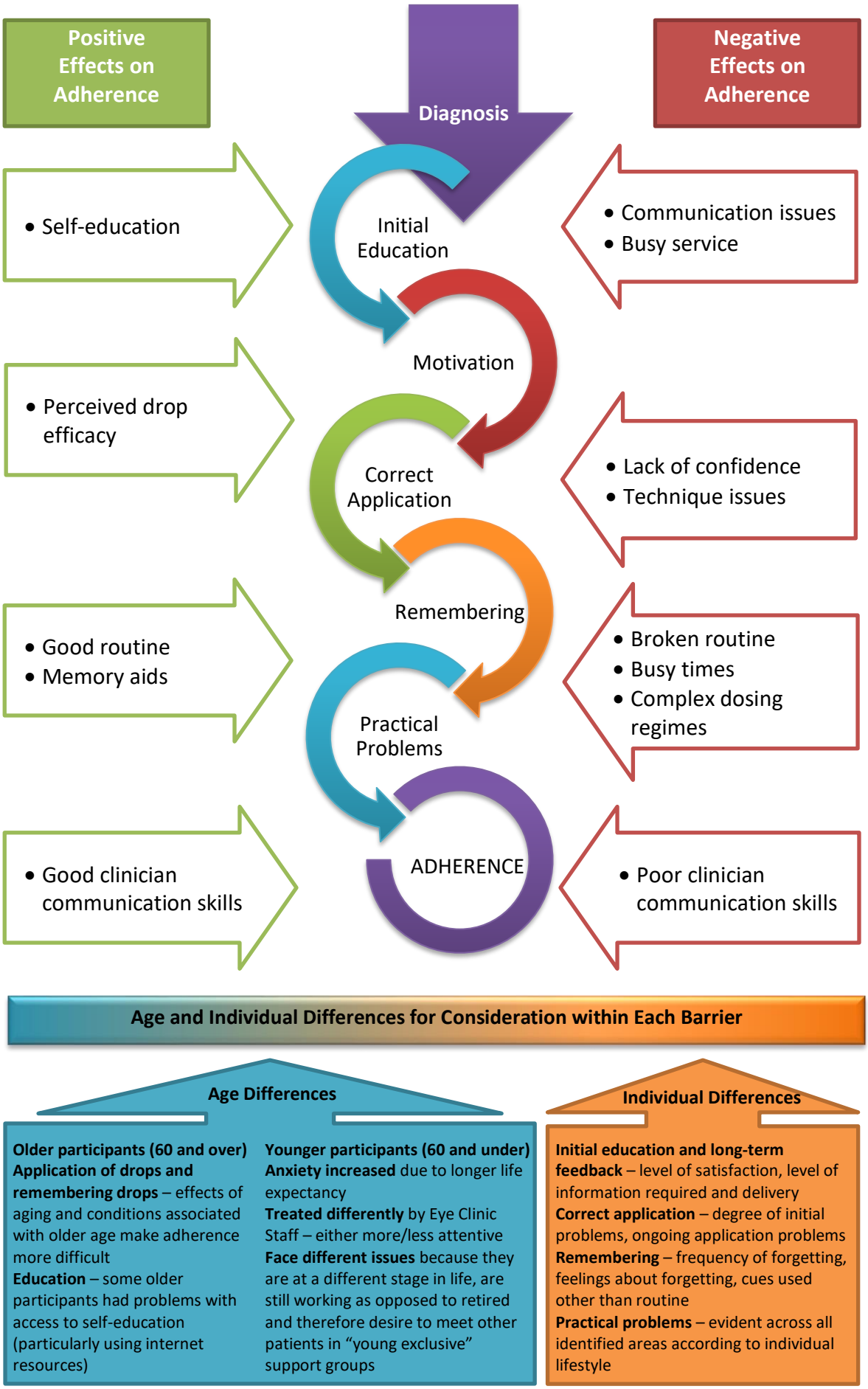


Figure 3.1 The Glaucoma Medication Adherence Model

One criticism of the Norell *et al*[97] work using a 'one to one' tailored program to provide education was the short follow-up time of 20 days, which meant there was no estimate of sustainability of intervention effect and no estimate of intervention cost. The design of the NAGs intervention needed to address these issues with an appropriate follow-up period to establish the longevity of any intervention effect on adherence and health economic analyses. The sample of participants was also not restricted to those who were known to be non-adherent as other studies have done, because there is no widely accepted level at which non-adherence is deemed unsafe, and adherence behaviour is not a stable phenomenon and known to decline over time.[177]

3.2.1 Evaluation of the Behaviour Change Counselling intervention

Measurement of intervention fidelity is required to ensure the reliability and validity of the behavioural programme.[178] There is often no evidence of any skill assessment undertaken for the practitioners delivering the intervention or measures of patient-centeredness[158] or the extent to which a person delivers the essential content.

There are a multitude of adaptations to the original form of MI used in RCTs. Miller and Rollnick[179] consider that as long as the intervention is primarily implementing the principles of MI rather than the principles of another approach, such as Cognitive Behavioural Therapy, and is delivered on a one-to-one and face-to-face basis, it is considered to be an 'Adaption of Motivational Interviewing' (AMI). Thus, when there is uncertainty about how MI has been adapted, there is a need to ensure that the intervention is fully described and that practitioner skills are assessed and measured to ensure patient-centeredness is achieved.

There have been a number of instruments used to measure patient-centeredness in its pure form as reviewed by Hudon *et al* in 2011 using the conceptual framework of patient-centred care;[155] however, these are not specific to health behaviour change techniques. The Motivational Interviewing Skill Code (MISC) and Behavioural Change Counselling Index (BECCI) are specific measures of motivational interviewing techniques used for behaviour change counselling. MISC applies three phases of analysis be means of direct observation of a recorded clinical encounter. The first phase uses a Likert-type scale in order to

observe the encounter in terms of the interaction between the client and therapist. In the second phase, specific behaviours of the client and therapist are coded and counted and the third phase calculates the talk time of the client and therapist. The scores from each section are computed which produces an overall summary score which can be compared to the benchmarks which depict proficiency in MI.[180] Lane *et al*. suggest that that although MISC provides counts of actual behaviours, it does not provide an assessment of the overall strength of the behaviour.[158] Even though the MISC has been revised in 2008 to an altogether more streamlined process which no longer includes the third part of timing the talk time,[181] there are a number of subsections that are not essential for users of BCC to assess, such as reflective listening strategy.[158]

Choosing the most appropriate health professional to deliver a behaviour change intervention for patients newly diagnosed with glaucoma within the secondary care setting had to be considered carefully. Whilst clinicians may appear a natural choice as they are well placed to deliver the intervention as an extension to the patient consultation, staffing costs are expensive in comparison to nursing and health care assistants, and their time is limited in clinical practice as well as in training. Training health practitioners to use BCC can be problematic since practitioners inherently learn a practitioner-centred technique as they deliver information to their patients in a prescriptive way. Thus, changing to the motivational interviewing approach can be difficult. In addition the time frame for training practitioners tends to be limited.[163] For this reason, pharmacists, nursing staff, and health care assistants are potentially better assigned to deliver patient-centred services as part of their existing roles and time given to learning MI techniques. BECCI was developed in order to evaluate the skills and competence of practitioners using BCC in particular.[158]

BECCI focuses on the practitioner consulting behaviour rather than the response of the patient. A one-phase analysis is employed using Likert-type scales to indicate either frequency or strength of practitioner behaviour on 11 themes.[158] An overall BECCI score can be calculated using the mean of all the scored items. Thus, the BECCI may be an appropriate method evaluating practitioner skills and patient-centeredness within a study.

A) Agenda and time setting

B) Establish patient's initial thoughts / attitude towards the prescribed medication

C) Establish patient's baseline knowledge and therefore information needs – confirm type of glaucoma

D) Agree agenda incorporating patient needs; address all of the information outlined in discussion topics below but tailored to patient knowledge level as reported at stage C.

Discussion topics:

What is glaucoma?

What causes glaucoma?

What creates the pressure?

How will this affect me?

Treatment with eye drops

Drop Application Techniques

E) Establish patient's thoughts / attitude towards the prescribed medication. Tailor further information and discuss:

Side effects

F) Determine patient's optimism for treatment and address any ambivalence.

G) Discuss patient's self-efficacy and develop strategies to enhance self. Tailor further information and discuss:

Drop taking regimen

H) Discuss patient's outcome expectancy, if ambivalence identified, return to decisional balance and then key question.

Figure 3.2 Behaviour Change Counselling Template

3.3 Method

3.3.1 Study aim and objectives

The purpose of the study was to determine whether additional education and advice about glaucoma using a BCC intervention, improved adherence with topical anti-glaucoma therapy when compared to standard care. The duration of the study was 8 months in order to assess the longevity of the intervention effect on adherence. The objectives were to:

- Determine the effect of the intervention on adherence compared to standard care alone
- Establish the pattern of adherence over an 8-month period to determine if there is a longevity of effect on adherence
- Report any predictors of non-adherence based upon social, demographic, medical and family history information
- Establish if IOP could be used as a surrogate marker of adherence
- Examine different methods of adherence measurement
- Describe user experiences of the educational intervention and self perception of adherence in order to gain a better understanding of the components of the intervention that might improve adherence.

3.3.2 Study design

The study was a randomised controlled intervention study. A flow-chart of the study design is shown in Figure 3.3. The duration of the study was eight months in order to cover a longer period of follow-up than previously reported glaucoma intervention studies; standard practice care at NNUH at the time of the study conception was to assess response to treatment at two months and then 6-months post treatment initiation. Follow-up study visits were planned to coincide with the routine treatment plans. The study received ethical approval from the Norfolk Research Ethics Committee, (appendix1) and research governance approvals from the East Norfolk and Waveney Research Governance Committee (appendix 2). The study was registered on a public database**;** Current Controlled Trials, ISRCTN89683704.

3.3.2.1 Setting, recruitment and treatment allocation

The study was conducted in the Glaucoma Clinic at NNUH. Patients newly diagnosed, or previously untreated, with either glaucoma or OH requiring treatment with travoprost, (using established standard criteria as documented in the European Glaucoma Society Guidelines),[31] were invited to participate. Patients were 18 years of age or older, able to give informed consent, and had adequate ability to read and understand English. Patients requiring care-home staff or home-help (not provided by a co-habiting partner or family member) to apply eye drops were excluded. Patients were made aware that they would be randomised to either the standard care or the intervention group, and that their adherence to travoprost would be monitored for the duration of the study.

Potential participants were identified at the time of clinic consultation by their clinician and referred to a research assistant to explain the nature of the research and obtain consent following standard consent procedures.

Eligible patients were randomised using an automated telephone randomisation system to ensure allocation concealment. Randomisation was stratified by diagnosis (either glaucoma, or OH / glaucoma suspect) and experience of the glaucoma service (new or follow-up patient advised to use medication). Stratification controlled for possible variances, since previous studies have shown that patients with suspected glaucoma or OH without the presence of manifest glaucomatous disease are less adherent than those with evidence of manifest glaucoma.[80, 81] Also, patients previously reviewed as out-patients but not started on anti-glaucoma treatment, had an increased opportunity to ask questions or self-educate before therapy initiation and becoming eligible to participate in the study. Patients declining study participation, following consent, had demographic information collected or determined (age, gender and index of multiple deprivation, (IMD)).

3.3.2.2 The control group

Patients attended a specialist glaucoma clinic for treatment initiation. Initiation included undergoing appropriate tests and a consultation of approximately 10

minutes with a specialist glaucoma clinician. The consultation consisted of the following:

- A brief explanation about glaucoma or OH
- A summary of the proposed future management
- Guidance regarding drop administration
- The relevance of glaucoma with respect to driving and future vision

The Control group received what was accepted as 'standard care' for the NNUH ophthalmic glaucoma service including a patient information leaflet providing information about glaucoma.

3.3.2.3 The intervention group

Following the standard care consultation at NNUH, the intervention group received a BCC intervention provided by the Glaucoma Support Assistants (GSAs). GSAs are described in Chapter 3.3.3. A telephone advice-line for patients and their carers to respond to glaucoma related queries was also provided.

3.3.2.4 The Travalert® Dosing Aid (TDA)

The TDA (Alcon Laboratories, Inc., Forth Worth, TX, USA) electronically stores the time, date and number of drops administered. The TDA can only be used in conjunction with Travatan® (travoprost) and Duotrav® (travoprost/timolol combination) eye drops due to aperture size restricting other shaped bottles from fitting the aid. Three studies using the TDA have reported that it accurately records drop administration.[93, 99, 100] An additional feature of the TDA is the alarm and digital visual reminder window which informs participants when it is time to use their eye drops. For the purposes of the study, the alarm feature was disabled during the study period and the visual reminder was covered over by a sticker to prevent participants using this visual cue as a reminder to use their eye drops. Participants were given a demonstration of the TDA and provided with written operating instructions (appendix 3).[105] Participants were asked to use the TDA to admister their travoprost eye drops for the duration of the study.

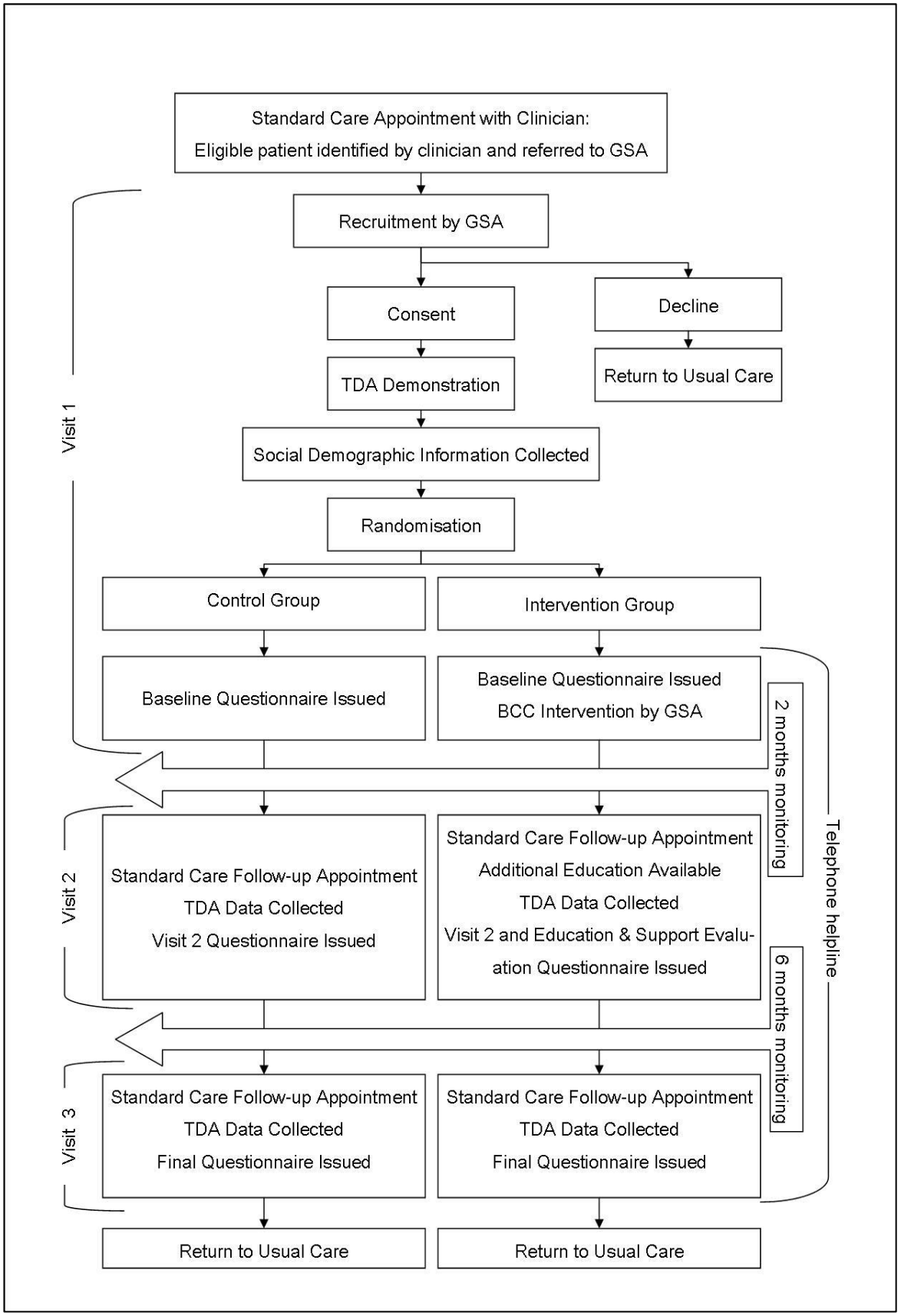


Figure 3.3. Illustration of the participant study pathway

3.3.2.5 Intraocular pressure (IOP) measurements

All patients attending the Eye Department at NNUH have their IOP measured by their clinician using Goldmann applanation tonometry at each visit.[27] The IOP value for each eye at each visit was obtained from the participants' medical records. Clinicians were masked to patients participating in the study, and participants were encouraged not to report their participation to clinicians involved with their care.

3.3.2.6 Social demographics and medical history

A researcher lead questionnaire was used to collect patient demographics; age, IMD, type of housing, educational qualifications, family history of glaucoma (appendix 4). Co-morbidity was classified using the Charlson Co-morbidity Index[182] from information available in participant medical records to characterise demographics.

3.3.2.7 Questionnaires

A participant self-administered questionnaire was completed after the baseline visit/visit 1 (appendix 5), Visit 2 and Final Visit (appendix 6) and returned by post to capture the following information:

Self-reported adherence: Two self-report adherence measures were utilised, (i) a modified MMAS[124] and (ii) the Frequency of Missed Dose (FMD). The MMAS is a four-item measure described in Chapter 1.2.7.2 (see appendix 8) that was modified in order that the final question incorporated multiple response options from which participants could report any other reasons for non-adherence using a 7-item list of suggested reasons; forgot ran out of drops, side effects of drops, difficult to use drops, change in routine, fell asleep, felt unwell and an 'other' option (as shown in appendix 6, questions 3-6). The FMD is a quantitative measure of eye drop doses missed each month (see appendix 8).

Satisfaction with information received: SIMS[174] was used to quantify satisfaction with information received about travoprost (appendix 5, question 1 and appendix 6, question 7). Three different analyses can be carried out from SIMS; medicine

information profiles, total satisfaction rating and sub-scale scores of action and usage of medications and potential problems of medication. A previous study carried out by Gellaitry *et al.,* used SIMS methodology to profile patient satisfaction with information received about HAART (Highly Active Anti-Retroviral Therapy) among patients attending HIV clinics in Brighton.[176] The SIMS showed good internal reliability with a Cronbach α- coefficient of 0.92. Gelliatry *et al.* were able to conclude that individuals faced with treatment decisions varied widely in their perception of information they had received. Furthermore, those individuals who acted positively to the offer of HAART were more satisfied with the information they had received about treatment than those who declined it.[176]

The SIMS tool has been evaluated previously in a variety of clinical settings, both for ease of use, internal consistency and test-retest reliability.[174] Although not validated for use in glaucoma patients, SIMS has been sampled in various disease and treatment characteristic groups including other asymptomatic conditions such as early diabetes or hypertension.

Potential predictors of adherence:

- Use of medications (appendix 5, question 2 and appendix 6, question 9)
- Problems with use of eye drops (appendix 6, question 1)
- Previous experience of using eye drops (appendix 5, question 4)
- If drops are applied by a carer (appendix 5, question 3 and appendix 6, question 10)
- satisfaction with information about glaucoma, effects on vision and driving (appendix 5, question 5 and appendix 6, question 11)
- more information required (appendix 5, question 6 and appendix 6, question12)
- additional information sought about glaucoma (appendix 6, question 8)

In addition, at Visit 2, the intervention group were asked to rate the acceptability of the education and support service provided (appendix 7). A 5-point Likert scale (strongly agree, agree, neutral, disagree, strongly disagree) was used to rate their satisfaction with the information provided by the GSAs. Eight questions were given, 4 relating to the helpfulness of the information given about glaucoma, how to apply eye drops as part of a daily routine and information provided by the

telephone helpline service, and 4 questions relating to patient reported outcomes of improvement to understanding of glaucoma, better use of drops as part of a routine and if they would recommend the service to other patients with glaucoma.

3.3.2.8 Resources Log

Time spent with each participant by NAGs research staff in the out-patient department or on the telephone helpline was recorded.

3.3.2.9 Repeat prescription refills

In the UK, patient repeat prescription history is maintained by their General Practitioner (GP). In order to retrieve this information, with participant consent, the researcher wrote to each individual participant's GP to ask for their repeat prescribing records specific for their glaucoma/OH condition including, drug name, date of issue, and prescribed days of treatment. Payment was made for this administrative task via an existing research payment contract held by the Primary Care Research Network and participating GPs. From these data a measure of expected repeat prescription orders and actual repeat prescription orders were used to calculate the Medication Possession Ratio (MPR) as displayed in Figure 3.4. The MPR indicates over or under usage of eye drop refills and persistence with use of medication.

3.3.3 Glaucoma Support Assistants and training

Five GSA roles were created specifically for the purpose of this study. Prior to recruitment, the GSAs had worked within within NNUH eye department in standard NHS nursing and technician roles (Band 4 glaucoma research technician, Band 5 ophthalmic nurse, Band 6 glaucoma nurse specialist (x2) and Band 6 glaucoma research co-ordinator), all with experience of working with glaucoma patients. Five GSAs were utilised to ensure the results of the study were attributable to the intervention method rather than the specific context of any one individual delivering the intervention.

The GSAs participated in BCC training and quality assurance sessions. Training Session 1 was a 4 hour session which introduced to the causes of non-adherence and predictors of behaviour and MI theory. Session 2 was a 2 hour session and was role-play facilitated by a qualified MI coach. Individualised guidance was provided in response to any reported or observed problems. The GSAs practiced MI and BCC skills within their usual clinical duties for the following 2 months.

The GSAs also underwent a training session with the Glaucoma Specialist Consultant to ensure competency in the knowledge and skills required to deliver education to patients about glaucoma and related issues.

The GSAs had the freedom to conduct the counselling session in their own BCC style. Education was tailored to individual patients, but followed the BCC template (Figure 3.2).

3.3.3.1 Fidelity testing

Six months after completion of training, the GSAs underwent a formal assessment of their BCC skills and information given to participants to fulfil the BCC template and assess whether the consultation style meet expectations. The GSAs were each videoed with the same actress who was playing the role of a patient newly diagnosed with glaucoma. The actress' 'brief' was prepared by the Glaucoma Specialist Consultant and the MI coach.

The BECCI instrument is designed for trainers to score practitioners' use of Behaviour Change Counselling in consultations either in real or simulated situations. Each assessor used the BECCI scoring sheet to score each item under the four domains as detailed in Table 3.1. Three assessors were used and their scores averaged as detailed in Table 3.1; a low score indicating that the action was not carried out up to a higher score indicating it was carried out to a great extent. The videoed role-play sessions were independently reviewed according to the BECCI[158] criteria by the MI coach and a further 2 MI expert's independent from the research study as described in Chapter 3.2.1. Table 3.1 summarises the BECCI scores by the three assessors. The mean average BECCI score reveals that the GSAs used BCC to some extent during the simulated session. Feedback from the MI coach found that 3 GSAs did not clearly discuss with the patient that

there would be no tangible immediate effect from using the eye drops. Two GSAs did not discuss the patient's expectations of adherence to treatment and for each of the following criteria, one GSA did not clearly address the issue during the role-play: eye drop application technique, patient's thoughts/attitudes regarding the prescribed medication, patient's optimism and perceived self-efficacy regarding adherence to the prescribed travoprost. Individualised, written feedback was provided to each of the GSAs.

Table 3.1 Average BECCI scores of role play assessment; 0 (not at all) to 4 (a great extent)

BECCI criterion	GSA 1	GSA 2	GSA 3	GSA 4	GSA 5
Domain 1. Agenda setting and permission seeking					
1. The practitioner invites the patient to talk about behaviour change	1.5	2.0	2.0	2.1	1.7
2. The practitioner demonstrates sensitivity to talking about other issues	2.3	2.0	2.7	3.0	2.0
Domain 2. The why and how of change in behaviour					
3. Practitioner encourages patient to talk about current behaviour or status quo	2.3	2.3	2.7	2.7	3.0
4. Practitioner encourages patient to talk about behaviour change	2.0	2.0	2.3	2.7	2.7
5. Practitioner asks questions to elicit how patient thinks and feels about the topic	2.0	2.3	3.0	3.0	3.0
6. Practitioner uses empathic listening statements when patient talks about the topic	2.0	3.0	2.7	3.0	2.7
7. Practitioner uses summaries to bring together what the patient says about the topic	2.3	1.0	0.7	2.3	2.0
Domain 3. The whole consultation					
8. Practitioner acknowledges challenges about behaviour change that the patient faces	1.3	2.3	2.7	2.0	1.7
9. When practitioner provides information, it is sensitive to patient concerns and understanding	2.7	2.7	3.0	3.0	2.3
10. Practitioner actively conveys respect for patient choice about behaviour change	1.3	2.3	2.3	1.7	1.7
Domain 4. Talk about targets					
11. Practitioner and patient exchange ideas about how the patient could change current behaviour	2.3	2.0	2.0	2.3	2.0
Practitioner BECCI score					
Mean score excluding domain 1	2.1	2.2	2.4	2.6	2.3

3.3.4 Rationale for sample size calculations

Glaucoma intervention studies that had used medication monitors to observe adherence found a range of adherence rates; a mean of 76 ± 24% of prescribed pilocarpine doses when dosing four times a day,[122] and 72 ± 19% when dosing twice daily and 62 ± 16% when dosing three times daily with Brimonidine.[183] However, in these studies, adherence behaviour was observed for a shorter duration using a more complicated dosing regimen than the proposed study. The absence of an accepted adherence rate with once daily glaucoma medication and limited robust research[55] to indicate the likely effect of an intervention on adherence to glaucoma medication at the time of the study design led to estimates being derived from general medicine. Adherence to treatment for hypertension suggested that 40% failed to take a consistent therapeutic dose of medication and use of electronic monitoring of adherence found adherence using a MEMS device was 58%.[184] Therefore, without a like study for comparison, a 20% increase in adherence to glaucoma medication was estimated for sample size power calculations. Assuming an adherence rate of 60% in the control group and 80% in the intervention group, having 81 people in each group was calculated to provide 80% power to detect a difference using a Chi-Squared test, at a 5% level of significance. Based on an estimated, approximate 20% drop-out rate, the aim was to recruit 200 participants.

3.3.5 Primary outcome measure

Adherence was determined using the number of adherent doses recorded by the TDA, divided by the expected number of doses for the monitoring period using the adjusted adherence calculator.[105] The adherence calculation and the rules for determining an adherent dose are shown in Figure 3.4. Two adherence scores were calculated; the average of the total 8 month study duration and the average of the final 2 months of follow-up. The average adherence score for the final 2 months of follow-up was also given as a dichotomous classification based on 'adherent' if the average number of TDA recorded doses was ≥80% of expected and 'non-adherent' if <80%.

$$Adherence\ \% = \left(\frac{No.of\ adherent\ doses *}{Expected\ no.doses\ for\ monitoring\ period}\right) \times 100$$

* Adherent dose = >one recorded application during the expected dosing time [#]

[#] Expected dosing time = calculated mean average dosing time for duration of study +/- 2 hours (occuring between 17:00 and 04:59 hours)

$$MPRa = \frac{Sum\ of\ \text{days supply}\ of\ all\ glaucoma\ medications\ during\ observation\ period^{\#}}{Sum\ of\ \text{days of medication required}\ during\ observation\ period *}$$

Mean no. of days/2.5 ml size bottle (ou dosing)= 51.5 (Fiscilla et al. 2003)
*Observation period: days from index prescription until end of study, or change of treatment

$$MPRb = \frac{Absolute\ sum\ of\ days +/- a\ 28\ day\ prescription\ refill\ period}{Sum\ of\ \text{days of medication required}\ during\ observation\ period *}$$

*Observation period: days from index prescription until end of study (change of treatment inclusive)

Figure 3.4 Calculations used for outcome measures; Adherence percentage and Medication Possession Ratios (a and b)

3.3.6 Secondary outcome measures

Outcome measures were collected at three different time points; Baseline, Visit 2 and Final Visit:

- The IOP measurement for each treated eye was recorded from the hospital records and the mean of both eyes calculated for each time point. Two values were calculated for two time periods; percentage reduction in IOP between baseline to Visit 2, and from Baseline to Final Visit, and the absolute reduction in IOP between Baseline to Visit 2 and Baseline to Final Visit.
- Repeat prescription information was used to calculate MPR; MPRa used the average travoprost drop count[115, 185] and MPRb used the UK general prescribing instruction to renew eye drop prescriptions every 28 days (Figure 3.4). An MPR less than 0 indicated not enough medication to meet the required dosing regimen.
- Self-reported adherence using the MMAS score was calculated for each participant. Participants that answered 'yes' to a question score 1, thus

scores ranged from 0-4. Participants who scored 0/1 were dichotomised to the adherent group, participants scoring 2-4 were dichotomised to the non-adherent group. Participants reporting missing their medication more than once a month on the FMD scale were dichotomised as non-adherent.

- Self- reported reasons given for non-adherence using a 7-item list were quantified for each participant.
- SIMS scores ranged from 0 to 17, 0 indicating dissatisfication and 17, complete satisfaction. An overall median SIMS score was calculated for each participant and a median score for the two separate domains 'action and usage of travoprost' and 'potential problems of travoprost'.
- Demographic variables were quantified either by classification codes or scoring scales for number of prescribed medications (which included anything listed in the hospital records), IMD, and the Charlson score.
- TDA data were used to produce a chronology plot to diplay the days (24-hours) between each dosing event.
- Intervention satisfaction scores were reported for using the Likert scale (strongly agree, agree, neutral, disagree, strongly disagree) to rate their satisfaction with the information provided by the GSAs.

3.3.7 Statistical analysis

Initially, descriptive statistics were used to characterise the demographics of the study population. All analysis used the Statistical Package for Social Sciences (SPSS) version 21.

Histograms were visually checked to review the distribution of the data before deciding on the appropriate statistical analysis method and all analyses were based on an intention-to-treat principle.

3.3.7.1 Primary objective

The mean adherence measured by the TDA were calculated for the control and intervention groups. The sample characteristics of the data were reviewed to understand the spread, but with an expected sample greater than 50 participants in each group parametric tests still perform well with non-normal data, but medians were calculated to better define the measure of central tendency if required.

Missing data were imputed using a multivariate normal imputation model after suitable transformations, to ensure that the variables were normally distributed. A total of 10 imputed datasets were created, each analysed separately and the results averaged using Rubin's equations. A sensitivity analysis was carried out to assess the effects of missing data. A comparison of the observed and imputed primary outcome data were compared using t-tests and Chi-squared for dichotomised data. If significant differences were present then imputed data would be used for the remainder of the planned analysis.

The primary analysis compared the mean adherence for the total 8-month period for the control group with the intervention group using a t-test. The t-test was repeated using the combined month 7 and 8 post-randomisation percentage adherence. The proportion of individuals with ≥80% were compared between groups using the Chi-squared test.

A repeated measures analysis-of-variance was carried out (with time measured in months) to assess for any difference between intervention and control groups over time.

Because the TDA adherence data were analysed using three different methods a comparison of these measures was undertaken to assess any significant differences between them using t-tests for mean adherence and a Chi-squared test for dichotomised adherence data.

3.3.7.2 Secondary objectives

Intraocular pressure: Mean IOP measure was reported for each time point, difference in IOP and percentage difference in IOP for the control and intervention groups. The difference between the control and intervention groups was compared using t-tests as the sample was greater than 50 in each group.

Mean percentage adherence measured by the TDA at month 2 and was correlated with absolute IOP reduction and percentage reduction between Baseline and Visit 2 for the control and intervention groups using a Spearman's rho to establish if there were any initial positive correlations in IOP control and use of medication.

The month 7 and 8 combined mean percentage adherence measured by the TDA and was correlated with absolute IOP reduction and percentage reduction between Baseline and the Final Visit for the control and intervention groups using a Spearman's rho to establish if there were any positive correlations in IOP control and use of medication for the duration of the observation period. Spearman's rho was chosen as the most appropriate test to use with a non-linear relationship and non-parametric data.

Medication possession ratio: The mean MPR was reported for the control and intervention groups using two measures, 28-day MPR and bottle contents MPR as previously described. The MPR was compared between the control and intervention group using a t-test as there were more than 50 in the sample.

The measure of variability was reported for both the control and intervention groups using the median and interquartile range (IQR). The sum of the MPR for the control and intervention group were also calculated to compare differences in overall medication possession between the two groups.

The month 7 and 8 combined mean percentage adherence measured by the TDA was correlated with the MPR for the total period of the study for both the control and intervention groups using a Spearman's rho to establish if there was a positive correlation between MPR and TDA measured adherence. Spearman's rho was chosen as the most appropriate test to use with a non-linear relationship and non-parametric data.

Satisfaction with Information about travoprost: The mean SIMS scores were reported for control and intervention groups and differences between the two groups compared using a Mann-Whitney U test to establish any differences between the two groups. A Mann-Whitney U test was chosen as the data were non-parametric, with ordinal data for the dependent variable and an independent variable was two independent groups using categorical data.

The month 7 and 8 combined mean percentage adherence measured by the TDA and was correlated with the mean SIMS scores for both the control and intervention groups using a Spearman's rho to establish if there was a positive correlation between SIMS and adherence. The correlation was carried out with data from each time point to establish if there were any differences during the

course of the study. Spearman's rho was chosen as the most appropriate to test to use with a non-linear relationship and non-parametric data.

The specific items that constitute SIMS were reported for both the control and intervention groups and mean scores for items that comprised 'action and usage' and 'potential problems of travoprost' to establish differences in satisfaction with medication information between the two groups.

Self-reported adherence: MMAS and FMD scores were used to report the percentage of participants that were adherent in the control and intervention groups. The differences between the control and intervention groups were compared using a t-test as there were more than 50 in each sample group.

Agreement between dichotomised mean percentage adherence measured by the TDA and MMAS and FMD for both the control and intervention using a Cohen's Kappa test at Visit 2 and Final Visit was used to establish if there was a positive association between self-reported and TDA measured adherence. A Cohen's Kappa test was used because the variables were binary measuring the same dependent variable (adherence).

Reasons for non-adherence: Percentage of participants reporting their reasons for non-adherence using the MMAS four-item scale component and the 7-item list were reported and compared between the control and intervention groups using t-tests.

Graphical representation of adherence behaviour: The graphical representations of adherence chronological plots were used to visualise and classify patterns of adherence behaviour. The methodology and categories described by Ajit *et al*. in a 3 month study[61] were used to classify 4 patterns of adherence; (i) adherence greater than 80%, (ii) discontinuation of dosing after a short time interval, (iii) frequent drug holidays, and (iv) variable with frequent missed doses. The longevity of monitoring for NAGS compared with the Ajit et al. study required additional categories at the point of analysis.

The mean adherence measured by the TDA were reported for each classified group and compared between control and intervention groups using t-tests to establish any differences between the two groups.

Adherence predictors: A stepwise regression model was used to identify possible predictors for adherence to travoprost. For categorical variables logistic regression was used and simple linear regression for scale variables to predict the probability. An unadjusted multivariate model was constructed to identify independent predictors of adherence. Variables that were identified to be more statistically significant in the model were selected and entered into the adjusted model to establish statistical significance.

Information provision: Percentage of participants reporting satisfaction with information received about glaucoma, effects on vision and driving at Baseline, Visit 2 and the Final Visit. T-tests were used to compare responses between the control and intervention groups at each time point.

Specific unanswered questions reported by participants were classified and quantified.

Sources of additional information sought independently by participants were classified and quantified.

Problems with eye drops: reported problems were classified and quantified.

Intervention evaluation: Number and type of telephone calls made to the GSA service were categorised and quantified.

Percentage of participants reporting satisfaction with the GSA service were reported and additionally comments were described. Satisfaction with the GSA service was correlated to adherence using a Spearman's rho test.

Comparison of Glaucoma Support Assistant effects: The mean time that each GSA spent with each participant and percentage of adherent participants per GSA was reported to establish if there was 'therapist effect' in which GSAs were more effective in delivering the intervention than others. Time spent with participants compared with TDA measured adherence was analysed using a Spearman's rho to establish if length of therapy caused the intervention to be more effective.

Individuals who declined participation: The demographics (age, gender and IMD score) of the group who had declined participation were compared to the study sample using the Mann Whitney-U for age and IMD, and a Chi-square test for gender.

3.4 Results

3.4.1 Recruitment

Eligible participants were recruited from mid-November 2009 to mid-December 2010 (13 months). Research specific procedures were incorporated into participant out-patient appointments, which were commonly standardised on initiation of treatment as part of standard care at three time points; appointment when treatment initiated (Baseline), 2 months post initiation of treatment (Visit 2), and 8 months post initiation of treatment (Final Visit). The intervention was given at the baseline visit following consent and randomisation and collection of baseline demographics. Follow-up data were collected at Visit 2 and Final Visit.

3.4.2 Participants and data collection

The Consort diagram in Figure 3.5 provides details of the exclusion rate, number of patients declining participation, participant treatment allocation and data attrition rate. Whilst a significant amount of TDA data was not collected, an intention to treat analysis avoided any potential bias associated with non-random loss of participants.

3.4.3 Protocol deviations

Study follow-up visits were dependent upon patient follow-up appointments generated by the NNUH Glaucoma Outpatient Clinic service. At the time of the study standard care appointments would be scheduled for 2 and 8 months post commencement of treatment. In practice, the 2 month and 8 months follow-up visits scheduled were not always adhered to, either because there was lack of available appointments because of pressures on the Hospital Eye Service or, patients did not attend appointments, beyond the control of the Glaucoma Outpatient Clinic service. Protocol deviations arose where participants did not attend a follow-up appointment within the target window as shown in Table 3.2.

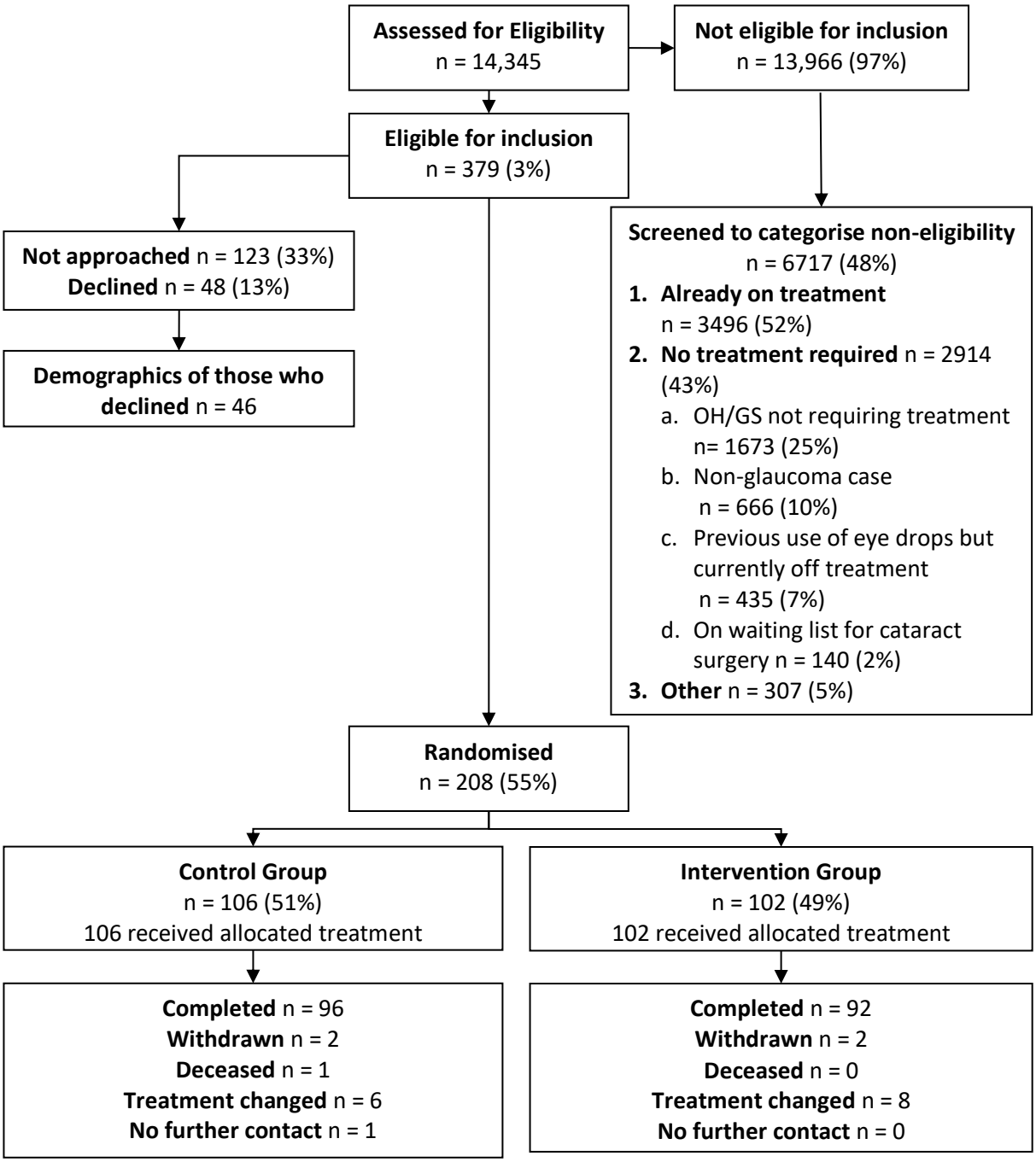


Figure 3.5 The Consolidated Standards of Reporting Trials diagram

When participant out-patient appointments occurred outside of the specified time window, the corresponding data collected from the questionnaires and TDA were at different time points compared to the rest of the cohort. Where the deviations did occur they were well balanced between the intervention and control group. The deviations were felt to have a negligible effect on the data collected from questionnaires. However, when calculating the percentage adherence rate for the final two months (months seven and eight) TDA data collected after day 252 after

baseline was ignored, thus ensuring that the final two months adherence score was always calculated from data collected between months seven - nine. Data from participants that stopped using the TDA before months seven and eight were annotated as 'missing data'. There were no protocol deviations that led to loses of recruitment or failure to deliver the intervention.

Table 3.2 Protocol deviations

	Control (range in deviation of days)	**Intervention** (range in deviation of days)
Visit 2 target window (56 days +/- 42 days)	n=4 (+10 to +43)	n=1 (+18)
Final Visit target window (224 days +/- 42 days)	n=3 (+3 to +9)	n=3 (-62 to +43)

3.4.4 Missing data

The reasons for incomplete adherence data are summarised in Table 3.3. Questionnaire data provided the most complete datasets over the 8-month period relative to data collected from health centres and the TDA. The reason for the failure of the TDA was not always possible to establish. In some cases the internal mechanics of the device appeared to have been tampered with by the participant but it was not possible to determine in which cases the device had failed due to deliberate tampering or genuine device malfunction. MPR data were missing where health centres refused to provide the prescribing data when requested.

Table 3.3 Reason for missing data compared between measures

Reason for missing data	Number of participants with missing data						
	*MMAS Questionnaire		#FMD Questionnaire		Prescribing record	~TDA	
	2 months	8 months	2 months	8 months	Total period	2 months	8 months
Questionnaire or ~TDA not returned / used / fully completed by patient	17	13	11	8	-	8	12
Data not provided by health centre	-	-	-	-	49	-	-
Device / battery failure	-	-	-	-	-	12	32
Participant withdrawn or stopped or changed treatment	1	18	1	18	24	19	48
Lost to follow-up / Deceased	2	2	2	2	2	2	2
Total Missing	**20 (10%)**	**33 (16%)**	**14 (7%)**	**28 (13%)**	**75 (36%)**	**41 (20%)**	**94 (45%)**

***MMAS (Morisky Medication Adherence Score)**

#FMD (Frequency Missed Dose)

~TDA (Travalert Dosing Aid)

The TDA data was used as the primary outcome measure, thus the data collected using this method was further categorised to ensure that the control and intervention groups were evenly matched as shown in Figure 3.6. Missing data was evenly matched in both groups, but a greater number of participants stopped using travoprost (due to either side effects and/or lack of efficacy) in the intervention group than in the control group. Consequently, the intervention group had less complete data than the control group.

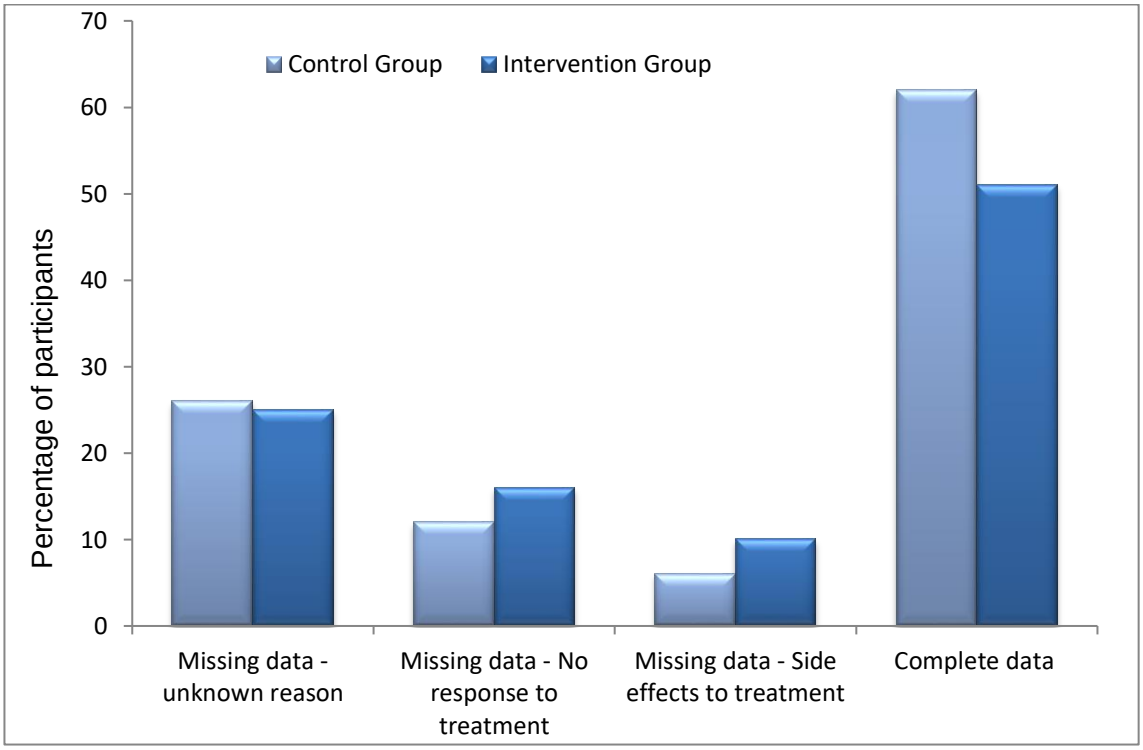


Figure 3.6 Comparison of missing TDA data for the control and intervention groups

3.4.5 Individuals who declined participation

A total of 46 patients declined to participate in the study. When age, gender, and IMD demographics were compared between those who agreed to participate and those who declined, the samples had no statistically significant differences; age (Mann Whitney U, p=0.257), gender (Chi-square p=0.253) and IMD (Mann Whitney U, p= 0.379).

3.4.6 Baseline data

The demographic characteristics of the sample population are summarised in Table 3.4 and were evenly balanced between groups. The participants were predominantly of white British ethnicity and, at the time of recruitment, largely had no family history of glaucoma and had been diagnosed with POAG as opposed to having OH or being a glaucoma suspect. The cohort was evenly matched as to whether they were new patients or had been seen previously in the glaucoma clinic.

Table 3.4 Population characteristics

	Control		Intervention	
	N	**%**	**N**	**%**
Gender				
Male	58	54.7	47	46.1
Female	48	45.3	55	53.9
Ethnicity				
White	104	98.1	102	100
Other	2	1.9	0	0
Housing Tenure				
Home owner	92	86.8	82	80.4
Renter (council)	6	5.7	11	10.8
Renter (private)	5	4.7	4	3.9
Other	3	2.8	5	4.9
Marital Status				
Married/partner	75	70.8	73	71.6
Divorced/separated	5	4.7	7	6.9
Widowed	19	17.9	17	16.7
Single	7	6.6	5	4.9
Highest Qualification				
GCSE	44	41.5	45	44.1
A-levels	4	3.8	5	4.9
Degree	11	10.4	8	7.8
Post-graduate	8	7.5	2	2
Other	37	34.9	42	41.2
Parents with glaucoma				
No	79	74.5	70	68.6
Yes	22	20.08	24	23.5
Not known/no contact	5	4.7	8	7.8
Siblings with glaucoma				
No	93	87.7	85	83.3
Yes	8	7.5	9	8.8
Not known/no contact	5	4.7	8	7.8
Children with glaucoma				
No	102	96.2	95	93.1
Yes	2	1.9	0	0
Not known/no contact	2	1.9	7	6.9
Diagnosis and new/follow-up care				
POAG/NTG new patient	33	31.1	32	31.4
POAG/NTG follow-up patient	40	37.7	37	36.3
GS/OH new patient	16	15.1	15	14.7
GS/OH follow-up patient	17	16.0	18	17.6
	Mean	**SD**	**Mean**	**SD**
Age	70.06	10.9	70.7	11.3
Intraocular pressure	23.4	10.9	22.2	5.4
Charlson Score	1.6	2.2	1.4	2.1
Number of medications	2.8	2.9	2.6	2.9
IMD	12.7	7.7	15.4	11.2

3.4.7 Primary outcome

The distribution of adherence measured by the TDA for 167 participants with complete TDA data had a positive skew in both the control and intervention group indicating that the majority of participants had a high percentage adherence rate regardless of randomisation. The mean adherence over the total 8-month monitoring period was 77.2% in the control group, but the difference (2.4%; 95% CI, -4.2, 9.0) between the two groups was small and not statistically significant (p=0.471). Median adherence for the total period was 80.61% (IQ=63.9, 93.3, n=84) for the control group and 80.9% (IQ= 65.3, 93.1, n=83) for the intervention group.

There was also no difference in the mean adherence for the final 2 months of monitoring; 79.3% in the control group, the difference (1.6%; 95% CI, -6.8, 10.0) between the two groups being minimal (p=0.703). There was no statistically significant difference in the proportion of individuals with ≥80% adherence (p=0.631) between the two groups: control group 62.5% and intervention group 66.7%.

A repeated measures analysis of percentage adherence rate for each month found no difference in adherence between the two groups (p=0.685) or any interaction between month and group (p=0.894), the details of which are provided in Figure 3.7.

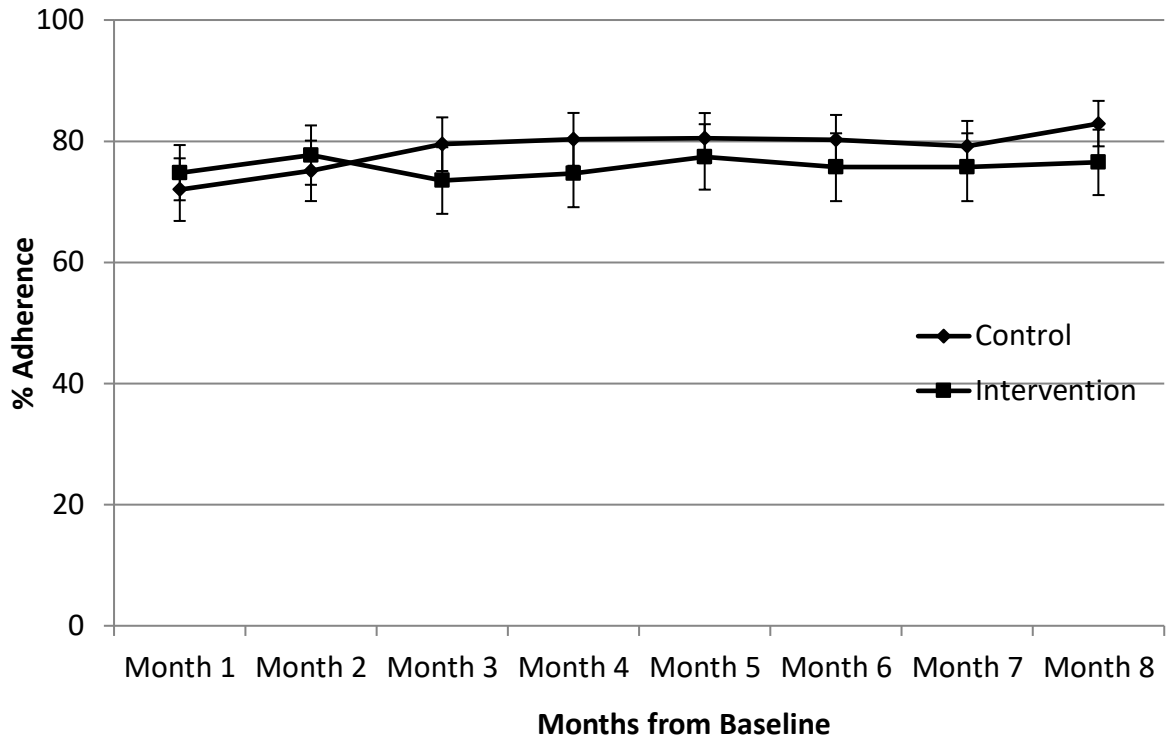


Figure 3.7 Monthly mean percentage adherence with confidence intervals for control and intervention groups

3.4.8 Comparison of primary outcome measures of adherence

Adherence levels measured by the TDA and calculated using three different methods are presented in Table 3.5 using both observed and imputed data. The mean adherence rates calculated for the total period and the final 2 months of monitoring were high in both groups and thus the proportion of individuals with ≥80% adherence was also high in both groups. There were no statistically significant differences in adherence levels measured between the two groups.

There was no large differences between the results using observed and imputed data sets, thus all further analyses were based upon observed data only.

Table 3.5 Comparison of the primary outcome measures of adherence calculated with observed and imputed data

	Observed data				Imputed data			
	Control	**Intervention**			**Control**	**Intervention**		
	Mean (SD)	**Mean (SD)**	**P-value**	**Mean difference (95% CI)**	**Mean (SD) n = 106**	**Mean (SD) n = 102**	**P-value**	**Mean difference**
Mean average over the monitoring period	77.2 (19.5) n=84	74.8 (23.5) n=83	0.471	2.4 (-4.2, 9.0)	77.0 (19.3)	75.4 (22.2)	0.617	1.48
Mean average for final 2 months of monitoring	79.3 (21.7) n=64	77.7 (25.2) n=60	0.703	1.6 (-6.8, 10.0)	78.0 (22.2)	76.9 (22.8)	0.997	0.01
Dichotomised final two months	**Proportion (%)**	**Proportion (%)**	**P-value**	**% difference**	**Proportion (%)**	**Proportion (%)**	**P-value**	**% difference**
≥ 80% adherent	40 (62.5)	40 (66.7)	0.628	-4.0	(57.1)	(60.8)	0.654	-3.7
< 80% adherent	24 (37.5)	20 (33.3)			(42.9)	(39.2)		

3.4.9 Secondary outcomes

3.4.9.1 Association between IOP and adherence

The difference in IOP control was compared between control and intervention groups at three time points; initiation of treatment (Baseline), 2 months (Visit 2) and 8 months (Final Visit) as presented in Table 3.6. IOP reduction using two different methods of calculating IOP reduction (percentage difference in and absolute IOP reduction) and at two different time points is also displayed in Table 3.6. There was a small difference between groups but these were not statistically different.

Table 3.6 Comparison of measures of intraocular pressure between control and intervention groups

	Control Mean IOP (SD)	Intervention Mean IOP (SD)	p-value	CI
Baseline	23.68 (5.82) n=105	22.36 (5.51) n=102	0.096	1.31 -0.23, 2.87
Visit 2	16.22 (3.98) n=105	15.87 (3.87) n=102	0.520	0.35 -0.73, 1.43
Final Visit	16.43 (4.25) n=84	16.16 (3.92) n=83	0.675	0.27 -0.98, 1.51
Difference in % IOP reduction Baseline – Visit 2	30.40 (20.26) n=105	26.69 (18.19) n=101	0.168	3.72 -1.58, 9.01
Difference in % IOP reduction Baseline – Final Visit	27.58 (19.18) n=85	25.30 (19.71) n=83	0.448	2.28 -3.64, 8.21
Difference in IOP Baseline – Visit 2	7.64 (5.17) n=104	6.48 (5.33) n=101	0.098	1.16 -0.22, 2.53
Difference in IOP Baseline - Final Visit	7.00 (5.19) n=85	6.28 (5.33) n=83	0.398	0.69 -0.91, 2.29

The IOP reduction between Baseline to Visit 2 and Baseline to Final Visit was correlated with adherence measured by the TDA, the results for the intervention and control groups are displayed in Table 3.7. Only the IOP reduction at the Final Visit in the intervention group showed a small weak positive correlation but this was not statistically significant.

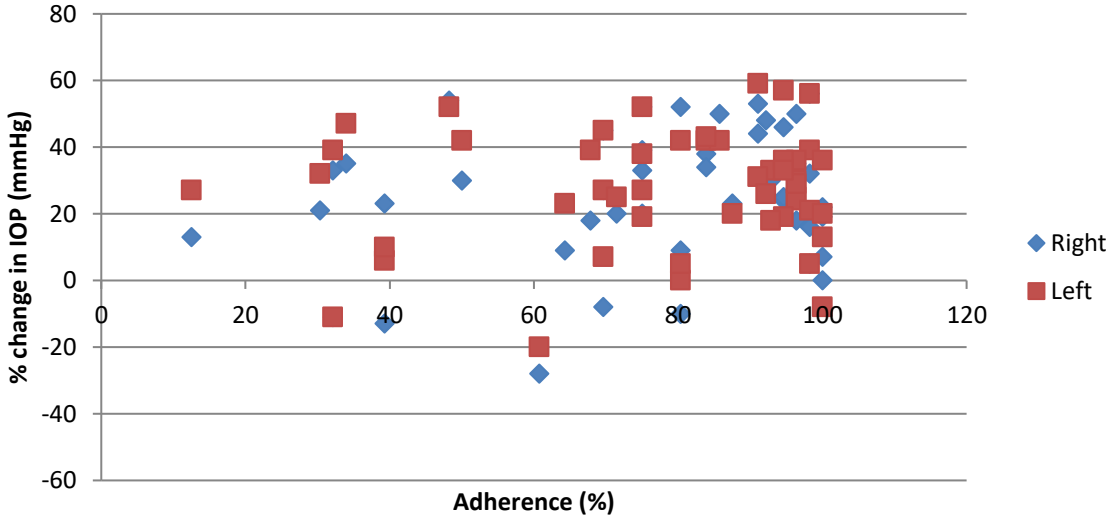
Table 3.7 Correlation of IOP reduction

	Control group		Intervention group	
	Spearman's r	p-value	Spearman's r	p-value
Correlation with mean % adherence for month 2				
	n=83		n =85	
Difference in IOP Baseline – Visit 2	0.031	0.782	0.004	0.969
IOP % reduction Baseline – Visit 2	0.030	0.785	0.006	0.958
(Correlation with mean % adherence for month 7 and 8)				
	n=60		n=55	
Difference in IOP Baseline - Final Visit	0.059	0.657	0.237	0.082
IOP % reduction Baseline – Final Visit	0.048	0.717	0.225	0.099

† Correlation of two different measures of IOP reduction (absolute and % reduction) compared with mean % adherence measured by the TDA. The data is shown for control and intervention groups and for two time points; baseline to month 2, and baseline to final two months.

An unplanned analysis was undertaken to establish if IOP could be used as a surrogate marker of adherence, the relationship was examined further. Rather than using the average IOP measure of both eyes, the right and left eye data were examined separately. Since the variance between eyes is usually less than between groups because of their combined mutual correlation (since they are not independent samples), data collected from both eyes could underestimate any true variance.[186, 187] Figure 3.8 shows the plots for the control and intervention groups and the weak positive correlation with small statistical significance with right eye data in the intervention group.

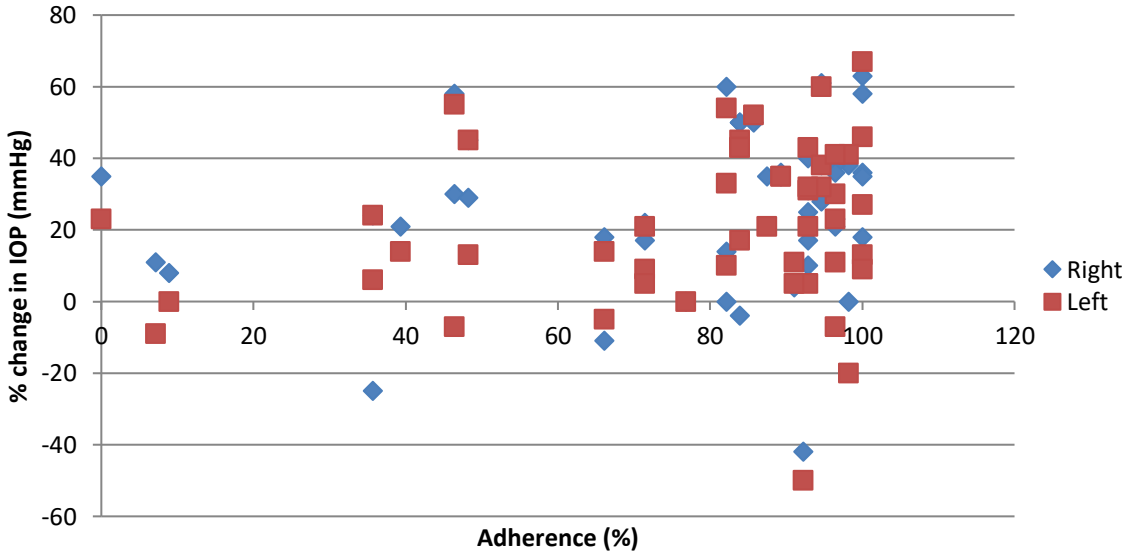
Control group



Spearman's: Right eye: r =0.103; p=0.450 (n=56)

Left eye r = -0.014; p=0.923 (n=53)

Intervention group



Spearman's: Right eye: r=0.258; p=0.067 (n=51)

Left eye: r=0.200; p=0.146 (n=54)

Figure 3.8 Relationship between adherence measured by the TDA and percentage IOP change between Baseline and Final Visit

3.4.9.2 Medication possession ratio

The mean possession ratio was 1.95 (SD 0.69) for the control group and 1.88 (SD 0.83) for the intervention group, but this was not statistically different between the two groups (p=0.590, mean difference 0.07, CI -0.19 – 0.33).

The MPR calculation is based upon contents of the bottle, whereas the '28 day MPR' is based upon a 28-day prescription re-fill recommendation. Using a 28 day MPR, for both control and intervention groups most participants fall within an MPR of 0.00 – 5.00 (21 participants in both groups) as demonstrated in Figure 3.9 which suggests that most participants have the correct prescription ratio based upon a prescription refill every 28 days. Comparison of the medians as displayed in Table 3.8 revealed that the control group had a lower median and interquartile range than the intervention group and the sum of the intervention group (116.59) was greater than the control group (96.18). Therefore, the intervention group had more medication than required for a 28 day prescription refill, and the control group were more likely to run out of medication during the observation period, although this difference was not statistically significant when compared between groups (p=0.798, mean difference -0.41, CI -3.57 – 2.75).

Table 3.8 Median and interquartile ranges of 28-day refill prescriptions

Quartiles	Control group Median	Intervention group Median
25	-4.73	-3.67
50	0.75	1.00
75	5.44	6.00

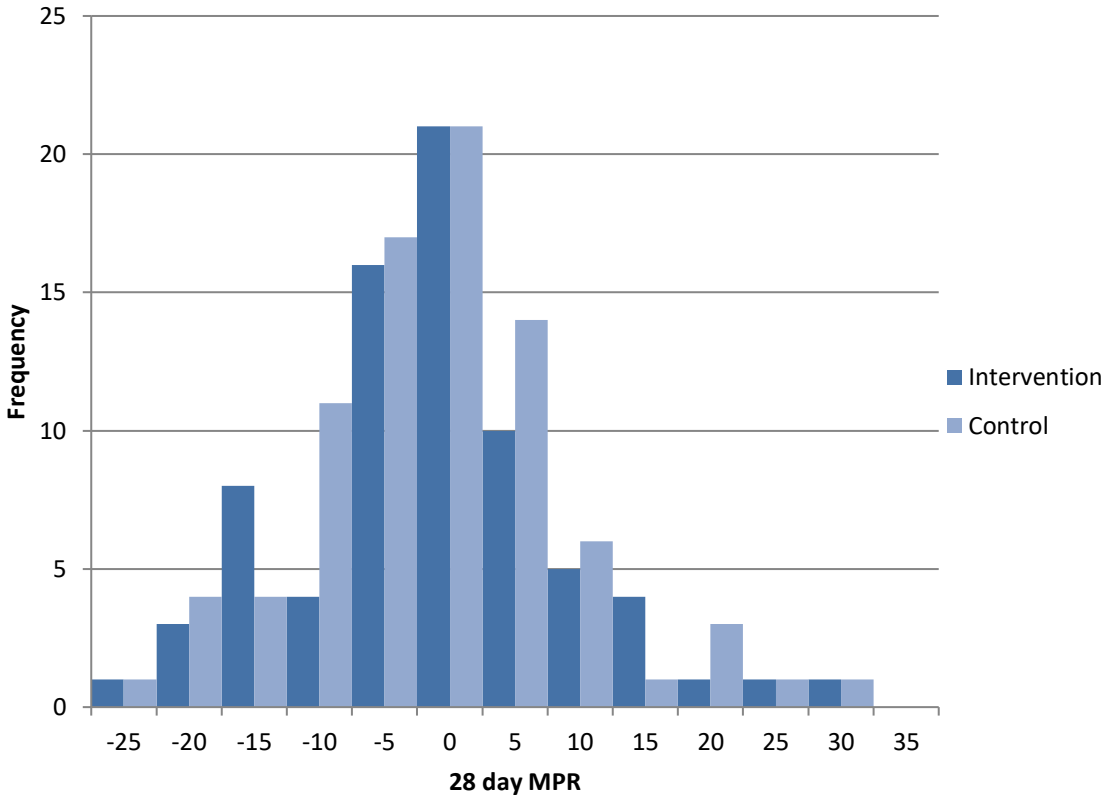


Figure 3.9 Medication possession ratio from retrospective pharmacy prescription 28-day re-fill data comparing intervention and control groups

There was no significant correlation between either MPR or 28-day refill MPR with adherence as presented in Table 3.9.

Table 3.9 Correlation of month 7 and 8 percentage adherence with medication prescription ratios

	Control group Spearman's co-efficient	Intervention group Spearman's co-efficient
MPR	0.209 (p=0.133)	-0.076 (p=0.619)
28-day refill MPR	0.149 (p=0.283)	0.086 (p=0.571)

3.4.9.3 Satisfaction with information about travoprost

The initial satisfaction with information about travoprost questionnaire was fully completed by 182 participants; 94 controls and 88 from the intervention group. The median SIMS score for the control and intervention groups at each visit are

shown in Table 3.10. Satisfaction with information about travoprost was higher in the intervention group (p<0.001) at all three time points. Satisfaction with information increased over time in the control group. There was no statistically significant positive correlation between satisfaction with information and increased adherence to medication at any time point as indicated in Table 3.11.

Table 3.10 Comparison of SIMS scores between intervention and control groups at Baseline, Visit 2 and Final Visits

	Control Median (IQ)	Intervention Median (IQ)	Mann-Whitney U (Mean Rank)
Baseline	7.5 (5.0, 11.0) n=94	15.0 (13.0, 17.0) n=88	Z=-8.791 p<0.001 (58.46 – 126.79)
Visit 2	10.0 (8.0, 14.0) n=92	15.0 (13.0, 17.0) n=76	Z=-5.604 p<0.001 (65.55 – 107.43)
Final Visit	11.0 (8.0, 14.0) n=85	16.0 (11.8, 17.0) n=74	Z=-4.529 p<0.001 (64.81 – 97.45)

Table 3.11 Correlation of SIMS scores and month 7 and 8 percentage adherence

	Control		Intervention	
	Spearman's coefficient	P-value	Spearman's coefficient	P-value
Baseline	-0.083 (n=57)	0.539	0.186 (n=52)	0.186
Visit 2	-0.287 (n=57)	0.030	0.126 (n=44)	0.415
Final Visit	-0.257 (n=58)	0.052	0.136 (n=49)	0.350

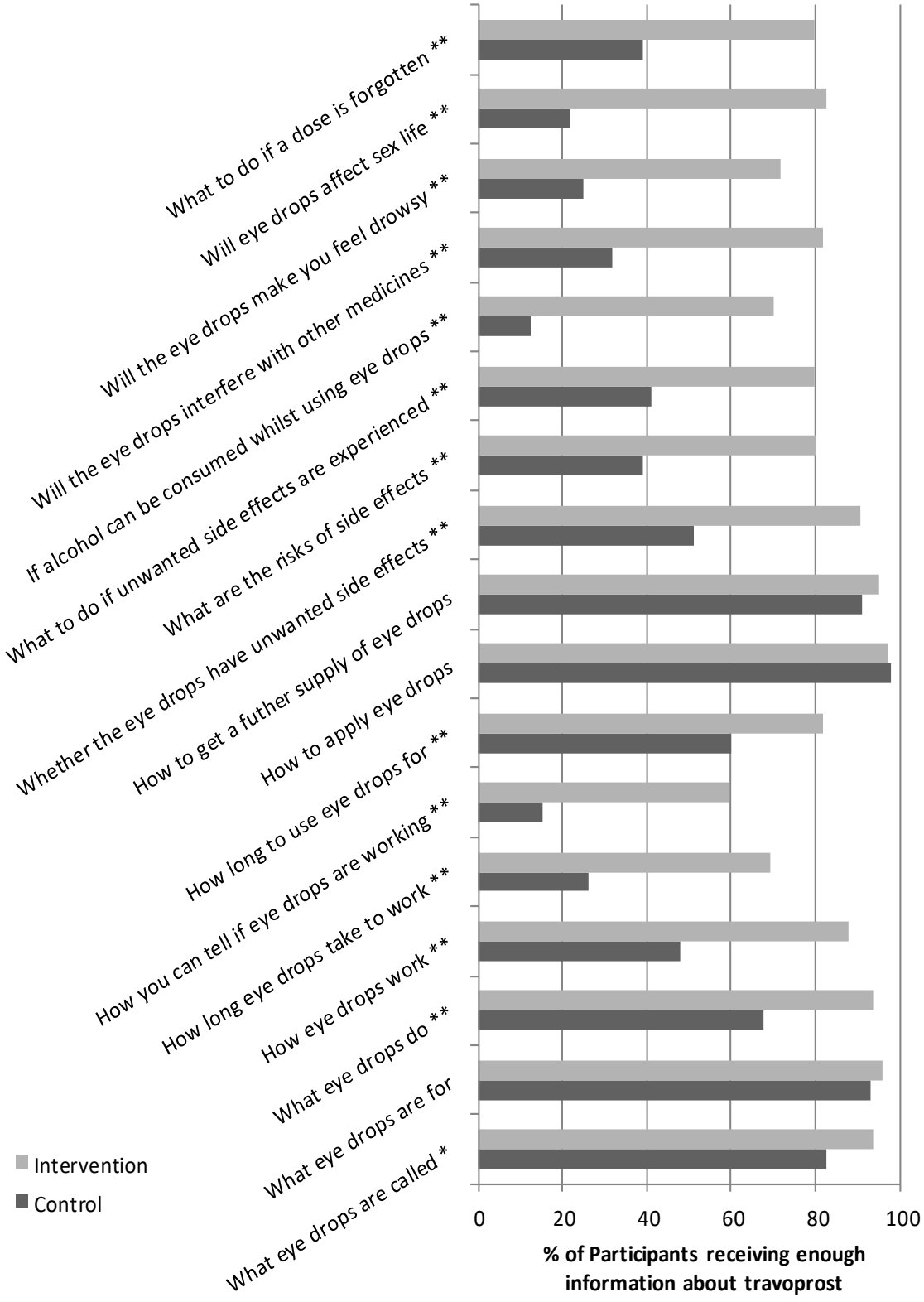
3.4.9.3.1 Satisfaction with information about travopost profile

Figures 3.10 – 3.12 provide a comparative illustration of the specific items of SIMS information that intervention and control participants felt they lacked at three different time points; Figure 3.10 displays Baseline, Figure 3.11 displays Visit 2 and Figure 3.12 displays Final Visit.

Following the Baseline visit, participants in the intervention group were more satisfied with all information items than the control group participants, apart from ‘how to apply eye drops?’ (97.0%) where the control group satisfaction was marginally higher (98.1%). ‘How to get a further supply of eye drops?’ was also the item reported by both groups to have the highest satisfaction with information. The lowest satisfaction scores in the control group were reported for ‘if alcohol can be consumed whilst using eye drops?’ (12.6%) and in the intervention group ‘how you can tell if eye drops are working?’ (59.8%).

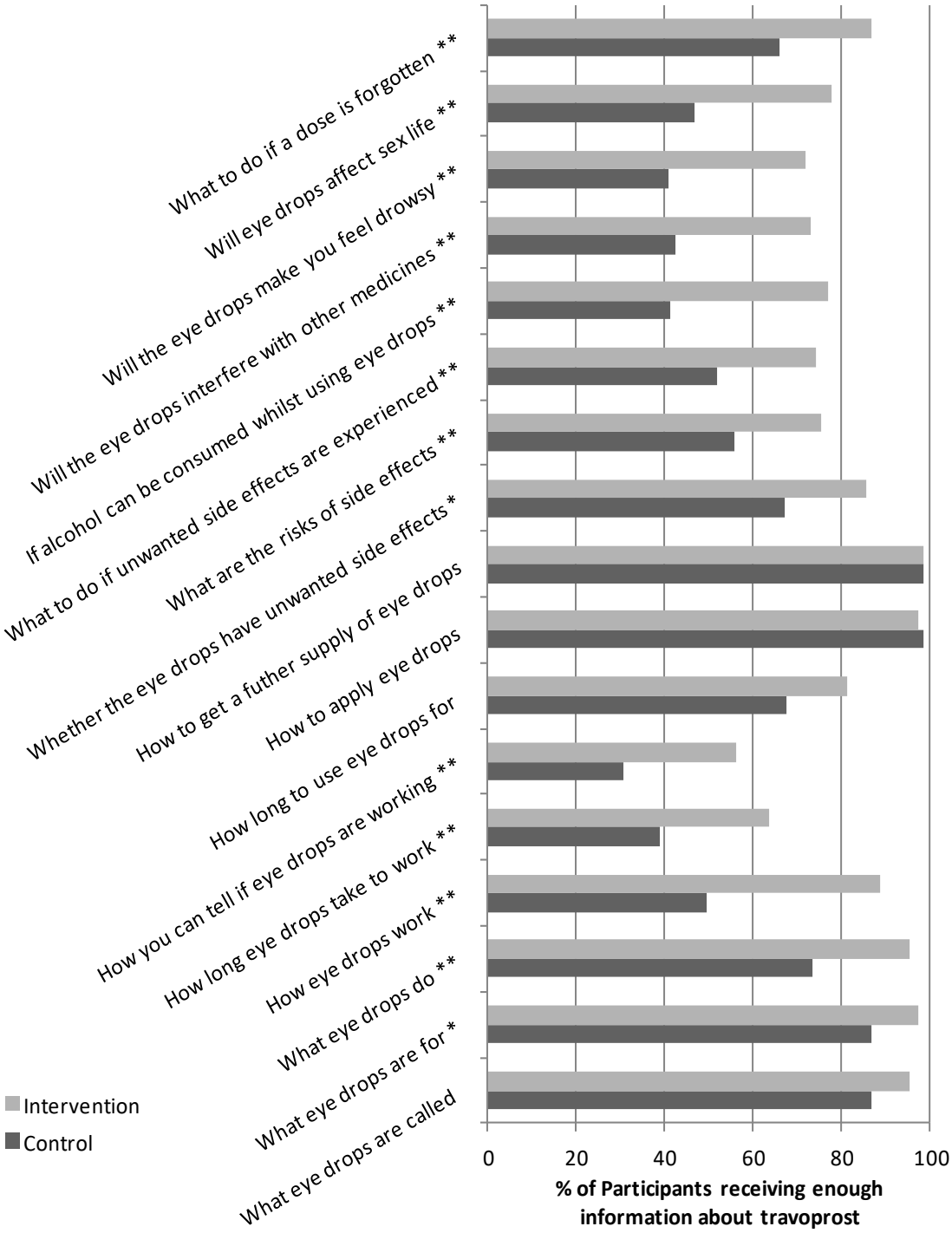
At Visit 2, the control group had a greater satisfaction with ‘if alcohol can be consumed whilst using eye drops?’ (41.6%) than at Visit 1, and were least satisfied with ‘how you can tell if eye drops are working’ (30.7%) which was also the lowest item in the intervention group (56.5%). The control group were most satisfied with ‘how to apply eye drops?’ (99.0%) and ‘how to get a further supply of eye drops?’ (99.0%), both higher than the intervention group (97.8% and 98.9% respectively).

At the Final Visit, the control and intervention group were still least satisfied with ‘how you can tell if eye drops are working?’ (36.3% and 62.4% respectively) which remained low at every time point. The greatest satisfaction for both control and intervention groups still remained ‘how to apply eye drops?’ (98.1% and 97.0% respectively).



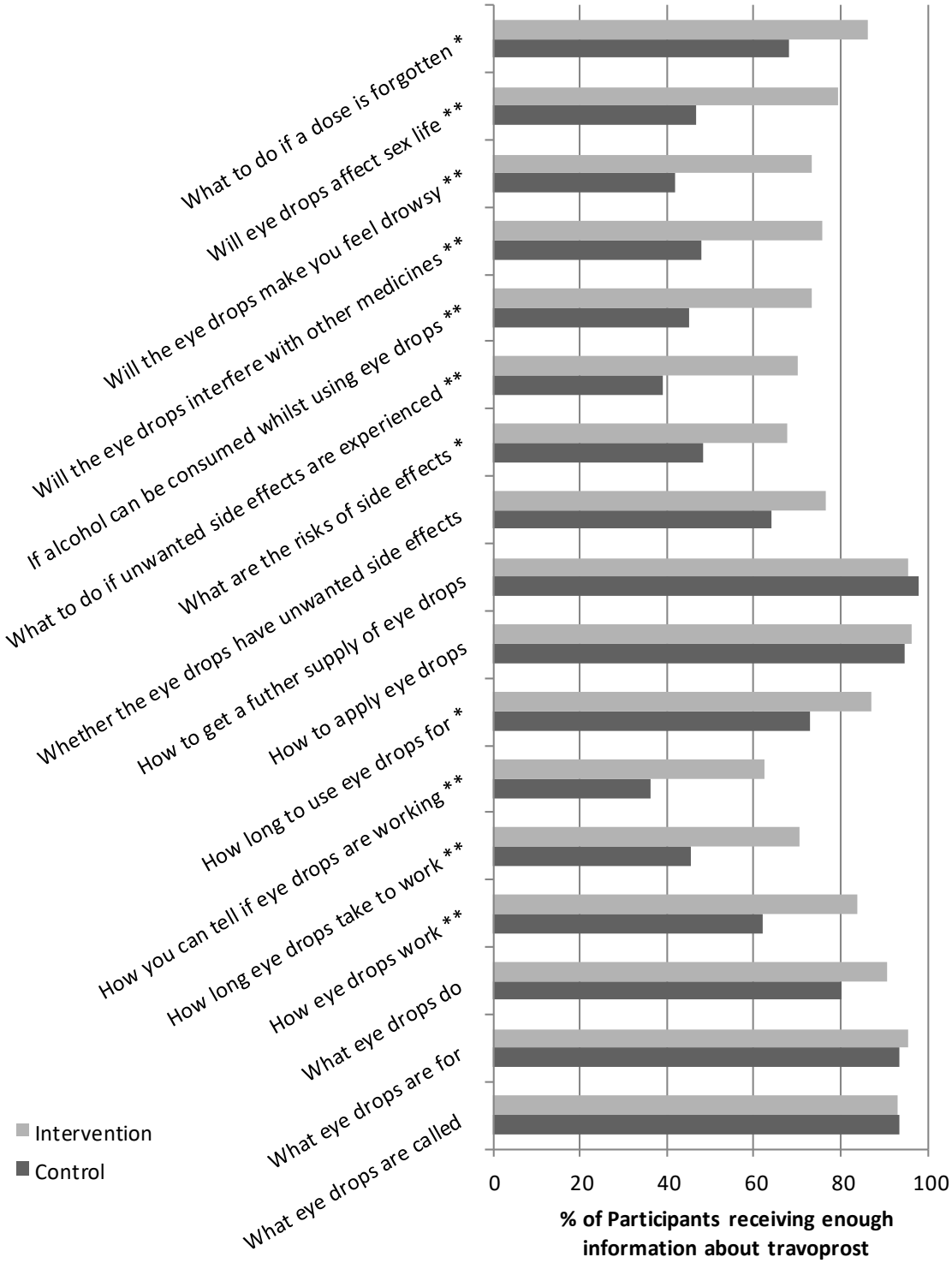
Where difference in means were statistically significant: * >0.01 **>0.001

Figure 3.10 Comparison of control and intervention groups SIMS results following Basleine visit



Where difference in means were statistically significant: * >0.01 **>0.001

Figure 3.11 Comparison of the control and intervention groups SIMS results following Visit 2



Where difference in means were statistically significant: * >0.01 **>0.001

Figure 3.12 Comparison of the control and intervention groups SIMS results following the Final Visit

3.4.9.3.2 Action/usage and potential problems with travoprost

Participant responses to the SIMS questionnaire were also categorised into items related to 'action and usage of travoprost' (items 1-9) or 'potential problems with travoprost' (items 10-17).[174] Table 3.12 provides the comparative data between the control and intervention groups. The control group felt that they had significantly more information about the action and usage of travoprost than the potential problems of travoprost at all three time points. The intervention group remained completely constant with their satisfaction of action and usage of travoprost over the three time points, but become slightly less satisfied with the information about the potential problems.

Table 3.12 Mean percentage of participants satisfied with information about travoprost for control and intervention groups

	Control Mean %		Intervention Mean %	
	Items 1-9*	**Items 10-17#**	**Items 1-9***	**Items 10-17#**
Baseline	65	33	86	80
Visit 2	70	52	86	78
Final Visit	75	50	86	75

***Action and usage of travoprost (items 1-9)**	**#Potentional problems of travoprost (items 10-17)**
1. What eye drops are called	10. Whether the eye drops have unwanted side effects
2. What eye drops are for	11. What are the risks of side effects
3. What eye drops do	12. What to do if unwanted side effects are experienced
4. How eye drops work	13. If alcohol can be consumed whilst using eye drops
5. How long eye drops take to work	14. Will the eye drops interfere with other medicines
6. How you can tell if eye drops are working	15. Will the eye drops make you feel drowsy
7. How long to use eye drops for	16. Will eye drops affect sex life
8. How to apply eye drops	17. What to do if a dose is forgotten
9. How to get a further supply of eye drops	

3.4.9.4 Self-reported adherence

Patient self-report of adherence was measured using two different methodologies; MMAS and FMD which are presented in Table 3.13 together with a comparison of the results between the control and intervention groups. There was no significant difference in self-reported adherence between groups at either Visit 2 or the Final Visit using MMAS. However, the FMD measure did reveal that the intervention group had a statistically significant greater report of adherence than the control group at Visit 2 but this was not repeated at any other time point.

Table 3.13 Comparison of self-reported adherence using two different measures

	Control % Adherent	**Intervention** % Adherent	**P-value**	**Mean Diff (95% CI)**
MMAS Visit 2	71.4 (n=98)	74.4 (n=90)	0.462	0.059 (-0.10, 0.22)
MMAS Final Visit	55.4 (n=92)	65.1 (n=83)	0.164	0.125 (-0.05, 0.30)
FMD Visit 2	61.8 (n=102)	74.2 (n=93)	0.010*	0.30 (0.07, 0.54)
FMD Final Visit	54.8 (n=93)	59.8 (n=87)	0.318	0.14 (-0.13, 0.40)

*Statistically significant

3.4.9.4.1 Agreement between TDA and self-report

Table 3.14 shows a cross tabulation of both self-report methodologies (FMD and MMAS) compared to the TDA adherence score at two different time points (Visit 2 and Final Visit) for both control and intervention groups. A Cohen's Kappa test was used to measure the agreement between self-report measures and TDA adherence scores. There was no agreement between adherence measured by the TDA and self-report methods which was statistically significant for the FMD measure and the MMAS only in the control group for the Final Visit.

Table 3.14 Comparison between TDA identified non-adherence to self-report measures

Self-report measure		Control group TDA			Intervention group TDA		
		Adherent (n)	Non-adherent (n)	**Agreement (Kappa)**	Adherent (n)	Non-adherent (n)	**Agreement (Kappa)**
MMAS Visit 2 n=61	Adherent	14	8	-0.129 p=0.177	11	8	-0.161 p=0.108
	Non-adherent	31	8		29	8	
MMAS Final Visit n=62	Adherent	8	15	-0.290 p=0.015*	11	8	-0.090 p=0.433
	Non-adherent	26	13		24	11	
FMD Visit 2 n=62	Adherent	11	13	-0.314 p=0.003*	8	11	-0.313 p=0.003*
	Non-adherent	31	7		31	7	
FMD Final Visit n=63	Adherent	8	16	-0.330 p=0.005*	7	11	-0.242 p=0.036*
	Non-Adherent	27	12		26	12	

*Statistically significant

3.4.9.4.2 Morisky Measure Adherence Score

There are four component questions of MMAS which can be used to assess the reason for non-adherence within the groups as presented in Table 3.15 which compares the component questions used to classify non-adherence for each group at Visit 2 and the Final Visit. The biggest reported reason for non-adherence is forgetting to use eye drops, with the other 3 categories having minimal impact on adherence. There is no statistically significant difference in type of self-reported non-adherence between the control and intervention groups at either time point.

Table 3.15 Comparison of MMAS component questions for control and intervention groups at Visit 2 and the Final Visit

	Visit 2			Final Visit		
	Control n (%)	**Interven -tion** n (%)	**p-value**	**Control** n (%)	**Interven -tion** n (%)	**p-value**
Are you casual at times about using your eye drops?	5 (4.9)	4 (4.3)	0.830	8 (8.7)	6 (6.9)	0.656
When your vision feels better do you sometimes stop using your eye drops?	1 (1)	0 (0)	0.344	0 (0)	0 (0)	-
If your vision feels worse when you use the eye drops, do you sometimes stop using it?	2 (2)	2 (2.2)	0.958	0 (0)	0 (0)	0.134
Do you sometimes forget to use your eye drops?	25 (24.3)	20 (21.1)	0.591	39 (41.1)	29 (32.2)	0.215

3.4.9.4.3 Reasons for non-adherence

Participants reporting non-adherence were asked to report reasons from a 7-item list as presented in Table 3.16. The biggest reported reason for non-adherence was forgetting to use the eye drops, with the other 6 categories having minimal impact on reported non-adherence. Between the control and intervention groups,

running out of drops at Visit 2 was the only statistically significant difference. Forgetting to use eye drops was reported more in both the control and intervention groups at the Final Visit compared to Visit 2.

Table 3.16 Comparison of reasons for missing drops between control and intervention groups at Visit 2 and Final Visit

	Visit 2			Final Visit		
	Control n (%)	**Interven -tion** n (%)	**p-value**	**Control** n (%)	**Interven -tion** n (%)	**p-value**
Forgot	23 (23.5)	22 (22.2)	0.836	37 (40.7)	32 (34.4)	0.384
Ran out of drops	3 (3.1)	12 (12.1)	0.016	4 (4.4)	6 (6.5)	0.541
Side effects of drops	4 (4.1)	3 (3.0)	0.692	2 (2.2)	4 (4.3)	0.425
Difficult to use drops	2 (2.0)	1 (1.0)	0.557	1 (1.1)	0	0.313
Change in routine	6 (5.7)	5 (5.0)	0.821	6 (5.7)	4 (4.0)	0.571
Fell asleep	1 (0.9)	2 (2.0)	0.535	0	0	-
Felt unwell	0	0	-	0	2 (2.0)	0.147

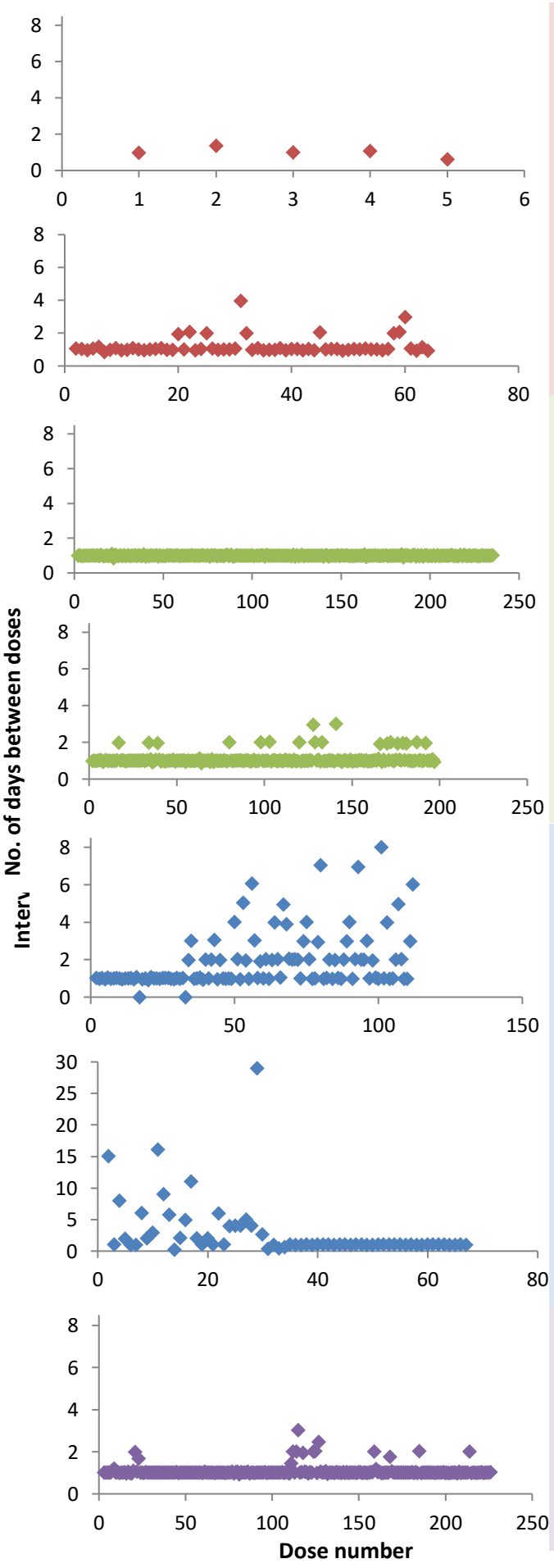
3.4.9.5 Graphical representation

Figure 3.13 displays the TDA recorded adherence behaviour patterns from the available data n = 154. The four patterns of classification described by Ajit *et al.*[95] were modified to differentiate between two further behaviour patterns. Not only could we depict participants with good adherence defined as >80% (Type 2b) but those with excellent adherence ≥97% (Type 2a). Participants who took 'drug holidays' (missed doses for 7 or more consecutive days) also fell into two categories, those who primarily missed doses during a 'drug holiday' (Type 3b) and those whose behaviour was mixed between having 'drug holidays' and variable dosing in between these periods (Type 3a) as illustrated in Figure 3.13. Table 3.17 displays the comparison of these magnitude of these behaviour types between the control and intervention groups. There was a small statistically significant difference between control and intervention groups in Type 3b which may suggest that non-adherence in the intervention group was primarily due to a mix of variable dosing combined with drug holidays.

Table 3.17 Comparison of adherence behaviour types between control and intervention groups

		Control		Intervention			
		Mean % adherence	**SD**	**Mean % adherence**	**SD**	**t-test** Mean (CI)	**p-value**
Good adherence < 80%	2a	98.2	0.98	97.5	1.05	0.67 (-0.91, 2.25)	0.328
	2b	86.95	4.98	90.05	4.83	-3.1 (-7.03, 0.83)	0.115
Poor adherence > 80%	3a	56.73	10.06	61.64	14.24	-4.9 (-15.63, 5.81)	0.331
	3b	63.67	14.83	37.50	21.47	26.17 (-0.94, 53.27)	0.056
	4	65.67	15.28	72.67	3.79	-7.0 (-43.08, 29.08)	0.492

2a = Adherence ≥ 97%
2b = Adherence ≥ 80% <96%. More variable than 2a with variable missed doses.
3a = Adherence < 80% drug holidays (≥ 7 days without dosing) mixed with variable dosing
3b = Adherence < 80% drug holidays (≥ 7 days without dosing) with <30 variable missed doses.
4 = Adherence < 80% with variable and frequent missed doses



Type 1

Side effects
Control = 6%
Intervention = 10%

***No response to treatment**
Control = 11%
Intervention 6%

*Note difference in horizontal axes

Type 2

2a Adherence ≥ 97%
Control=19%
Intervention=12%

No more than 27 days missed over the entire period. Mean adherence for this example is 100%.

2b Adherence ≥ 80% <96%
Control=32%
Intervention=45%

More variable than 2a with frequent and variable missed doses. Mean adherence for this example is 90%.

Type 3 – Drug Holidays
(≥ 7 days without dosing)

3a Adherence < 80% drug holidays with variable dosing
Control =18%
Intervention=24%

Mixed with variable and frequent missed doses. Mean adherence for this example is 50%.

***3b Adherence <80%**
Control=10%
Intervention=14%

With <30 variable missed doses. Mean adherence for example is 33%.
*Note change in vertical axis

Type 4

Adherence < 80% with variable and frequent missed doses
Control=21%
Intervention=6%

Mean adherence for this example is 77%.

Figure 3.13 Graphical representation of adherence behaviours

3.4.9.6 Predictors of adherence

Demographic characteristics and other related behaviour characteristics listed in Table 3.4 were added to the probabilistic model to determine possible predictors of adherent behaviour. As the measure of adherence was not statistically different between the control and intervention groups, the predictive model used the combined adherence data from both groups.

Due to ethnicity of the group being predominantly a British population (1.9%), the effect of ethnicity on adherence was not included in the analysis.

The results are summarised in Table 3.18 and show that marital status, using other medication at the same time as travoprost and IMD (index of multiple deprivation) may have predicted more adherent behaviour. These three variables were selected and entered into the adjusted model. Use of medication at the same time as travoprost was a predictor of adherence.

3.4.10 Information provision

Participants in both the control and intervention groups were asked to self-rate their satisfaction with the level of information they were given about glaucoma, effects on vision and driving. The questionnaires that ascertained this information were given at three different time points during the study; after the Baseline Visit, after Visit 2 and after the Final Visit. As is presented in Table 3.19, the intervention group were much more satisfied with the information they received and an independent samples t-test between the control and intervention group confirmed a statistically significant difference between the level of satisfaction between the two groups at all time points.

After the initial visit 26 participants (24.5%) from the control group and 12 participants (11.8%) from the intervention reported that they required more information. At the Final Visit this had reduced to 12 participants (11.3%) from the control group and 4 participants (3.9%) from the intervention group, which was statistically significant; p=0.027 at the Baseline Visit and p=0.044 for the Final Visit. The number of participants that required further information did decrease over time in both groups (p=0.002, t-test).

Table 3.18 Baseline predictors of adherence, based on more than 80% adherence for the whole cohort

	Adherent		Unadjusted		Selected*	
Predictor	Yes	No (%)	OR (95%,CI)	p-value	OR (95%,CI)	p-value
Gender						
Male	41	21 (33.9)	1.15 (0.55, 2.40)	0.707		
Female	39	23 (37.1)	1			
Home Owner						
Yes	67	35 (34.3)	1.33 (0.52, 3.40)	0.558		
No	13	9 (40.9)	1			
Marital Status						
Married/partner	51	33 (39.3)	1		1	
Not married/partner, widowed or single	29	11 (27.5)	1.71 (0.75, 3.88)	0.202	2.03 (0.58, 7.05)	0.267
Education						
Left school ≤ 16	30	17 (36.2)	1			
Further education > 16	49	27 (35.5)	1.03 (0.48, 2.20)	0.942		
Positive family history (Parent, sibling or child)						
No	58	32 (35.6)	1	0.978		
Yes	22	12 (35.3)	1.01 (0.44, 2.31)			
Diagnosis						
POAG	57	32 (36.0)	1			
NTG	23	12 (34.3)	1.08 (0.47, 2.45)	0.861		
First appointment or seen before						
New patient	38	21 (35.6)	1			
Follow-up patient	42	23 (35.4)	1.01 (0.48, 2.11)	0.981		
Application of drops (Visit 1)						
Self	64	39 (37.9)	1			
Help	13	5 (27.8)	1.58 (0.52, 4.79)	0.415		
Need more information						
Yes	16	6 (27.3)	1.65 (0.59, 4.62)	0.342		
No	55	34 (38.2)	1			
Other medication used at same time						
Yes	29	10 (25.6)	2.75 (1.05, 7.22)	0.040	3.81 (1.34, 10.87)	0.012
No	19	18 (48.6)	1		1	
Previous use of eye drops						
Never	52	28 (35.0)	1.14 (0.53, 2.48)	0.735		
Occasional / Frequent	26	16 (38.1)	1			
Mean Age (SD)	71.47 (11.7)	68.82 (10.48)	1.02 (0.99, 1.06)	0.212		
Mean Charlson Score (SD)	1.4 (2.1)	1.39 (1.85)	1.00 (0.84, 1.20)	0.971		
Mean Number of medications (SD)	2.56 (2.8)	2.64 (2.60)	0.99 (0.86, 1.13)	0.884		
Mean Intraocular pressure (SD)	22.94 (5.71)	22.58 (5.14)	1.01 (0.95, 1.08)	0.728		
Mean IMD (SD)	14.39 (10.0)	11.68 (8.39)	1.04 (0.99, 1.08)	0.139	1.06 (0.99, 1.13)	0.107
Mean SIMS at visit 1 (SD)	10.93 (4.77)	11.68 (4.46)	0.97 (0.89, 1.05)	0.410		

* Using forward selection

Table 3.19 Satisfaction with information

	Glaucoma	Effect on vision	Effect on driving
Visit 1 / Baseline			
Control n = 105 (%)	74 (70.5)	56 (53.3)	49 (46.2)
Intervention n = 98 (%)	91(92.9)	82 (83.7)	82 (83.7)
p-value	<0.001	<0.001	<0.001
Visit 2			
Control n = 102 (%)	72 (70.5)	58 (56.9)	53 (52.0)
Intervention n = 94 (%)	88 (93.6)	76 (80.9)	72 (76.6)
p-value	<0.001	<0.001	<0.001
Final Visit			
Control n = 92 (%)	73 (79.3)	64 (69.6)	48 (52.2)
Intervention n = 88 (%)	82 (92.1)	73 (83.9)	74 (84.1)
p-value	0.014	0.024	<0.001

† Satisfaction with information received compared between control and intervention groups at three different time points. Information received was subdivided into three categories; glaucoma, effect on vision and effect on driving.

Participants were asked to report unanswered questions they may have had after each visit. The type of questions were analysed qualitatively and their frequency shown in Table 3.20. The topics with greatest number of unanswered questions were information about glaucoma (13), effects on driving, swimming and informing the DVLA (12), how it will effect long term vision (7) and side effects of drops (13).

Table 3.20 Topic areas of unanswered questions following each visit for control and intervention groups

	Initial visit	Second visit	Final Visit	Topic area of questions
Control	4	2	5	More information about glaucoma
Intervention	1	1	0	
Control	6	3	2	Driving / swimming / watching TV / Informing DVLA
Intervention	0	1	0	
Control	3	0	0	Administration of eye drops
Intervention	2	0	0	
Control	1	1	1	Risk to family
Intervention	0	0	0	
Control	3	0	0	Vitamins, diet and lifestyle
Intervention	1	0	1	
Control	3	2	2	How it will affect long term vision
Intervention	0	0	1	
Control	5	1	0	Information about how eye drops work and if you can tell it is working
Intervention	0	0	0	
Control	1	0	0	How will glaucoma in one eye effect the other eye
Intervention	0	0	0	
Control	1	0	1	How it will effect use of contact lenses
Intervention	0	0	0	
Control	3	0	0	Interaction with other medicines
Intervention	0	0	0	
Control	2	3	2	Side effects of drops
Intervention	1	3	2	
Control	4	0	0	Alcohol consumption
Intervention	1	0	0	
Control	2	1	1	How long to use drops for
Intervention	0	1	0	
Control	0	1	1	Surgery for glaucoma or laser treatments available
Intervention	0	0	0	
Control	0	0	1	Specific information about individual prognosis and treatment
Intervention	1	0	0	
Control	1	0	0	How to get a further supply of eye drops
Intervention	0	0	0	
Control	39	14	16	**Total**
Intervention	7	6	4	

3.4.11 Seeking additional advice and information

Participants were asked to report if they had sought any additional advice or information about glaucoma from other independent sources, such as from leaflets or from the internet. After the second visit, 40 (37.7%) participants in the control group reported seeking further information compared to 20 (19.6%) from the intervention group. After the Final Visit, 37 (34.9%) of the control group sought further information compared to 22 (21.6%) from the intervention group. The sources of further information are described in Table 3.21, the internet being the most popular.

Table 3.21 Where additional information was sought reported following Visit 2 and Final Visit

Visit 2	Final Visit	Where additional information has been sought
39	35	Internet
3	8	Leaflets from hospital
0	3	Leaflets from GP surgery
10	7	Other leaflets (unspecified)
0	1	Pharmacy
2	2	From medication leaflet
5	5	Medical enclopedia
1	1	Optician
1	0	Other glaucoma suffrers
2	0	GP/Practice nurse

3.4.12 Problems with use of eye drops

Participants were asked to report if they had experienced any problems with their eye drops. After Visit 2, 30 (28.3%) participants in the control group reported experiencing a problem compared to 21 (20.6%) of the the intervention group. After the Final Visit, 25 (23.6%) had experienced a problem compared to 28 (27.5%) in the intervention group. Table 3.22 describes the type of problems experienced at each time point between the two groups.

Table 3.22 The type of problems experienced with eye drops, reported after the Visit 2 and Final Visit

	Visit 2	Final Visit	Type of problem
Control	15	10	Adverse event relating to eye drop use
Intervention	7	12	
Control	13	11	Difficulty in applying eye drops
Intervention	14	11	
Control	0	0	Remembering to use eye drops
Intervention	0	1	
Control	0	1	Drops not available from pharmacy
Intervention	0	0	

3.4.13 Evaluation of the intervention

3.4.13.1 Telephone helpline

There were 100 calls made to the telephone helpline from 64% of participants from the intervention group over the course of the study. Eighteen participants made multiple calls (2-5 calls each). Removing calls made for study related issues (only 31%), calls were categorised into the following:

- Enquiries for further information: 16% (n=11)
- Participants suffering side effects: 81% (n=56)
- Information about driving and the DVLA: 3% (n=2)

3.4.13.2 The Behaviour Change Counselling intervention

The majority of the intervention group participants found the Glaucoma Education and Support Service helpful and improved their understanding of glaucoma and use of eye drops as presented in Table 3.23. There was a positive correlation with satisfaction of information provided by the Glaucoma Support Assistants and adherence (0.243, p=0.022).

Participants were invited to make any additional comments or suggestions about the service.

- Twelve comments described the Glaucoma Support Assistants who delivered the services. Comments included that they were helpful, kind, friendly, considerate, supportive and gave outstanding care.
- Twelve comments described the service; Time was given to listen to patients and allow them to talk, patients were made to feel welcome (important to one participant who did not like hospitals), felt as though they were an individual, beneficial to have a service that offers encouragement, an essential service.
- Seven comments related to usefulness of the service; Participants learnt more than they would have done, the service could help others, gave participants confidence, participants felt included in the treatment decisions, the help was comforting, good to be given the opportunity to discuss eye drops specifically.

Table 3.23 Satisfaction and effects of the Behaviour Change Counselling intervention and telephone helpline

	Neutral	Agree	Strongly Agree	Disagree	Strongly Disagree	Not used/not provided
Participant satisfaction with the Glaucoma Education and Support Service						
Found information about glaucoma helpful. N= 88	5 (5.7)	53 (60.2)	28 (31.8)	0	0	2 (2.3)
Found information about how to apply eye drops helpful. N= 89	2 (2.2)	55 (61.8)	30 (33.7)	2 (2.2)	0	0
Found discussion about the best was to fit my eye drops use into my daily routine helpful. N=89	7 (7.9)	51 (57.3)	30 (33.7)	0	0	1 (1.1)
Found the telephone helpline helpful. N=85	6 (7.1)	22 (25.9)	20 (23.5)	1 (1.2)	0	36 (42.4)
Recommend the education and support service to other patients. N=88	5 (5.7)	45 (51.1)	38 (43.2)	0	0	0
Effect of Glaucoma Education and Support Service						
Better understanding of glaucoma. N=86	11 (12.8)	47 (54.7)	28 (32.6)	0	0	0
Better able to use my eye drops. N=88	11 (12.5)	51 (58.0)	26 (29.5)	0	0	0
Confident about using eye drops regularly. N=88	11 (12.5)	46 (52.3)	29 (33.0)	2 (2.0)	0	0

Other comments (28) were made regarding study related issues, such as questionnaires, and information about the DVLA. The DVLA is not connected with the NHS health service and patients are asked to contact the DVLA directly for concerns about their driving licence.

The intervention was presented at the initial visit but all participants were given the opportunity to ask for further information at their follow-up visit; 47% did not request any further information.

3.4.14 Comparison of Glaucoma Support Assistants

Since the intervention was individualised to the patient, the intervention outcomes were examined between GSAs. Table 3.24 presents the number of interventions delivered by each GSA and the time taken to deliver the intervention with each participant, the number of patients with complete TDA data collected, and the number and percentage of adherent cases. There was no statistically significant association between GSA and adherent cases (Fishers Exact p= 0.860). Increased time spent with the Glaucoma Support Assistant (GSA) during the intervention did not correlate with improved adherence (Spearmans coefficient -0.083, p=0.528).

Table 3.24 Comparison of therapist effects

GSA	Number of BCC interventions delivered	Mean time to deliver intervention (SD)	No. of participants with completeTDA data (%)	No. of participants with complete TDA data that were adherent (%)
1	7	23.25 (13.61)	7 (100)	4 (57)
2	30	32.93 (7.43)	19 (63)	12 (63)
3	16	22.12 (10.13)	9 (56)	6 (67)
4	15	30.47 (5.1)	8 (53)	7 (88)
5	22	27.41 (6.6)	14 (64)	9 (64)

3.5 Discussion

The intervention used in NAGS failed to achieve greater adherence to newly initiated topical glaucoma treatment. Adherence in the control group was considerably higher than previously reported estimates used in general medicine which informed the power calculations.[56] Thus, improving adherence, in an already adherent population, would have been difficult to achieve.

Previous studies examining interventions to improve adherence to glaucoma medication have enrolled patients identified to be poorly adherent in an attempt to create the best conditions to measure greater effect sizes[188] or have measured adherence pre- and post- intervention to make a comparison of individual differences.[146] However, NAGS examined the potential of an intervention to improve adherence at the point of medication initiation in accordance with previous research findings.[42] Furthermore, outside of the study environment, current clinical practice cannot accurately predict patients likely to have poor adherence[118] and measuring such behaviour would have taken several months to achieve such that it was neither appropriate nor feasible to target a poorly adherent cohort in the study. Whilst it may be argued that improving adherence in those who are known to be non-adherent is more cost effective, the advantages of improving adherence in patients with glaucoma is substantial enough to suggest that all patients should be included in these intervention strategies.

NAGS was designed to monitor participants for a longer period than other studies of its kind, in attempt to observe adherence over time. If the length of monitoring period does have an effect on adherence behaviour, comparisons between studies of different durations should not be made. Therefore, three outcome measures were appropriately reported, median percentage adherence for the study period, a monthly mean percentage score, and mean percentage of the final 2 months of monitoring to take into account the longevity of the study. However, there were no differences in reported adherence with any of the methods.

3.5.1 Secondary Adherence Outcome Measures:

In addition to the TDA data as the primary method to measure adherence, the study used three other methods to measure adherence; the objective measures were reduction in intraocular pressure and medication prescription counts, and a subjective participant self-report method. Good correlation between adherence measured by the TDA and objective measures and/or self-report methods could have indicated these to be useful proxy measures of adherence in clinical practice. The following section explores these measures in more detail.

3.5.1.1. Reduction in intraocular pressure

Reduction of IOP was evaluated using two different methods; absolute and percentage reduction. No differences were found between the absolute and percentage reduction methods and there was no significant correlation between TDA measured adherence. There was no differences in IOP control between the intervention and control groups most likely due to limitations of the methodological approach and the pharmacodynamics of prostaglandin analogues, rather than conclusive evidence that the intervention failed to improve IOP control. Previous studies using similar methods also found that IOP reduction had no relationship to adherence.[95, 146] Assessing IOP due to individual differences (types of glaucoma and diurnal variance) together with regression to the mean, led to 'noisy data'.[189, 190]

3.5.1.2 Medication possession ratio

The calculation of MPRs with eye drops was found to be complex due to inaccuracies in the data caused by variation in prescribing conduct. In addition, unlike tablets or syrups, it is not possible to determine the volume of liquid correctly instilled in the eye as it relies upon the dexterity of the patient to instil the correct amount of liquid into the eye on the first attempt. If a patient were to miss the eye for example, they may need to apply another drop whilst with prolonged squeezing excessive liquid flows from the bottle resulting in the administration of more than one measured drop. Thus, absence of a fixed dose measure with respect to eye drops and differences in prescribing protocols can easily lead to erroneous MPR calculations. Inaccurate calculation of MPR may have been the

reason why the present study failed to identify a strong correlation between TDA and MPR measures. In a previous UK study using MPR calculations, the same 28-day calculation for refills was used but the authors did not describe any of the potential inaccuracies or limitations in collecting the data as described in the present study.[139] The present study observations are worth further consideration since the complexity of repeat prescription administration itself, and variation in health care professional practice with respect to prescribing medication, may have a role to play in patient attitudes to medication use.[115]

3.5.1.3 Self-reported adherence

Self-reported non-adherence remains a popular method to collect adherence information in clinical practice and research. However, there was a discrepancy between self-reported non-adherence and TDA measured non-adherence. Whilst self-reported non-adherence was greater at eight months than at two months, TDA measured non-adherence did not increase at any time during the eight month follow-up period. If one were to accept that the level of electronic monitoring accuracy remained constant over the monitoring period, then participants were poor reporters of adherence since their reporting became less accurate over time or they were inclined to over-report adherence within the first two months of observation. The social desirability to report adherent behaviour or memory bias could be the cause for the discrepancy between self-report and the objective measure of non-adherence.[79, 95, 119] More recent evidence has shown that 31% of patients (n=75) overestimated their adherence when using a VAS to self-report compared with MEMS-measured percentage adherence score and those who were newly diagnosed with glaucoma were more likely to over report their adherence (OR, 3.07, CI, 1.22-7.75).[94]

3.5.1.4 Graphical representation

The TDA data provided graphical representations of participant patterns of drop usage.[79, 95] Comparing patterns of drop usage determined that ‘drug holidays’ were the predominate type of non-adherent behaviour in both groups rather than just incidental missed doses. Drug holidays may be indicative of a more intentional non-adherent behaviour trait when a patient chooses not to use their medication for longer periods of time.[42, 127] However, non-adherence in the

intervention group was more likely to be due to a mix of drug holidays and incidental missed doses. Thus, reviewing medication usage patterns rather than average adherence scores may be more useful in establishing the cause(s) of observed non-adherence. Adherence pattern observation in turn can provide invaluable information for guiding the selection of intervention(s) most appropriate for supporting patients to adhere to their prescribed therapy.

3.5.2 Missing data

Self-report questionnaires provided the most complete datasets for the eight month period of study. Conversely, almost a quarter of the MPR data were missing due to health centres not providing prescribing data for research purposes despite being offered payment for this administrative task. Only one similar UK study using prospective collection of prescribing data has been identified from the literature[139] but in that study the authors did not report any limitations in data collection. Other UK studies using prescribing data have used retrospective data collection methods[191-194] of which missing or inaccurate data was often noted as a possible limitation, although the magnitude of the problem was not quantified.

Previous studies have reported that the TDA accurately recorded drop administration, but the longest of these studies was only for a three month period.[93, 95, 100] The NAGS study found that the TDA was relatively successful at measuring adherence for the initial two month period. However by eight months of follow-up, data attrition was high. Retrieval of data from the TDA due to device failure, which was outside of the control of either patient or researcher, accounted for the greatest loss of daily electronic data for the eight month period. Some TDAs were returned and had malfunctioned and this might have been caused by participants tampering with the internal batteries and mechanics of the TDA. The stickers used to cover the visual display had often been peeled off so that patients could see when the tear drop appeared. In addition, when treatment was changed, it rendered the TDA useless since the TDA aperture only holds Travatan shaped bottles. Therefore, calculating the average adherence score using TDA over the total monitoring period was the least successful of the three studied methods and was a significant limitation of this study.

If non-adherent participants had failed to return their TDA devices, thus creating more missing TDA data, this could have caused a study bias. However, a

subsequent analysis of the data found that the magnitude of adherence at two months was comparable for participants with full eight-month data and those who subsequently went on to have missing TDA data. Therefore, those who had missing TDA data but still provided self-reported adherence data were not likely to have been a less adherent cohort in comparison with those who had full TDA data.

3.5.3 Reasons for non-adherence

Participants reported more non-adherence due to forgetfulness than any other reason which is in line with previous research.[42, 73, 107, 143] Forgetfulness was reported as the reason for non-adherence more at the Final Visit in comparison to Visit 2. Conceivably, participants may have felt more confident to report forgetfulness when the study had reached its conclusion than at the beginning of the study process knowing they would meet a researcher at follow-up visits. Or, as new users of eye drops, participants may not have felt at ease to disclose this behaviour to the researcher. Forgetfulness is a behaviour that arguably could be exhibited as a result of either unintentional or intentional non-adherence. Thus interventions based upon BCC might improve non-adherence caused by intentional non-adherence, together with the use of dosing aid reminders and routine rehearsal more appropriate to unintentional non-adherence.[127]

3.5.4 Predictors of non-adherence

In addition to understanding the reasons which may influence non-adherent behaviour, identifying factors which may predict patients likely to be non-adherent would also enable healthcare professionals to target resources to vulnerable individuals requiring additional support. The NAGS study found that patients were more adherent to travoprost if the drop-administration time coincided with the time they used ‘other medications’. Thus, administration of multiple medications may be a potential advantage for patients to be adherent to eye drops and understanding the reasons may be useful when developing future interventions. Participants already in the routine of using their ‘other medications’ at the time of starting eye drops may have found that administration of an eye drop to an established good routine was easier than for participants who had to learn and remember a new routine. The good routine or medication use may have been

established through the longevity of medication use, or, unlike glaucoma which until significant damage has occurred has no discernible symptoms, 'other medication' is indicated for a condition which has symptoms and can in themselves act as the motivator to use medication.

3.5.5 Satisfaction with information

The NAGS intervention group were more satisfied with information received about use of their travoprost when compared to the control group, measured by SIMS, but this had no measurable effect on adherence. Responses to individual items of the SIMS suggested that the control group lacked information about the potential problems of using travoprost; standard care requires greater information provision with respect to these aspects, but whether this would improve adherence has not been established. Satisfaction with information about travoprost increased over time in the control group and suggests that patients seek/obtain information from additional sources post treatment initiation or that the desire for information declines over time.

Although there were no significant results that showed the long-term benefits of the intervention for the treatment of glaucoma, the NAGS study found that additional information, tailored to the individual, was able to achieve higher satisfaction with regards to care and drop taking techniques. The control group reported the need for more information and had many more unanswered questions than the intervention group, particularly when newly initiated on treatment, and had to seek most of the information they required from the internet. At month two the control group reported missing more doses than the intervention group due to eye drops running out, which suggests that information given during the intervention did prevent this particular barrier to good adherence which wasn't addressed by standard care alone. However, adverse events related to use of eye drops and problems applying eye drops were still reported to be a problem in both the intervention and control groups.

3.5.6 The intervention

The support and education given by the GSAs was well received by participants and those reporting higher levels satisfaction with the service were more adherent.

As the majority of the calls to the telephone helpline provided by the GSAs related to side effects of using travoprost, a further potential benefit of the intervention became evident during the course of the study. A GSA telephone service may have a wider benefit to the NHS and patients, not captured in the analysis of this study. Currently patients' experiencing side effects with their eye drops will require further advice from their prescribing clinician at their hospital eye service/glaucoma clinic. Patients will either contact the consultant's secretary directly, or will have to consult their community General Practitioner who subsequently contacts the prescribing consultant on the patients' behalf. The patient may then either be referred to the Hospital Eye Casualty Service for further examination, or the case history reviewed by a clinician or consultant and appropriate advice given. Whatever route the side-effect query is presented, resolution involves a considerable amount of administrative and clinician time. Furthermore, this system can sometimes leave the patient for days without a satisfactory solution to their side-effect query, which is far from adequate. The helpline enabled a one-to-one discussion between the patient and GSA with sufficient knowledge to give immediate advice and reassurance to the patient. The GSA had access to the patients' glaucoma related medical records and could discuss an appropriate course of action with a specialist clinician immediately and organise either a new prescription or emergency appointment if necessary. The potential cost savings and patient satisfaction with a streamlined, 'one-stop' advice line for drop side-effects were not captured in the methodology used for this study, but a wider audit could be undertaken of the potential cost benefits.

More than half of participants in the intervention group asked for further information when they attended their follow-up visits with the GSAs, which may suggest that the intervention should have been expanded to provide another session of tailored information provision at the follow-up appointment at month two and month eight post the initial intervention. A more recent group-based education intervention study also concluded that having two intervention sessions may have enabled important messages to be reinforced and had a greater impact on adherence.[92] A group-based education session would also be an interesting intervention idea to use for future development of the NAGs intervention, enabling an interactive style of learning for patients who prefer this option of self-education.

3.5.7 Study Limitations and strengths

By far the greatest limitation was the TDA data attrition rate as described in Section 3.5.2 which led to 45% of the primary outcome measure being missing. The TDA was therefore a poor method of collecting adherence data.

The NAGS intervention was led by specialist nurses and technicians already working within the hospital eye service which demonstrated the ease with which such an intervention could be incorporated into clinical practice. However, during the study period, ensuring there was no contamination between the GSAs who worked on the study part-time and had received enhanced training in motivational interviewing skills, and also worked in the standard care clinic part-time was more problematic. Every effort was made to ensure that participants did not come into contact with GSAs during their follow-up period, but it was not possible to account for any influences these staff and the study itself had on routine practices of all clinical staff during the study.

Whilst there was no demographic bias in those participants who chose participate compared to those who declined, for variables that were collected (age, gender and IMD), studies of adherence may be intrinsically biased through selection of patients who attend appointments and engage in healthcare; thus non-adherent patients are more likely to be missing from the sample and those agreeing to participate may be more adherent to medication than those who decline.[195] The results of the NAGS study relate to a relatively affluent, primarily white British population prescribed glaucoma mono-therapy, and may not be generalisable to other populations that may have different cultural practices. Mono-therapy is also thought to aid adherence, with more complex regimens being problematic for patients.[14, 42, 143] Thus, caution must be taken when extrapolating the results of adherence studies focused on one particular cohort. Investigating the effect of the NAGS intervention on a population expected to have lower adherence and using multiple topical anti-glaucoma therapies would be of value to understand the needs of different patient populations.

Although the primary outcome measure was the adherence rate reported as a continuous variable, a dichotomised variable was calculated by splitting participants into those who were adherent (≥80%) and non-adherent (<79%). The dichotomised adherence score was used to compare TDA measured adherence with self-report scores and the logistic regression analysis of predictors of non-

adherence. It could be argued that the 80% cut off was an arbitrary figure but further, although convenient to the analysis, that comparison of grouped data causes a loss in the variance of the data which ultimately causes a loss in statistical power and thus was a poor choice of analysis.

Many intervention studies do not fully describe and check the fidelity of the intervention. However, NAGS used Behaviour Change Counselling Template as shown in Figure 3.2 to ensure that all intervention interaction contained the same content and the intervention had been checked for fidelity using the BECCI scale to ensure that the consultation style met expectations and feedback could be given to the individual GSAs to help improve their BCC approach. However, although fidelity was assessed at the start of the study, this was not assessed again in the later stages of the study to ensure that reliability was still evident.

3.5.7.1 Study bias

Using five different GSA's ensured that the intervention design was generalisable and repeatable rather than specific to how one particular 'therapist' carried out the intervention. There were no differences in the number of adherent cases per GSA which confirms that there was not bias in the way that an individual 'therapist' delivered the intervention. However, to improve the fidelity all interaction between GSA's and participants could have been videoed and then reviewed by a MI expert to ensure that all interventions met the required criteria of a BCC intervention.

Hawthorne effects may have occurred in the NAGS study whereby the act of study participation improved motivation and thus increased adherence in both groups.[57, 196] These observational methods often alert patients to the fact that their behaviour is being monitored which can cause a reactivity bias resulting in increased adherence to medication.[57, 197] A more recently published intervention study also found that their control group were highly motivated and had benefited from the rapport established with the researchers.[188] Using a modified consent procedure which avoids the need for researchers to take consent prior to participation would reduce the extra attention that participants receive when they agree to take part in research. Standardisation of instructions given to participants at the time of recruitment may also control for external variances in measured adherence caused by the way information is conveyed and comprehended.

The electronic monitoring used in the present study may also have caused a reactivity bias not identified in previous studies. Adherence measured electronically did not diminish over time as previously reported[57, 197] and the results did not replicate previous theories of the likely reactivity bias time found in observational studies. Either participants in the NAGS study were naturally very adherent, or there may have been a more long term reactivity bias caused by study participation and/or the monitoring effects of the TDA that improved adherence behaviour for the duration of follow-up. These phenomena, often referred to as mere measurement effects, are proposed to cause behavioural changes in intervention studies and are the subject of ongoing debate.[198] However, these phenomena are not well documented and the extent that study participation and reactivity to adherence monitoring may inflate adherence relative to the natural environment is poorly understood.

3.5.8 Summary

Despite the intervention design being grounded in the theory and producing high levels of patient satisfaction, the NAGS study did not demonstrate improved adherence with a behaviour change intervention. The results may indicate that standard care offered by an NHS Glaucoma Clinic was sufficient to promote high adherence with travoprost for the population studied. However, with the majority of participants suggesting that the GSA service helped them to be more confident about using their drops, this model requires further development as a potential intervention to support patients using drops for glaucoma and ocular hypertension. Since the time of conception of the intervention used in this study, a large amount of work has been invested into gathering evidence to identifying the specific domains that explain behaviour change.[142, 199] A hierarchical structured taxonomy of behaviour change techniques has also been developed that can help researchers to report the characteristics of the active contents of interventions with precision and specificity to aid more rigorous reporting of the component parts of the intervention.[141] Undoubtedly with the benefit of advancing knowledge of use of behaviour change techniques and design of interventions, taking a stepwise approach to intervention design and evaluation of this study using these theoretical frameworks in the future could be pursued.

The NAGS study is the first known study to report eight months of follow-up using the TDA. At month two, only 10% of the TDA data was missing, which suggests it was the longevity of the study that lead to the failure of the TDA to gather complete data for the whole eight month period. Whilst the failure of the TDA increased the uncertainty around the adherence estimate, there was no evidence that the failure of the TDA differed between those who were adherent and those who were not, and thus did not bias the results. Thus, whilst electronic monitoring is often acclaimed to be the preferred method of adherence measurement, the NAGS study found that data were difficult to collect for the long monitoring period appropriate for the study of this chronic condition and might be sensitive to study reactivity bias. Clinical outcomes were also found to be unsuitable as proxy measures of adherence in this population and disease and self-reported adherence is unreliable.

No gold-standard method for measuring adherence currently exists and it is likely that the practicalities of data collection will continue to govern what is ultimately chosen as an appropriate measure of adherence for each individual study. Unfortunately, while a standardised and accurate measure for adherence remains undefined, studies will continue to produce heterogeneous adherence results. The NAGS study, used multiple adherence measures and reporting methods which ensured that comparisons could be made with studies of shorter duration and those using differing statistical analyses.

The analysis provided evidence of the potential bias induced by using self-report and electronic tools to measure adherence and the difficulties of using routine data to calculate MPRs, particularly with respect to eye drops within the UK prescribing system. Whilst multiple methods of adherence measurement used in parallel to quantify and classify adherence could maximise precision of adherence estimates and facilitate comparisons between studies, the potential effect that multiple measures of adherence have on patient behaviour is unknown. Potentially, the multiple measures of adherence used in the NAGS study may have had an effect on participant's behaviour. When research assessment prepares people to be more receptive to the intervention than would be the case if not participating in research this may either strengthen or weaken the observed intervention effects.[102, 103, 196] Further research was required to establish the extent of study participation and reactivity to assessment effects in this study. Thus, a follow-up

study was designed to explore the research user and provider perspective of the trial conduct and intervention.

Chapter 4. Exploring user experiences of the NAGS study

4.1 Introduction

The Norwich Adherence Glaucoma Study (NAGS) used an MI intervention in an attempt to improve adherence to glaucoma medication. In addition, an objective measure of adherence, the TDA, measured the primary outcome of adherence to medication. At the time of the study concept, design and implementation (2007), both MI and the TDA were novel approaches in glaucoma adherence research.

As NAGS was also the first RCT to use an MI approach to improve adherence to glaucoma medication it was important to gain a better understanding of the experiences of research participants and service providers. Thus, a qualitative research study was designed to explore two distinct areas of investigation; (1) areas of study conduct, training procedures, informed consent procedures together with an understanding of how the study was received by participants in order to assess the acceptability of the study methodology and, (2) gain a better appreciation of patient experiences of both the intervention and study design.

The gathering and analysing of qualitative data relies upon the researcher engaging with individual's experiences, stories and language and interpreting the meaning behind the accounts. The collection of data requires the researcher to find rapport with the participant(s) and interpretation of the data can be affected by researchers own experiences, involvement in the research and agenda. However, as the main researcher and responsible for the interpretation of the data, it is important and relevant to emphasise that I was also the principal researcher for the NAGS study and thus heavily involved in the design and implementation of NAGS and therefore had my own pre-existing opinions and expectations of the study findings.

4.2 Method

4.2.1 Aims and objectives

The aim of the User study was to gain an understanding of user experiences in NAGS with respect to study conduct and the impact of the intervention used in the study. The objectives were to:

- explore participant experiences of the intervention used in NAGS
- understand patient experiences of standard glaucoma care to enable a comparison to be made with the intervention used in NAGS
- explore participant experience of the study and related issues, such as informed consent, randomisation, use of the TDA and questionnaires
- explore GSA experiences of facilitating the study and delivering the intervention.

4.2.2 Rationale for using a qualitative approach

Qualitative research is broadly defined as "any kind of research that produces findings not arrived at by means of statistical procedures or other means of quantification."[200] Unlike quantitative research that seeks to determine causation, prediction and generalisation of findings, a qualitative research method allows for the exploration of meanings and concepts.[201] Whilst there is no single accepted way of carrying out qualitative research, it is often determined by the purpose and goals of the research, the participants, funding and position of the researchers themselves.[202] Qualitative methods can collect thoughts, opinions and feelings and draw together a deeper understanding of more complex processes that quantitative research cannot detail. Qualitative research instruments used for data collection include questionnaires, interviews and focus groups, observation and analysis of documents. Three instruments were considered for use in the User qualitative study; questionnaires, interviews and focus groups.

Questionnaires can gather large amounts of information from numerous people very quickly and cost-effectively. Furthermore, analysis of questionnaire data can be analysed more 'scientifically' than other forms of interviews. However, questionnaires may not be an adequate method for collecting information about emotions, behaviour and feelings; whereas face-to-face interactions enable

questions to be asked sensitively and in response to information provided by the respondents. During face-to-face interviews, interviewers can judge how truthful respondents are being and if the questions are being interpreted correctly. Thus, face-to-face interviews are often used if sensitive information needs to be discussed that requires heightened confidentiality or, when a deeper level of thought is required, which affords the respondent more time to explore their feelings with the researcher. However, focus groups help researchers to understand as much as possible about an issue among a group of people chosen to represent a larger cohort. Data are generated by interactions between group participants which is more naturalistic than interviews since individuals rarely make decisions on their own, but are guided and influenced by those around them.[202] Focus groups, therefore, attempt to mimic real-life interactions enabling participants to present their own views and opinions based on their own experiences but on reflection and in the context of other people's points of view. Furthermore, in focus groups, participants can ask questions of each other, seek clarification and prompt others to reveal more as discussions progress which enables the individual responses to become sharpened and refined. Focus groups can be synergistic in the sense that the group works together to generate data and insights.[202] Arranging focus group meetings is more problematic than one-to-one interviews since scheduling a time and venue to meet requires group agreement from numerous people.

For the follow-up User study, the use of focus groups involving NAGS participants together with study professionals, was felt to be the most appropriate qualitative method to utilise. In particular it was felt that a focus group study would best facilitate understanding participants' experiences of the intervention, their involvement in the study process and their behaviour during NAGS.

4.2.3 Setting, participants and recruitment

The User study recruited participants from NAGS at NNUH. The results of NAGS had not been analysed or reported at the time of undertaking the focus groups. Three focus groups were conducted in a local and accessible conferencing facility in September 2011.

The final 30 participants recruited into NAGS were informed that they would have the opportunity of taking part in a focus group to discuss their research project experiences to be held at the end of NAGS. Participants were asked to tick a respective box when consenting for NAGS to indicate if they would be interested in taking part in a focus group. Upon completion of NAGS, participants who registered their interest in joining a focus group were contacted by the researcher and asked if they were still willing to participate in a planned focus group.

For each participant who verbally consented to participation, an information sheet, consent form and covering letter were sent with a reply envelope. Potential participants for the User study were contacted the following week to ensure that they had received the information and to answer any further questions; the time and location of the focus groups were discussed and formalised.

A separate focus group was planned for the GSAs. Four GSAs were invited to take part in the focus group, but were under no obligation to take part. I was the fifth GSA and too involved in the design and implementation of NAGS and also analysed the focus group findings and therefore could not take part in the focus group. The GSAs were aware that I would be analysing the transcripts from the focus group and this may have influenced the discussion of NAGS between the GSAs, but there were encouraged to speak openly as no judgement was being made of their roles or thoughts about the processes.

4.2.4 Ethical and Research Governance Approvals

The User study received ethical approval from the Norfolk Research Ethics Committee (appendix 8), and research governance approval from Norfolk and Waveney Research Governance Committee (appendix 9).

4.2.6 Organisation of Focus Groups

All the focus group meetings were run by a moderator and an assistant moderator. The moderators were both PhD students trained in focus group methodology skills and independent of NAGS, so that they were unknown to the participants and un-aware of any potential problems or patient experiences that occurred during the study.

The discussions for each focus group meeting were expected to last one hour. Tea, coffee and light refreshments were served at each meeting and travel expenses were paid.

A discussion guide was tailored to each focus group and an example is shown in Figure 4.1.

1. What was the experience of being asked to take part in the study?
   - What was your motivation to participate?
   - Was it easy to take part?
   - Was the study explained properly?
   - Did you have enough time to consider taking part?
   - What did you think about the study paperwork?

2. How did you feel about being randomly put into either receiving more information or remaining in the control group?

3. Usual care
   Experiences of first appointment with clinician
   Setting and duration of that appointment

4. Intervention experiences (intervention group only)
   - What is your experience of your first appointment with the Glaucoma Support Assistants?
   - Setting and duration of that appointment?

5. Do you think the information or the way it was given to you could have been improved upon?

6. Do you think the GSAs are the best type of person to give you this information?
   - Do you think the timing of the information was appropriate?

7. What were your thoughts and experiences about using the dosing aid?

8. What did you think about the telephone helpline service?

9. What do you think was the most useful part of the study?

10. What was the most difficult part of the study?

11. What were your thoughts about the questionnaires?
    - How did you feel about answering the questions?

12. Are there any other changes you make to the study or information given?

13. Would you recommend this service for all new glaucoma patients?

Figure 4.1 Interview guide for participants completing NAGS

4.2.7 Analysis

The focus groups meetings were digitally audio recorded and transcribed into a script by an independent transcriber prior to analysis.

In most qualitative analyses, the data are preserved in their textual form and 'indexed' to develop analytical categories and theoretical explanations.[203] Analytical category data can be obtained either gradually or deductively. Gradual extraction of data is derived inductively, as in 'grounded theory', where hypotheses are developed as they emerge from the data. Deductive extraction of data utilises a top down approach, either at the beginning or part way through the data, as in a 'framework approach'.

Using grounded theory entails familiarisation with the data and defining the hypotheses from emerging themes that may centre on particular phrases, incidents or types of behaviour. Interesting or unfamiliar terms used can also form the basis of analytical categories.[204] Constant comparison is used to examine data relevant to each category which requires a coherent and systematic approach adding in as many nuances in the data as possible. Once collected, the data is indexed into the theoretical ideas developed during the research before the key themes are selected.

Whilst analysis using grounded theory is a lengthy process, framework analysis is more structured and the analytical process more explicit.[205] Framework analysis involves examination of the reasons for, or causes of, what exists from participant experiences and making these coherent, whilst retaining a hold of the original accounts and observations from which conclusions are derived. The framework approach has been successfully used in a range of different study types; in particular, in applied policy research where studies work to a short time scale, where objectives are shaped by specific information requirements in an aim to form a greater understanding of issues. Although the User study to explore participant and GSA experiences of NAGS was not as stringent in its aims as studies examining applied policy, answers to predetermined questions were sought. It was considered, therefore, that a framework approach could neatly examine these predetermined objectives whilst accommodating any new ideas or theory that might need to be explored.

Five distinct steps in a framework approach have been developed over the years by the specialist qualitative research body, Social and Community Planning Research [202, 206] and there were followed in the User study analysis:

1. Familiarisation of the data was achieved by reading the transcript and listening to original audio recording. Gaining a feel for the material as a whole identifying key ideas and recurrent themes.
2. Identification of a thematic framework was created by developing a list of possible topics, which was refined and sorted to develop themes based on the range of responses and issues reoccurring from the data. The framework was a mix of the emergent themes, those derived from the research question and from the aims that were incorporated into the interview guide.
3. The thematic framework was used to perform 'topic coding'[207] to annotate and label chunks of data judged to belong together so that collective data extracts could be further analysed. The thematic framework was applied systematically to transcripts with short text descriptors to elaborate the index heading
4. Charting enabled the data extracts to be refined into summaries of views and experiences and new labels applied to the data where necessary, a stage that required a considerable amount of abstraction and synthesis.
5. Mapping and interpretation was carried out using the charts to define concepts, map the range and nature of phenomena and find associations between themes with a view to providing explanations, influenced by the original research objectives as well as by the themes that emerged from the data.

A précis for each participant in the User study and each subtheme was written to aid the interpretative stage of the analysis this being a specific analytical step included in framework analysis.

4.2.7.1 Computer software

Qualitative research typically produces large amounts of data. Computer packages can improve the efficiency of qualitative data management[208] by providing a way of storing and retrieving cases, statements, phrases or words, and thereby replacing the time-consuming process of manual coding. However, the use of computer packages, are also claimed to distance the analyst from the data,[208] since they can take the place of the close and careful analysis that is required to enable the researcher to become immersed in the data. Thus, whilst

computer packages can help with the intensive process of analysis and management of the data they are not a substitute for the process of 'immersion' which is essential for the researcher to achieve the thorough knowledge of the data in order to make comparisons, identify patterns and develop interpretations.[205] It could be argued that the time and effort taken to learn how to use the computer programme, could be better spent processing the data manually and therefore absorbing oneself in the richness of the data.

During the analysis process it is often necessary for the researcher to change the labels appointed to categories as the data emerges and evolves. However, computer programmes can be labor intensive when reformatting the labels appointed to categories resulting in a reluctance from the researcher to change the category labels mid-analysis[209] thus losing the natural ability to form and mold categories appropriately.

Furthermore, as computer programmes can place greater emphasis on the quantitative analysis of transcripts, such as how many people said what words or phrases, more weight may be placed on the frequency of events whilst ignoring isolated incidences[210] which are still an important aspect of theme creation.

There are different packages available such as Ethnograph, Atlas and QSR NVIVO, but computer packages were not used to conduct the analysis of the User study. Instead the data collected for the User study was organised using Microsoft Word to cut and paste themes and facilitate data searching using the 'Find' function. Although considered somewhat old fashioned and laborious, the chosen method ensured that the researcher developed an intimate knowledge of the data.

4.2.5 Sampling

Statistical representativeness is not a requirement for qualitative research and is not normally sought. Instead, the aim of qualitative research is to identify specified groups of people who hold characteristics or live in circumstances relevant to the phenomena being studied in order to enrich the exploration of attitudes and aspects of behaviour relevant to the research. A homogenous group enables the researcher to demonstrate that the group studied is representative of the wider population which shares that common characteristic.[211] Therefore, a convenience sampling method was used to select 16 NAGS participants to take part in two

participant focus groups with a mix of both control and intervention participants in each group.

4.2.8 Validity

Although some may argue that the term validity is not applicable to qualitative research, most would agree that there is a need to measure quality, rigor and trustworthiness. As such, patient experiences were presented using excerpts from their interviews and the portrayal was made "truthful" as statements and descriptions were provided through use of the patient's own words.[202] Participants were selected from the final 30 NAGS participants, their shared experience should have been conceptually generalisable to all participants of NAGS, however as fidelity had only been assessed at the initial stages of NAGS, the reliability of the intervention remaining at the same conformity could not be assured.

4.2.8.1 Triangulation

Triangulation is any method used to give credibility and confidence in the conclusions drawn from a study. By using triangulation the researcher may use multiple methods, sources, researchers or theories to strengthen their evidence. There are two main types of triangulation, 'triangulation of sources' which involves checking the consistency of different data sources within the same method or, 'analyst triangulation', which is achieved by two or more persons independently analysing the same qualitative data and comparing their findings.[75]

Studies in health care have used triangulation of sources as a method of verification when studying the accounts of doctors, patients and managers in order to identify similarities and differences in views[210] and the different views have contributed significantly to the credibility of the findings. The User study aimed to triangulate sources by collecting the views of both the GSAs and participants from NAGS thus enabling experiences to be compared and contrasted from different viewpoints. In the User study 'Analyst triangulation' was more difficult to achieve as the researcher was working on the project in isolation. However, the final analysis was reviewed by the same independent researcher who had moderated the focus groups and together with a research supervisor to check for consistency in the transcripts and resulting themes.

4.3 Findings

The number of NAGS participants agreeing to take part in the focus group was lower than expected which meant that participants representative of different age, gender and control/intervention arms could not be selected. Rather a sample of the 16 participants who had consented to participate (8 from the control arm and 8 from the intervention arm) were recruited into two different focus groups, one group that took place in the morning and one in the evening based upon availability of the participant.

The characteristics of both focus groups are displayed in Table 4.1. There were equal numbers of control and intervention arm participants but these were not evenly distributed between the two groups. Eight participants were organised to attend Group-1 and seven in Group-2. Two female participants had consented to participate but were unexpectedly absent on the evening of the Group-2 meeting, resulting in a male dominated evening focus group.

Table 4.1 Participant demographics

	Total n=13	**Group 1 (morning) n=8**	**Group 2 (evening) n=5**
Male No. (%)	8 (62)	4 (50)	4 (80)
Control arm No. (%)	7 (54)	6 (75)	1 (20)

The final group was organised for GSAs alone and is discussed in Section 4.3.6.

4.3.1 Summary of analysis

The themes summarised in Figure 4.2 were applied to the data and were brought together under three main headings; (1) experiences of study participation, (2) patient experiences of control and intervention groups, (3) participant experiences of standard care and issues faced by patients with glaucoma. Only interpretation of the themes felt relevant to the aims and objectives of the User study have been reported in this chapter.

Study participation

Questionnaires

- Participants did not like the questionnaires as they felt ambiguous and irrelevant to eye condition in question
- Generally some participants felt sceptical towards the use of questionnaires

Recruitment and Randomisation

- Participants had received enough information about the study
- Participants had no concerns about the method used in the study
- GSAs made time for participants to ask questions which participants appreciated
- Participants were very happy to have taken part in the study
- Participants felt they were given sufficient time to decide whether to participate or not

Travalert Dosing Aid

- The TDA was large enough that it reminded participants to use their drops
- The TDA was easier to use than a drop bottle alone
- Participants were aware that it monitored adherence and reported modification of their behaviour accordingly
- Some participants thought that the TDA was the intervention rather than the education session; participants in the control group reported that they had received 'the intervention' because they had used a TDA.

Differences between control and intervention groups

Intervention group

- Participants found it reassuring being the intervention group and the GSA's were supportive
- The telephone helpline was useful particularly for advice if side effects occurred
- A tailored approach led to different experiences of the intervention

Control group

- Felt disappointed because they were not in the intervention group
- Participants sought further information as standard care information was not sufficient

Future recommendations

- Participants wanted more information about their own individual prognosis
- Information should be specific to each patient and not generalised
- The intervention should be made available to everyone to help support all patients, particularly important as glaucoma is asymptomatic

Figure 4.2 Summary of themes applied to the data part 1

Experiences of standard care and issues faced by patients with glaucoma

Informing family

- Patients with glaucoma must be told to inform members of their family and particularly their children

Driving and the DVLA

- Driving is essential for most people particularly in rural parts of Norfolk
- Drivers don't appear to be aware of their obligation to tell the DVLA if they have a medical condition
- Patients feel unsure about when they should report ocular hypertension or glaucoma to the DVLA
- Patients felt that clinicians have a duty to advise them about criteria for driving and reporting to the DVLA

Eye drops

- Patients don't like using eye drops just before driving
- It is difficult to see in the bottle to know when it is about to run out
- Easy to fall asleep before using them in the evening

Communication at Eye Clinic Appointments

- Doctors with poor communication / poor spoken English lead to lack of confidence in treatment plans
- Patients feel uncomfortable about asking questions
- Information is not offered you have to ask for it

Eye Clinic Appointments

- Long wait between tests at each eye clinic appointment which makes attending appointments difficult because of the length of time it takes
- Patients do not like seeing a different doctor at each visit, as it feels like there is no continuity in care
- Appointments are impersonal and feels like being on a production line
- Nurses need to take more time to explain why each test is being carried out

Standard Care Information

- Not enough information given about why eye drops are used and individual prognosis
- Diagnosis not clearly explained
- Photocopied leaflets are poor quality and diagrams are meaningless
- Patients would like opportunity to discuss eye problems in more detail
- Experiences of side effects are common

Figure 4.2 Summary of themes applied to the data part 2

4.3.2 Experiences of study participation

Overall, participants felt that taking part in NAGS was a positive experience and were happy to have participated. Participants were pleased that this topic area was being investigated and thought the study was a good idea.

> *"I had a good experience"* ***(F7, female, group-2, intervention arm)***

> *"I thought it was a good idea and if it helped in the long term, other people, then I am happy to participate"* ***(M3, male, group-2, control arm)***

> *"Yeah I was glad they were showing an interest."* ***(F2, female, group-2, control arm)***

4.3.2.1 Recruitment and randomisation

The information provided to the participants about NAGS was sufficient and helped them decide whether to participate or not. Good ethical practice dictates that participants should have enough time to decide if they would like to take part in research. The design of NAGS required that participants consented to take part before leaving the Eye Clinic on the day that treatment with travoprost eye drops was initiated. Whilst the NAGS method gave rise to ethical concerns about patients having adequate time to consider their participation, no such concerns were shared by any of the participants. Coming to a decision was felt to be easy as participation in the study held no significant risk to them. Participants also agreed that it was made clear that they had the option to withdraw from the study at any stage if they wanted to.

> *"I don't recall who recruited me in the first place but certainly I received all the information that I felt I needed..."* ***(M9, male, group-1, intervention arm)***

> *"I felt that [name of GSA] was very good, took us to one side and explained the whole thing. I think I was the last one to leave the clinic but she still had time for me. I felt she was very good."* ***(F5, female, group-2, control arm)***

"There seemed to be a lot of positive reasons why we should, rather than just one or two. I mean one or two would have done it for me" ***(M1, male, group-2, intervention arm)***

"I always had the option to come out" ***(M7, male, group-2, intervention arm)***

Participants from the control group discussed how taking part in NAGS itself had encouraged them to use their eye drops and interaction with the study staff had had a positive influence. The informed consent process had also provided all participants with more information and support than 'standard-care patients'. Furthermore, study information was reinforced at several time points throughout the study when attending follow-up appointments and completing questionnaires.

"That we have had this information reinforces us to take the drops… Because you know we have had more information than you know perhaps a lot of people would have had and it is probably good for the longer term." ***(M3, male, group-2, control arm)***

...but as far as the work that's been done here, as far as I'm concerned, I mean although I've only been on the control group but as I say, I found everybody absolutely great, you know, everybody's been very approachable, you know, they've always asked whether there's anything else they can do, you know. ***(M11, male, group-1, control arm)***

…we don't know what it would have been like if the study hadn't have been in the background and feeding us information, but we can only assume that more information we get is the better and at several times, so it is reinforced. ***(M3, male, group-2, control arm).***

4.3.2.2 Using the TDA

Generally, the TDA was well accepted by all participants as a good method to apply eye drops.

I find it really help that gadget with the bottle ***(M8, male, group-2, control arm)***

I would like to second that, I find that also ***(M3, male, group-2, control arm)***

Yeah I do ***(F7, female, group-2, intervention arm)***

Because you click it down once and it just gives a drop out ***(M8, male, group-2, control arm)***

*I've never tried it without the sort of frame that you put over your eye and I also use that with the other bottle which is not in a dispenser or anything like that and I find it works very well and I'd like to know where you can get those if I have any sort of accident with the one I've got…****(M13, male, group-1, intervention arm)***

However, there were a couple of participants who had difficulty using the TDA.

I couldn't it use it very well, I wasn't sure if it clicked or not so I just started putting them in ordinarily. ***(F5, female, group-2, control arm)***

Despite the fact it has got a guide on it, you still miss the eye. ***(M1, male, group-2, intervention arm)***

The TDA helped participants to remember to use their eye drops because the dispenser was larger than a normal bottle.

That's another point, because it is so large, I have mine every morning, you know, Duotrav I think it is, it is sitting by the edge of the bed and I wouldn't normally remember to take the drops but the fact that it is sitting there, you know, visibly, I usually think, yes, I haven't done that and pick it up. ***(M3, male, group-2, control arm)***

One of the participants had to change the type of eye drops he was using during the course of the study which meant he also had to stop using the TDA because it was not compatible with the shape of the new eye bottle. In comparison he found it was more difficult to remember to use his drops without the use of the TDA.

I agree with this gentleman [M3] because it was like there, in a box big enough, it just reminded you to do it… and I just found it easier because,

when I came off that and I went onto other stuff which wasn't in a dispenser, it was just in a little bottle, sometimes I had to take those twice a day, and sometimes I would forget the first one and I would take two that were closer together than more spaced out. So I just found it easier because it was visible really. ***(M4, male, group-2, control arm)***

4.3.2.3 Monitoring adherence with the TDA

Participants were aware that their eye drop usage was being monitored by the TDA during the study. The participants felt comfortable agreeing to the study knowing that the intention was to monitor their adherence but discussed how this increased the attention they paid to use of their eye drops and how this changed their behaviour.

But I wasn't bothered about whether it was being, my usage was being recorded, no, that didn't bother me. ***(M4, male, group-2, control arm)***

Yes, I mean I joked about it being like Big Brother, keep an eye on what I was doing [laughter from group], no pun intended,… ***(F2, female, group-2, control arm)***

I was worried the other way. If I missed I would do it again. If I pressed it and nothing happened I would do it again and I was worried it would register too many clicks. ***(M1, male, group-2, intervention arm)***

One participant described how he had kept also kept a daily record of the number of drops he had used the device and the system he used for scoring this.

I've kept a record, a daily record in fact of both the times, the number of drops and what I've used, the term 'hit' every time I've pressed the device. ***(M9, male, focus group 1, intervention group)***

4.3.2.4 Questionnaires

Participants did not like the questionnaires that had to be completed at home after each study visit. Some participants felt that the questionnaires were biased

towards researcher opinion and that participants might not answer accurately because they would not want to be too critical.

> *Well, my first thought with this questionnaire, as with every questionnaire I've ever seen in my life about any subject, [sigh] is that really the right question or what exactly does it mean or, you know, there's some ambiguity, this sort of thing…**(M12, male, group-1, intervention arm)***
>
> *Some of the questions I thought well are they relevant but then perhaps they're more relevant to other people.**(F10, female, group-1, intervention arm)***
>
> *I find questionnaires very easy to fill in… So I just, you know, it is usually like, very good, good, not good, you know, it is just, it is just, I don't think they are very accurate. **(M4, male, group-2, control arm)***
>
> *The questions are always slanted to the direction they want the answers. (**M1, male, group-2, intervention arm)***
>
> *I don't think questionnaires are that accurate because you don't really want to put anything bad unless it really is a bad service or so, you tend to put its either you know, whatever the best answer or the second best answer is, I stick on the nose.**(M4, male, group-2, control arm)***
>
> *Well you right can't judge what is very good or good because everybody's going to have a slightly different standard anyway. But I rarely put very good because, as you've just said I think they are very inaccurate measurements. I don't think I have ever said anything was bad because it wasn't in my particular case. **(F6, female, group-2, control arm)***
>
> *But will people answer it honestly. I don't know. **(F2, female, group-2, control arm)***

Participants also felt that the questions about eye drops affecting their sex life and drinking alcohol seemed irrelevant and became a source of amusement during the focus group discussion. Some participants stated that they did not answer those questions or that they added additional comments on the questionnaire. If participants felt that the questionnaires asked irrelevant and "silly" questions then

this may have affected participant attitudes to answer the questionnaire fully and with honesty.

Extract of conversation:

1. *I think some of the questions were very irrelevant…to the actual condition that we had, which amused me rather slightly… how does it affect your sex life? And I thought 'Good god'…it was on my questionnaire and I thought, that is a peculiar thing to ask when you have got glaucoma! Or haven't got glaucoma!* **(F6, female, group-2, control arm)**
2. *Don't go down that road* **(M8, male, group-2, control arm)**
3. *Well that is what I meant, it was a silly question!* **(F6, female, group-2, control arm)**
4. *Absolutely, I got my wife to fill that in!* **(M8, male, group-2, control arm)**
5. *Irrelevant* **(F6, female, group-2, control arm)**

4.3.3 Participant experiences of control and intervention arms

Both focus groups had evidence of confusion about the differences between the intervention and control arms. All participants had been given a TDA to measure their adherence to eye drops and participants were made aware of this at the time of consent. However, during discussions it became apparent that participants believed that they might only have received the TDA if they had been in the intervention group. In the first focus group, a participant from the control group began to question into which arm of the study he had been randomised and started to believe that he must have been the intervention arm because he had been using a TDA.

Similarly in the second focus group, a participant who had been in the intervention group, had not been aware that both control and intervention arms received the TDA. He discussed how he had thought the TDA was the intervention that made his care different to the control group. On learning that everybody received a TDA, he began to question into which group he had been recruited. He also explained that his clinician had changed his glaucoma diagnosis and the drops he was using during the time he was taking part in NAGS, and therefore he believed that if he

had been in the intervention group, surely these changes would have been discussed with him more thoroughly.

> *Can we come back to the patient in the control and intervention group? You know some people were saying about discussing all the notes from the consultants, would that happen with either group or just the intervention group… Well, why I'm asking this is because it's bringing up in my mind the point of this control and intervention and from the discussion round here I think possibly some of the problems and questions that we had would have been covered by the intervention group and not covered by the control group so that one or two of us, I mean this question I mentioned of mine with the changing of drops and them not working and have I got glaucoma or not got glaucoma, that could have been brought up in the intervention group…**(M12, male, group-1, intervention arm)***

4.3.3.1 Control group participant experiences

Some participants felt disappointed when they were randomised to the control group, but understood that it was for the benefit of the study. Control group participants were concerned that they would not be receiving the necessary information that would have been of benefit to them. However, most disappointed participants felt reassured by knowing they would receive further information at the end study if required. .

> *I was in the control group and I must admit I was a bit disappointed, I must admit that was my first reaction but then I thought well, you know this is what you have to do with research to make it, that's the way you have to conduct research. And I can find out information and if I wait a bit longer until the end of the study, I will get this information that they think will be appropriate. But yeah, the first initial gut feeling was arrrgghhhh. **(F2, female, group-2, control arm)***

> *I mean I certainly felt I could have benefited from more information than I had but I was in the control group so I accepted it, I could understand the reasons for that. **(M11, male, group-1, control arm)***

> *You see I was on the control group. I sometimes didn't feel I was getting enough information ……and there were a few other things that I wish I had*

been told and I thought I might have been told but obviously if I'd been in the intervention group I probably would have been told those things.... ***(M11, male, group-1, control arm)***

Some control participants described undertaking their own research to gain the further information they required but found that information researched could be conflicting. Control arm participants perceived that the information the intervention arm received was more likely to be reliable.

*But yeah, there is so much information out there and sometimes you would read one thing and then you would read another thing that conflicts and I thought well, may be the people who are in the intervention group will get something that is a bit more appropriate and reliable. But, yeah, there is a lot of information out there.****(F2, female, group-2, control arm)***

*Yeah me to. You know, directly I was diagnosed, I looked it up on the internet, what glaucoma was anyway, so you know, there is just as much information on the internet as what there was given in your leaflets.****(M8, male, group-2, control arm)***

4.3.3.2 The Intervention

The intervention was felt to be very useful as a support mechanism and provision of information. It appeared that the intervention also offered reassurance to participants should additional help and support have been required.

And again the point, sorry, the point I made earlier, to me it was a tremendous reassurance, this was something new, that I was with this group, the group was here and they were a hotline as well. So that to me was a very valuable feeling… That's right and certainly in terms of the treatment and the use of the eye drops and the side effects of the eye drops, things that could happen, all of that was explained by your team and the best way to use them, how to use them, techniques for using them and so forth, all that was sort of fabulous, fantastic … ***(M12, male, group-1, intervention arm)***

I got given information from X [GSA] and I must admit, I got given loads, absolutely loads and loads of information and several more booklets than you got…but I found her very good and I found it quite reassuring to have that backup there, but I felt I had loads of information and I felt if I needed more information I could either get it myself or I could ask them and they would get it for me. ...and I found it really useful, really helpful and I found them really informative with the information they gave out. ***(F10, female, group-1, intervention arm)***

Although trying to deliver a standardised intervention, the BCC method utilised was also designed to tailor information to an individual participant. Evidence suggested that a patient-centred approach led to a wide range of experiences.

I think obviously we've all had different experiences and I think it probably needs to be a bit more consistent but I had a very good experience but you didn't have quite so good an experience [referring to M13]. ***(F10, female, group-1, intervention arm)***

I'm a bit envious of these people who have got all this extra information ***(M13, male, group-1, intervention arm)***

Here, the participant felt aggrieved when they learnt that others might have received more information and support than they had, which suggested that patients were keen to receive as much information as possible and that this should be standardised in some way rather than be patient-led. In addition to good initial education, participants confirmed that they required on-going information about their diagnosis, prognosis, treatment side effects and emerging longer-term educational needs if they had arisen.

And it would be nice to have more information on the prognosis, you know, what does one expect? I mean I was told last time that it should stay the same if I keep taking the eye drops and that I will have to take them for probably the next twenty years before they look at changing them or, you know, removing them, by which time I shall be 85ish so I shan't be so concerned perhaps then as I am now! ***(M13, male, group-1, intervention)***

So as I've said previously, the interview that you had with the doctor, doesn't provide too much information and the remarks are somewhat staccato, i.e. they spend time taking notes or attempting to take notes whilst he was speaking, but it was unsuccessful. ***(M9, male, group-1, intervention arm)***

Despite being in the intervention arm and having seen a clinician at least three times during the course of the study, participants still appeared to have unanswered questions about their glaucoma which obviously had not been addressed by their clinician and participants had not felt empowered to ask.

4.3.3.2.1 Telephone helpline

The telephone helpline was reported to have been used by participants when suffering with side effects of using eye drops and not for other enquiries.

I did see [a GSA] and speak to [a GSA] quite a bit because when I was first diagnosed, the next day I was going on a three week holiday abroad and I read all the side effects and I was quite frightened because nobody at the time tells you any of the side effects about the travatan so I wouldn't take it for three weeks whilst I was on holiday in case something happened. ***(F7, female, group-2, intervention arm)***

*I had problems initially with the drops and the attachment that you put on…in fact it finished up with my wife putting most of the drops in and she still does but I've got to keep persevering. [The GSA's] certainly explained various techniques for doing this which were a help, like supporting here and so forth, so they gave all the help there and also I did this comfort thing in the eye, they were talking about the liqui-tears and things I can get to help that, so they were very very helpful there…****(M12, male, group-1, intervention arm)***

However, participants did find it reassuring to know that a telephone helpline was available.

*Ah yes, as far as the tests go and being in the intervention group, one of the things which, how can I put it, reassured me was the fact that they were there. If I had a problem I could ring [GSA] or any other colleagues at any time and they were there as a back-up help if I'd got particular problems…**(M12, male, group-1, intervention arm)***

4.3.4 Experiences of standard care

Some participants felt as though they were on a conveyer belt when attending routine appointments for their glaucoma care. The over-demand for clinic appointments in the NNUH Eye Clinic can cause long waiting times, but most patients appeared to continue being tolerant of this service on the basis that their eye sight was precious to them.

Some clinicians were reported as being very approachable, giving clear information, whereas others needed to improve their introduction, learn to speak clearly, explain treatments and reasons for prescribing treatment to ensure that patients' questions would be answered resulting in greater confidence in decisions suggested by clinicians. It was felt that improved communication would help patients overcome their anxieties about seeing a different clinician at each visit and concerns over lacking continuity of care.

Patients have a need for good information provision and in some instances this would appear to have been lacking. It was reported that the information leaflets provided from the clinic were not of adequate quality and needed to be printed in colour to be of use to the patient. It was suggested that certain patients could be given more information about the complexities of diagnosing glaucoma, particularly when they are a suspect for glaucoma rather than having manifest glaucoma; a better explanation might help patients understand why they sometimes receive conflicting information from clinicians.

Participants also discussed issues with respect to driving and reporting their eye condition to the DVLA. The issues pertaining to driving appeared highly emotive, which is not surprising given the consequences on patients' standard of everyday living if informed that they should not drive. Participants described the conflicting advice given by clinicians or the fact that no advice was given at all with respect to

the legality of driving. Several participants reported the difficulties in trying to communicate directly with the DVLA. The current DVLA administrative system was described as being difficult to navigate in order to obtain information, this making an already a stressful situation even more frustrating and worrying. It was clear that better communication was required but it was not clear as to whether this should have been provided directly to drivers by the DVLA as the regulating body, or if clinicians should have a clearer role within this process. Clinicians may not feel it is their place to become involved in the process of such regulatory affairs, but from the patients' perspective, many of who are naïve to their obligation as drivers to report all medical conditions to the DVLA, it was felt that clinicians should be the source of such advice.

4.3.5 Future intervention recommendations

Many participants felt that the intervention should be made available to all patients in the future considering it worthwhile to give people more support when using eye drops. Participants agreed that preventative medicine is very important to healthcare in general, but particularly for conditions such as glaucoma being asymptomatic in its early stages.

> *I think it probably would be a good idea to continue giving that extra support to people with glaucoma because as you said, it is a disease that doesn't really have any obvious symptoms so it is not like a lot of diseases where you take you medication and you see instant results, so I think it is probably something that you know, an area where it is worth giving people more support to take their drops.* ***(F2, female, group-2, control arm)***

Some participants felt that it would be easy for certain patients to ignore their glaucoma diagnosis; it was considered that the role of the GSA could be important to ensure that such patients understand the need to use their eye drops.

> *It is something that most people tend to ignore as well isn't it? I mean, I am a typical man… Tend to be laid back, so having this, not so much support, someone drumming it into me, you know, if you don't follow the procedures and use the drops, you are going to get tunnel vision. And it never even entered my conscious thinking that this might happen to me.*

Well, things like that happen to other people don't they? ***(M1, male, group-2, intervention arm)***

Yeah, looking back a question one can ask oneself is if we hadn't been in this group how do we think we would have got on? You know, would we have worried about this? Would we have had understood this? Would we have understood that? And the chances are that somewhere along the line we might have gone adrift. I mean X said 'oh, I can't be bothered to take my drops today' or whatever, you know, this sort of thing, how important is it because I don't recall actually getting that information from anywhere else other than this group. ***(M12, male, group-1, intervention arm)***

Most participants felt that if adequate information was provided and future prognosis explained, adherence to eye drops would be high, since few would knowingly risk losing their eye sight. Focus group analysis suggested that future development of an intervention would need to concentre on two different components. The first component should provide basic reliable information about glaucoma and the use of eye drops in a consistent and accessible format for patients. Patients may require access to this information at different time points during their glaucoma care pathway based upon personal circumstances, forgetting information previously provided, when there is a worsening of their glaucoma condition or when experiencing side effects to treatment. Patients need choice in where they might access information, either from their clinician, information leaflets or the internet and this is likely to be determined by the urgency for which the information is required. For example, if there were to be a sudden onset of a side effect, a telephone call may be made to the GP or hospital consultant. In less urgent cases, patients may wait until their next review appointment, or may search for information on the internet. The second component should relate to the patient-centred support that can provide specific information about diagnosis and prognosis over a life-time of living with glaucoma. It was considered that should all this information be provided adequately, adherence to eye drops would be certain.

Whilst provision of adequate information might overcome barriers caused by intentional non-adherence, un-intentional non-adherence was not discussed by

focus group participants, and only a couple of participants suggested that they may occasionally forget to use their eye drops.

> *I mean it's just occasionally I fall asleep before I've put the second lot in but then I wake up at 1 o'clock in the morning and think oh gosh, I'd better put those in quick!* ***(M13, male, group-1, intervention arm)***

It is clear that participants require information about glaucoma and their eye drops, but furthermore, they require more information about their diagnosis and prognosis; this aspect of information provision was not assessed by NAGS and so no recommendations could be made. However, the focus groups revealed that this was of great concern to individuals and should be an area of focus for the development of future interventions.

It would appear that due to the nature and complexity of glaucoma, providing diagnostic and management related information ideally needs to be provided using a patient centred approach, which can tailor information to an individual patient diagnosis in order to implement individual treatment plans and provide a potentially changing diagnosis over time. The decision as to who is best positioned to provide patient-centred glaucoma information also requires further investigation.

4.3.6 Glaucoma Support Assistants

The GSAs were well known and publicly identifiable and thus, so to ensure confidentiality, a summary of their discussion has been provided without direct quotes from the transcript. The themes for the GSA focus group are summarised in Figure 4.3 and were applied to the data. Only the interpretation of the themes felt relevant to the aims and objectives of the User study have been reported in this chapter.

Glaucoma Support Assistants

Intervention

- Effects of individualised support diluted by the need to maintain consistency in delivery of information
- Participants had too much information to take on board in one session and information sheets for patients to take home may have been helpful

Patient reaction to diagnosis

- Patients researched details about glaucoma to find out more information
- Older patients appeared more willing to accept whatever the clinician told them, whilst younger patients asked more questions
- Some patients were very worried and seemed scared

Study method

- TDAs became the main focus of the study
- Questionnaires were too difficult for patients to complete
- Haphazard completion of questionnaires because answers were contradictory
- Standardised intervention conflicted with a patient-centred approach

Figure 4.3 Summary of themes applied to the data from the GSA focus group

4.3.6.1 Characteristics of the GSA focus group

Three of the five GSAs employed specifically to work on NAGS took part in the focus group part of the research. Of the two GSAs that did not take part, one was the study facilitator and part of the management team and was thus not invited so as to reduce any potential bias; the other member consented to participation but was absent due to illness on the day of the focus group meeting.

4.3.6.2 The Intervention

The GSAs felt that although the intervention was intended to have a patient-centred and motivational approach, this conflicted with the study design that required a standardised intervention. Thus, whilst the concept was grounded in providing individualised education and support, any effects of this were diluted by the need to follow the education template designed for the study, so as to maintain consistency.

The GSAs also felt that there was a considerable amount of information discussed with patients during the intervention session, too much for all patients to assimilate in one session. The GSAs suggested that the use of reinforcing information by providing printed information, sheets for patients to take home with them to refer to at a later date as a reminder of the discussion, would have been beneficial. With the amount of information that needed to be shared with the participants during the intervention, less attention may have been given to motivating good adherence behaviour specifically.

4.3.6.3 Study methodology

The GSAs were concerned that the TDAs, used to measure adherence, had changed patient behaviour and had become the main focus of the study intervention for at least a proportion of the patients.

The GSAs felt that the questionnaires were difficult to complete, particularly for the older participants. The GSAs had received telephone calls from participants calling the research office (which was separate to the 'help-line' and used for general enquiries about the study) asking questions due to the fact that they were experiencing problems completing the questionnaires. The GSAs felt that the questionnaires had been completed haphazardly because answers often contradicted themselves. GSAs were also concerned that they gave the control group a greater awareness of some of the information that may not previously have been discussed with them by their clinician in the provision of standard care.

4.4 Discussion

The findings from the focus groups advocated the need for provision of education and support for patients with glaucoma in order to promote and maintain good adherence to medication. There was evidence to suggest that existing standard care did not meet the needs of patients and that the intervention used in NAGS had the potential to improve knowledge and quality of care for all patients with glaucoma. The majority of the participants from both control and intervention arms felt that the GSAs facilitating NAGS were extremely approachable and supportive. It would appear, therefore, that further exploration of the delivery and content of the intervention is required in order to fully discern the components of the intervention that were beneficial to participants. Arguably, the opportunity for participants to interact with a health care professional may have been the valuable element that led to satisfaction with care, rather than the 'information content' provided. Furthermore, it is well recognised that service recipients tend to report high levels of satisfaction because of the desire to give 'grateful testimonials'.[212]

Future development of an adherence enhancing intervention could include provision of information pertaining to individual patient diagnosis and future prognosis to better meet the needs for more personalised information. Participants recognised that descriptive and standard information about the disease, treatment and prognosis should form the basis of all basic glaucoma education. In addition to the standard written leaflets, participants used the internet to successfully acquire information. With the current trend towards increased use of the internet and mobile device applications, different vehicles to present information, should be considered to increase accessibility to information and reduce costs of intervention delivery. However, lifelong follow-up is required to assess the long-term changes (or stability) of glaucoma disease manifestation and due to the complex, slowly progressive and asymptomatic nature of glaucoma this information can be difficult to impart to all patients with glaucoma. Standardised information provided in leaflets cannot convey this individualised information regarding changes in prognosis and individual treatment plans. Thus, a longer-term mixed method approach intervention may be required.

A tailored approach to the delivery of specific information is essential and would allow for information to be reviewed and reinforced as often as required by the individual needs of each patient, over the lifetime span of glaucoma care and

follow-up. Greater information provision and interaction may help to empower patients to take a more active role in their glaucoma management and to ask questions of their clinicians regarding their long-term prognosis.

Reducing patient anxiety about retaining a driving licence in both the short and longer-term, better provision of advice about DVLA regulations and when to inform the DVLA is also essential. However, whether the NHS or the DVLA are responsible for making these improvements is an issue for further debate, outside the remit of the present research.

Some participants felt empowered to use the telephone support line to gain additional information, whereas others who had reported not receiving enough information during their BCC intervention session and still had unanswered questions had not chosen to access this service. Further investigation is required to understand why some participants felt comfortable with using a helpline to gain information, whereas others had not even considered it as an option. Plausibly, participants might have forgotten about the availability of the telephone service and a reminder or better advertisement of the service may have improved uptake. However, some participants reported not using the telephone helpline, but had felt reassured that the facility was available, had it been required. The variation in participant's preferences for sources of information and support needs further exploration, particularly as some participants reported feeling disappointed with the level of information they had received whilst in the intervention arm.

The participant experiences provided unexpected evidence of potential study reactivity effects that may have changed participants' behaviour towards use of medication. Simply asking a question, taking part in a study or monitoring adherence may have a consequential effect on health behaviour, such phenomena that cause performance bias are known as Hawthorne effects.[101]

There are many different sources of potential Hawthorne effects evidenced from the data. The informed consent process increased participants awareness of the research objective to improve adherence to glaucoma medication. Participants felt that the questionnaires were also a source of additional information that would not have been introduced as part of 'standard care'. Participants also benefitted, not only from the 'intervention itself,' but the attention and care given to them by the GSAs facilitating the study meaning that even control group participants

consequently had improved availability of information and satisfaction with care. The control group were aware that additional information given to the intervention group was being withheld from them, which made them feel that their 'standard care' was inferior to that of the intervention group. Whilst the control group were willing to search the internet for the additional information they required, they felt that the information was less reliable than that provided to the intervention group. Such perceptions and variation in knowledge may have had the potential to alter behaviour.

Participants liked using the TDA as a method to apply their eye drops successfully and whilst they had no objection to their adherence being monitored during the study, they felt this changed their behaviour during the course of the study. Thus participation in the study may have been the motivator for participants to be adherent to their drop regime rather than any effects of the intervention.

Overall, adherence to glaucoma medication was higher than expected in the NAGS control arm. Despite the use of rigorous research methods and adherence measures, the NAGS study may have overestimated adherence in both arms, relative to usual behaviour due to Hawthorne effects as described by the focus group participants. Medication event monitoring systems, such as the TDA, are widely considered to be the gold standard measure of adherence, but participant awareness of monitoring may have accounted for the lack of statistical evidence to show any difference between the control and intervention arm adherence levels. Furthermore, the steps taken to standardise the intervention may also have diluted the effect of a patient-centred intervention, causing a reduction in measured effect size. A retrospective consent method that could conceal information relating to randomisation, study objectives, and monitoring of adherence from participants may have led to more objective responses to the questionnaires and minimised any bias caused by Hawthorne effects. Thus establishing if the NAGS results had been compromised by these potential Hawthorne effects was considered necessary. A new area of research had become evident, although not pertinent to the development of a refined intervention, nevertheless essential to the justification in the determination of an appropriate and reliable research methodology for the measurement of adherence to glaucoma medication.

4.5 Methodological critique

The focus group setting appeared to encourage participants to share their options with one another and both focus groups largely mirrored each other in terms of content and opinion, adding to reliability of the findings of the User study. The framework approach successfully extracted participant and GSA opinions from the data.

There did not appear to be any relationship between age and gender with respect to participant opinion and random selection of participants was considered appropriate for the studied sample. Participants provided a broad representation of patient opinion and practical issues, relevant to the majority of UK glaucoma patients under NHS care. Although it is accepted that the findings may not be generalizable to all UK residents due to the low ethnic diversity found in the Norfolk population. Furthermore, those taking part in the focus groups User study may have had a more positive attitude towards the study and their glaucoma care, since those with negative experiences might not have volunteered to participate in such an exercise. However, User study participants shared opinions as to where NAGS had led to dissatisfaction, which demonstrated that not all those with a negative opinion avoided taking part in the focus group User study.

The focus group interviews were moderated and co-moderated by two independent researchers to minimise bias, but the principal researcher who was heavily involved in the design and implementation of NAGS was responsible for the analysis and creation of analysis themes. Thus, pre-existing opinions and expectations of the findings held by the researcher working in isolation on the in-depth analysis could be criticised. Another independent researcher undertaking an in-depth analysis to validate the findings would have improved reliability of the results. However, to ensure that the themes identified were considered representative of the raw data a research supervisor and the moderator who conducted the focus groups reviewed the finished analysis, both reporting that the analysis was grounded in participants discourse and appeared to be a good indication of real thoughts and perceptions.

Chapter 5. Exploring reactivity effects

5.1 Introduction

The Western Electrical Company employed 35,000 workers at the Hawthorne factory in Chicago to make telephone relays. During the 1920s and 30s the company performed numerous management studies in order to assess the effect of environmental factors such as lighting, temperature, rest patterns and food, on workforce productivity.[213] Over time, the Hawthorne factory studies revealed that regardless of how the environmental factor was manipulated there was always an increase in worker productivity. The evidence suggested that the psychological stimulus of being singled out and made to feel important as a direct result of being chosen to take the part in a study might have caused the increased output, rather than any direct causal link to the environmental factor under investigation. Thus, the term 'Hawthorne effect' was coined and is now used universally to describe the underlying phenomenon that human awareness of trial participation can cause uncontrolled and non-specific experimental effects that are detrimental to the outcome of studies.[101] Since then, the interpretation of the original research carried out at the Hawthorne factories has been strongly criticised.[213, 214] The observed effects may have been caused by other contributing factors such as managerial input, fear of losing one's job (particularly as the studies were at the time of 'The Great Depression'), the duration of rest breaks, human relationships, and because there was an overall lack of scientific rigour. Regardless of this debate, the term 'Hawthorne effect' remains a lasting legacy of the original Hawthorne studies.

An oral health study identified that a 'Hawthorne effect' alone can have sufficient impact to physically improve oral hygiene. Adolescent patients known to have poor oral hygiene were enrolled into a study in which a Hawthorne effect was intentionally induced. Forty patients were randomly assigned to either the experimental condition or a control group. The experimental condition simulated participation in a study by obtaining written informed consent and providing tubes of toothpaste that were labelled 'experimental'. The experimental group were given instructions to brush their teeth twice a day for two minutes and to return the toothpaste tube at the end of the study. Participants in the control group had no knowledge that they were taking part in a study and were given the standard care

instructions that, in order to achieve good oral hygiene, they should brush their teeth twice a day for two minutes, the same instructions given to the experimental group. After 6 months tooth surface area covered with plaque was measured. Participants in the simulated experimental condition had improvement in their oral hygiene of 27% ($p<0.05$) when compared to the control group,[215] thus demonstrating that participation in a study alone can introduce a behaviour effect that changed the measured outcome.

A Hawthorne effect could be embedded in a variety of mechanisms found within study participation for example the materials made available and intended by the researcher, feedback given to the participants during the research process, changes in patient motivation and goals and beliefs about the action effects induced by the intervention. However, a Hawthorne effect has become a catch-all term used by researchers to label any psychological or social factors that has not been controlled for, or that cannot be explained in a study to describe the changes in behaviour that occur purely because of participation in research.[210] Interpretation of what constitutes a Hawthorne effect is controversial and is discussed at length in a recent systematic review.[186] In the Hawthorne effect review, the authors strived to identify what constitutes the operationalisation of a true Hawthorne effect; weak uses of the term in the literature reviewed had made it difficult to identify studies to include in the systematic review and heterogeneity in the operationalisation of the Hawthorne effect in reported studies made interpretation of the results difficult. However the review concluded that participation in research can and does influence behaviour at least in some circumstances.

As we advance our understanding of the issues that Hawthorne effects present it would seem sensible to abandon the use of the term Hawthorne effect not least because there is probably no single effect that constitutes a Hawthorne effect.[186] McCambridge et al. stated that literature as a whole is principally concerned with the existence of Hawthorne effects and yet has not been designed to investigate the hypothesised mechanisms. Thus, development of a framework that elaborates the possible mechanisms of effects and thus targets a study is necessary.[186]

Other reactivity effects exist and can be manifested in a number of contexts. The ‘John Henry effect’, also known as ‘the reverse Hawthorne effect’, is thought to occur when participants in a control group are aware of their ‘control status’ and

compare themselves to the intervention group, subsequently attempting to actively improve their performance to overcome their perceived disadvantage of being in the control group.[216] Another term used in clinical trials is a 'nocebo effect' which occurs when participants are not masked to their study status; individuals may perceive they are receiving minimal care and therefore a second-rate service in comparison to those who are receiving an additional intervention.[101] Consequently, an unintended performance bias can occur because the groups of participants feel they have been treated differently.[217]

The 'Halo effect' describes changes in participant behaviour because of the novelty of the investigational intervention. In such cases, it is the unjustified belief that the intervention, such as education provision or new technology, is 'amazing' which inflates expectation of a positive effect that causes an improvement in behaviour rather than the effectiveness of the actual mode of action from the new intervention; this confirmation bias causes positive feelings, which can change ambiguous neutral traits to be viewed as positive.

'Experimenter effects' occur when researchers communicate their expectations about the outcome of the study to their participants, even subtly, thus influencing a change in behaviour to conform to those expectations. 'Subtle messages' can be imparted through assessments and questionnaires introduced as part of the study design and can impact upon respondent's subsequent attitudes, intentions and behaviours.[218] Answering questions about behavioural intentions increases the accessibility of these thoughts in the memory; subsequently they are more likely to come to mind and be acted out when presented with the same real-life situation. The very act of making a prediction about a potential future behaviour can induce that behaviour to be played out.[219] The changes in participant behaviour caused by measuring participants responses are known as 'mere measurement effects'[196] [220] [221] or more recently the question-behaviour effect (QBE).[222] A study which randomised participants to receive a questionnaire about the benefits of blood donation found that those who received the questionnaire were more likely to register and attend a subsequent blood donation session than those who did not receive the questionnaire.[223] A meta-analysis of brief interventions designed to change alcohol drinking behaviour also found that answering questions altered subsequent reported behaviour.[196] A recent systematic review found some

evidence of QBE on health-related behaviours, but bias within studies and publication bias may have overestimated the observed small effect size.

As technology has advanced, monitoring different types of behaviour by use of electronic devices such as MEMS, motion sensors and pedometers have become fashionable. Studies have shown that measuring participants use of medication can potentially cause a reactivity effect; as previously discussed, the social stigma attached to conforming to prescribed treatment may change participants behaviour or, it may be that medication container itself acts as a novel visual prompt or cue.[47] As a result, the behaviour observed is a modified version of natural behaviour. The magnitude of influence that mere measurement effects may produce have not been thoroughly investigated,[209] and previous studies of the effects of electronic monitoring have remained inconclusive.[204] However, one prospective RCT found that electronic monitoring in patients with type-2 diabetes led to a small increase in adherence.[47]

A dementia study using a 2 x 2 factorial design of Ginkgo biloba versus a placebo control, together with intensive versus minimal follow-up, revealed that intensive follow-up had a small effect on participant-rated quality of life (QoL) scores.[101] The authors of the dementia study believed that the concentrated contact with participants in the intensive follow-up group may have improved the relationship with the caregiver which lead the patient to have a better recognition of their own needs resulting in more 'honest' reporting.[224]

Specific participation effects likely to be found in clinical trials can be subdivided into components; protocol effects due to the way that treatment is delivered, care effects due to the incidental aspects of providing care, Hawthorne effects when doctor and/or patient behaviours change because they are under observation and placebo effects when patients are aware of trial participation. Participation effects are also called 'inclusion benefit effects' and refer to any demonstrable benefit induced because of participation in research that has not been controlled for. However, a systematic review of oncology clinical trials found there was little quality evidence to show that trial participation did actually lead to improved outcomes[219] and thus the causal relationship between trial participation and improved outcomes are difficult to evidence.

As previously described, research effects can prepare people to be more receptive to the study intervention than would otherwise be expected, causing a bias which

may either strengthen or weaken the true intervention effect size and threaten the validity of any conclusions that are.[102, 103] As such, there appears to be an increasing interest in the possible reactivity effects found in behavioural studies.[196, 208] Due to the heterogeneity of reactivity effects and lack of rigorous studies, it is not possible to make inferences about the magnitude of reactivity effects on behaviour. Habitual behaviours such as adherence to medication are likely to show only small effects in comparison to 'one off' behaviours that are easy to perform, such as donating blood.[208] The effects of bias caused by research reactivity, if they exist at all, are likely to vary across differing studies, interventions, outcome measures and study methods. Because the measured effects of behaviour change interventions are known to be small, even the slightest of measurement errors are of particular significance since they may obscure any tangible findings. Behaviour change interventions therefore need to invest heavily in avoiding potential reactivity effects whenever possible.[208]

5.1.1 Reactivity effects in glaucoma adherence studies

Reactivity effects found in studies measuring adherence to glaucoma medication have been documented.[72, 93] In an attempt to reduce potential reactivity effects when observing adherence behaviour to eye drops, different researchers have tried concealing MEMS devices from participants.[47, 122, 183, 225, 226] The studies by Kass *et al*.[122, 225] used a monitoring device hidden within eye drop bottles. Participants were told that the bottles were "free samples" and that it was important to return the free sample at the next visit so that the pharmaceutical company could provide more medication when empty bottles were collected. The study conducted by Rossi *et al.*[47] provided patients with a TDA during routine follow-up and used a retrospective consent method; participants therefore, were unaware both of their study participation and monitoring of their adherence. A study by Hermann *et al*.[226] using an electronic monitoring device compared the difference in adherence behaviour in participants that were told that their monitoring device measured the temperature of the medication, compared to a group that were told that the device monitored adherence.

The study by Herman et al.[226] had its own a control group so the observed difference caused by reactivity effects was easy to establish. However, the study was not powered sufficiently to show any discernible differences between the

groups (n=36). Participants taking part in the Kass *et al.* study [122] administered a mean 82.7% (CI ± 3.6) of prescribed timolol doses and 76.0% (CI ± 3.5) of prescribed pilocarpine doses and the study by Rossi *et al.* found a mean adherence of 77% (CI ± 6.95) to travoprost doses.[47] As the studies by Kass *et al*.[122] and Rossi et al.[47] masked all their participants to the fact that their adherence was being monitored, it might be considered possible to compare these results to studies that used an unmasked method of measuring adherence to assess differences. For example, the NAGS results had a median adherence score of 80.9% (IQ=65.3, 93.1, n=83) in the control group which is higher than the masked results from Kass et al.[122] and Rossi et al.[47], but as discussed in Chapter 1.2.5, due to the differences in the definition of adherence, dosing regimens and length of monitoring periods, variances in measured adherence could be attributed to many varying factors. An example of this problem is perhaps better evidenced when considering the study by Robin *et al.* [72] which used a similar observational study to NAGS, also using a MEMS, and informed participants that their adherence to eye drops would be monitored. However, adherence was measured in terms of percentage of pharmacologic dosage covered by dosing, a different measure to percentage of adherence doses taken, which was used in NAGS, making the comparison of results between studies difficult. However, Robin *et al*. found that measured adherence was much higher than they had expected at 97% ± 6.7%.and the authors felt this could possibly have been due to the monitoring effects of the MEMS.

5.1.2 Reactivity effects in NAGS

The study of reactivity effects is a relativity new area of research with conflicting opinions as to whether reactivity bias actually exists. It was felt, therefore, that identifying the potential reactivity effects which might have been present in NAGS, required further examination. Figure 5.1 details previously described reactivity effects identified from the literature coupled with a description of the possible reactivity effect in NAGS. In light of so many conceivable reactivity effects it became evident that there was a significant chance that the NAGS results could have affected the studies internal validity. Although reactivity effects are thought to cause only small changes,[47, 196, 208] there is no known literature that suggests, if, or how the effect size is affected when a number of different reactivity effects

combine together. The overall effect could cause a synergistic relationship resulting in greater reactivity effects than would be found in studies that have fewer reactivity effects. Thus, if use of the TDA did change behaviour, it was important to establish if a reason for this could be identified and how likely it was to have occurred when participants were taking part in NAGS.

A follow-up study was required with a qualitative approach to examine and understand how adherence behaviours might be affected when using the TDA compared to administering eye drops with the standard bottle of eye drops, specifically looking for evidence of reactivity effects.

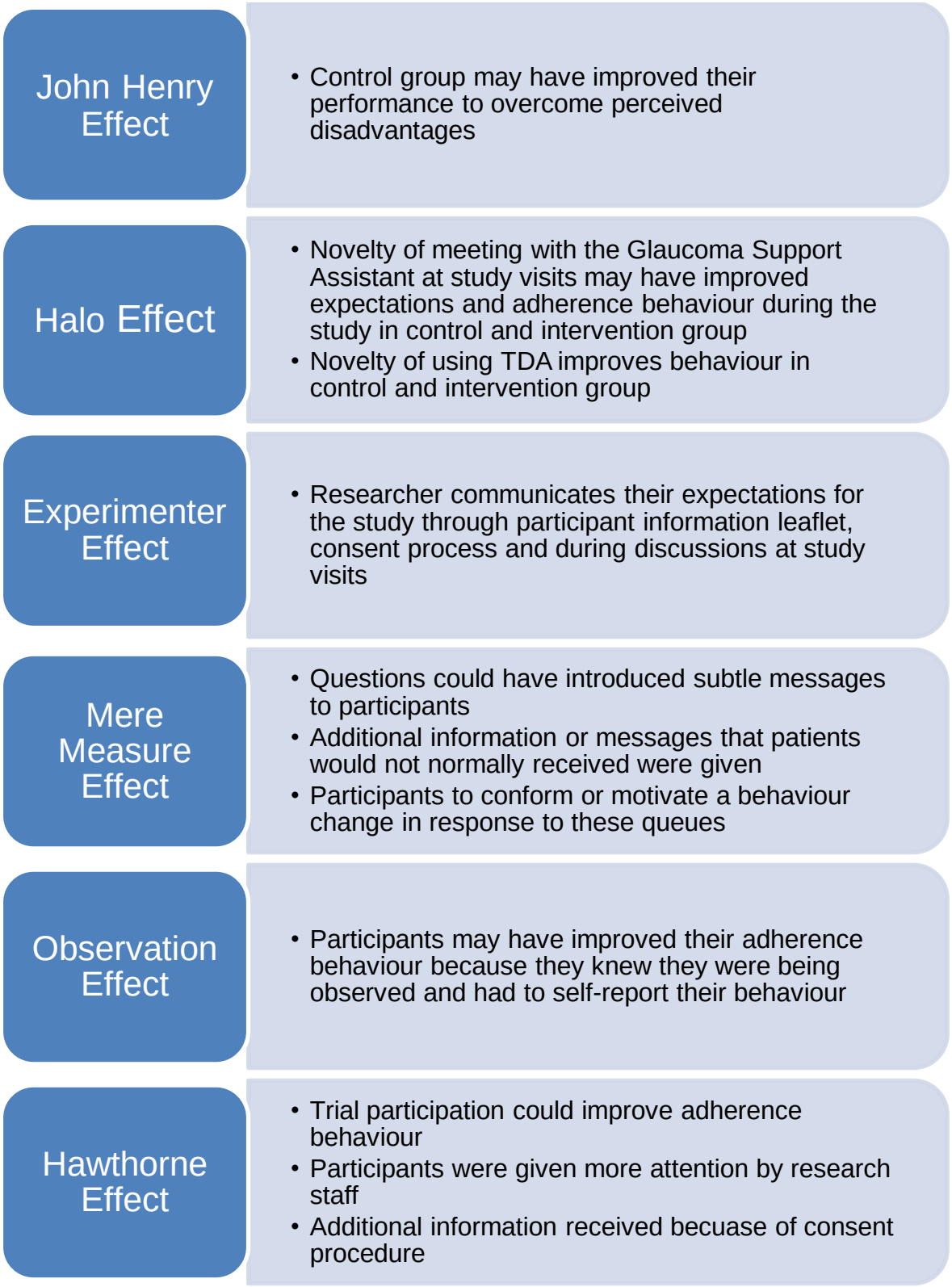


Figure 5.1 Potential reactivity effects associated with NAGS

5.2 Method

5.2.1 Aims and objectives

The aim of the study to investigate reactivity effects was to observe the effect of using the TDA on adherence to travoprost. The objectives were to elicit patient experiences of administering travoprost eye drops using the bottle alone compared with use of the bottle *with* the TDA specifically exploring potential reactivity effects that this might have on adherence behaviour.

5.2.2 Study design

A flow-chart of the study design is shown in Figure 5.2. The study received ethical approval from the Norfolk Research Ethics Committee, (appendix 10) and research governance approvals from the East Norfolk and Waveney Research Governance Committee (appendix 11).

5.2.3 Setting, participants and recruitment

Patients attending the glaucoma out-patient clinic at NNUH diagnosed with either POAG or OH, previously naïve to treatment with eye drops, and prescribed travoprost were invited to participate. Patients were over 18 years of age, able to give signed informed consent, as well as being able to read and understand English. Patients whose eye drops were applied by care home staff, carers such as relatives or friends, or home-helpers were excluded, since the study sought to understand patients own experiences of applying drops and not those of their carers who can influence drop taking routines, techniques and motivations.

All patients attending for their standard care follow-up appointment, who met the criteria were referred to the researcher by their clinician. The researcher informed each patient about the study and gave them an information leaflet. Patients were given time to consider their participation before written consent was obtained. A short questionnaire-interview was carried out by the researcher to establish demographic information such as; age, gender and type of glaucoma in order to maximise variation within the sample.[209]

Participants were assigned a study number for the duration of the study, allocated consecutively. Participants assigned an odd study number were allocated to Group A, 'use of TDA first' and even numbers to Group B, 'use of TDA second'. Group A were asked to use the TDA for one month followed by the bottle alone for the second month. Conversely participants assigned to Group B used the bottle alone for the first month then switched to using the TDA for the second month.

Patients were withdrawn from the study if travoprost eye drops were stopped for any reason, such as poor efficacy, hypersensitivity or other unwanted side effects.

5.2.4 Travalert Dosing Aid

The study used the TDA which electronically stores the time, date and number of drops administered during the study period as described in Paragraph 3.3.2.4. For the purposes of the study, the alarm feature was disabled during the study period as in NAGS. However, many of the returned TDAs used in NAGS appeared to have had been tampered with and the stickers which prevented participants seeing the visual cue window that displays a 'tear drop' when it was time to administer a dose had been removed. To prevent the desire for curious patients to remove the stickers themselves, it was felt better to leave the visual cue window clearly visable to all participants from the outset. Therefore, in contrast to NAGS that covered the visual reminder with a sticker, the visual cue window was not covered and programmed to appear at between 9 pm and 1 am.

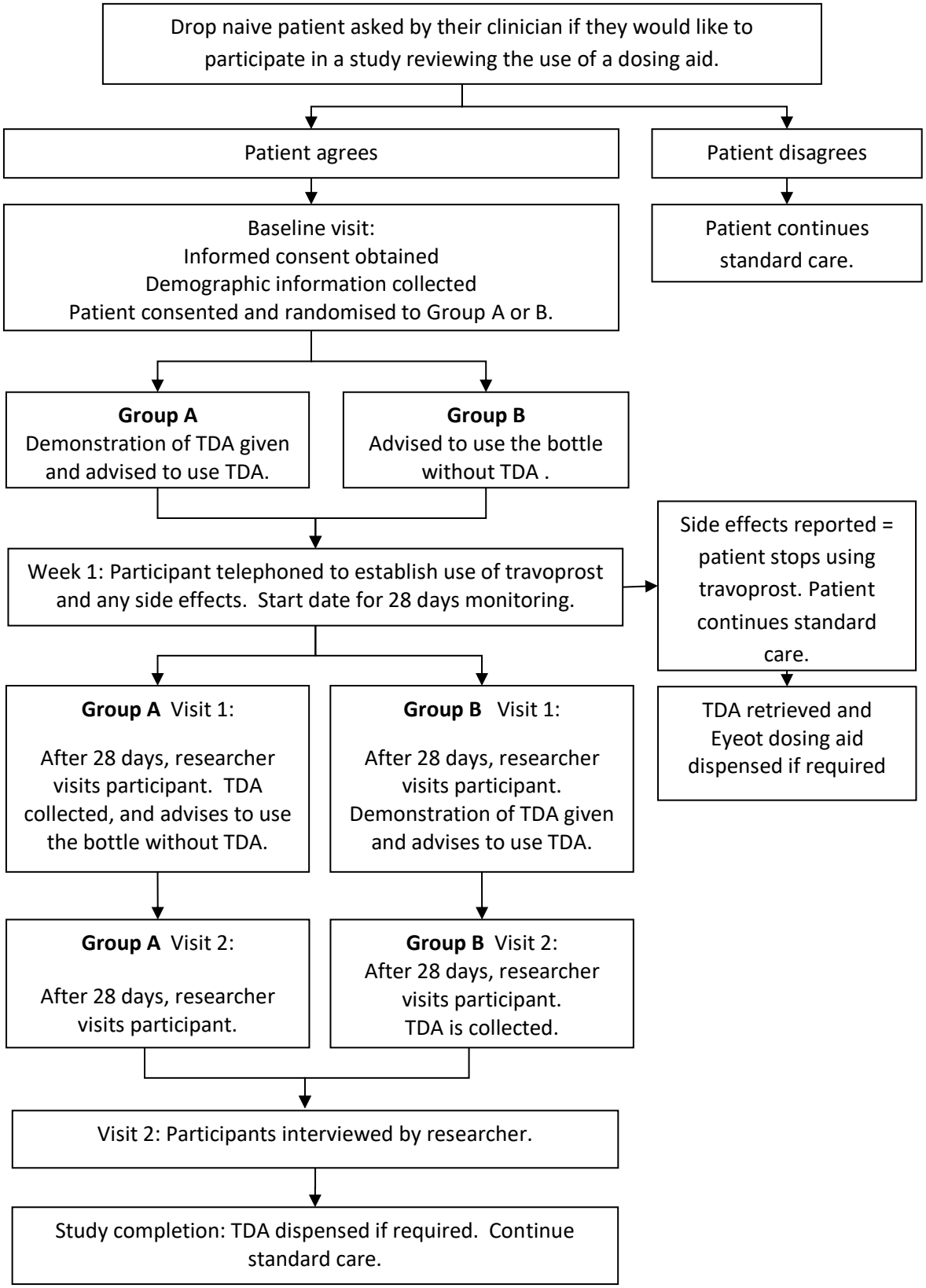


Figure 5.2 Patient flow through the qualitative study to observe the effect of using the TDA

5.2.5 Group A, 'use of TDA first'

At the time of recruitment, the researcher demonstrated how to use the TDA and dispensed it with an instruction sheet (See appendix 12). Participants were informed that the TDA would monitor their adherence to eye drops by storing the dates and time of each use during the 28-day study period and that the information would be reviewed by the researcher at the end of the study period. One week post-baseline visit, the researcher telephoned the participant to check their ability to use the TDA and to check that they were not experiencing side effects to travoprost which might prevent continuation in the study. Once the successful use of eye drops with the TDA had been confirmed the participant continued to apply the eye drops for 28 days, after which the researcher visited the participant at home to collect the TDA. Participants were then asked to apply their eye drops using only the bottle for a further 28 days at which point the trial period was concluded and an interview scheduled with the researcher.

5.2.6 Group B, 'use of TDA second'

At the time of recruitment participants were asked to apply their eye drops as is standard practice with a bottle alone. Participants were informed that after one month the researcher would contact them to organise a visit to their home to demonstrate how to use the TDA and dispense it with an instruction sheet (See appendix 12).

One week post-baseline visit, the researcher telephoned the participant to check their ability to use the eye drops and ensure that there were no side effects to travoprost, which might prevent continuation in the study. Once successful use of eye drops was confirmed the participant continued to apply the eye drops for 28 days.

After using the TDA for 28 days, the researcher visited the participant at home to dispense the TDA and participants were asked to apply their eye drops using the TDA for a further 28 days. The participants were informed that the TDA would monitor the time and date of each application of drops and that the data would be reviewed by the researcher at the end of the study. At the end of the 28-day period, the researcher scheduled an interview with the participant.

5.2.7 Semi-structured interviewsz`

As discussed in Chapter 4.2.2, a qualitative research method allowed for the exploration of meanings and concepts[201] to be explored. One-to-one interviews were chosen to encourage discussion of sensitive information and to enable exploration of feelings and underlying motivations to use eye drops, the TDA and participation in research with the researcher. Adherence to medication was not a topic that participants in the NAGS focus group, described in Chapter 3, chose to discuss openly. One possible reason for this is the social stigma attached to using medication that might have prohibited a feeling of freedom to discuss such issues in a group setting. Thus, it was felt that the issue of adherence could be explored more sensitively and freely using one-to-one interviews, allowing participants to speak openly about their experiences and personal perspectives of applying eye drops using the two different methods of application.

The interviews were carried out in the participant's own home to make them feel more comfortable and to "dilute" the relationship between the researcher and the hospital. However, participants were given the option of conducting their interview at the hospital, if they felt more comfortable with this, rather than having the researcher visit their home.

Each interview followed the interview guide shown in Figure 5.3. The interview structure was flexible to allow the researcher to continue discussion of any associated topic if it was felt relevant. The order of questions was flexible so that conversation flowed naturally with the narrative of each participant. Through the use of prompts, the researcher directed the conversation, where necessary, so that it remained focused on the topic. All interviews were digitally recorded and field notes taken by the researcher either by jotting down brief notes during the interview and/or fuller notes made after each interview had drawn to a close and the researcher returned to their office.

The data collected from each TDA was also discussed with each participant at the end of each interview. For participants who were in Group A the data were printed out and taken with the researcher to the interview, for those in Group B, the TDA was collected at the time of their interview and the researcher downloaded the TDA data on the laptop computer.

5.2.8 After the study

Standard care continued when participants completed the study. Participants where supplied with a TDA to keep if they had found it useful during the period of the study.

5.2.9 Sampling

The study to explore reactivity bias used purposeful sampling to select a maximum of twenty interviews. There are no fixed rules as to the number of interviews that are required in qualitative research, therefore after each interview had been conducted an initial analysis was carried out to assess the nature and diversity of the data. The researcher was then able to decide when a varied range of patients had been interviewed and when the data were reporting the same emerging themes.

5.2.10 Analysis

All interviews were digitally recorded and then transcribed by an independent transcriber. The data were analysed by the researcher using a framework approach, as described in Chapter 4.2.7. In contrast to the analysis of user experience of NAGS described in Chapter 4 using three focus groups, the present study was likely to generate more data from the use of up to twenty interviews. Although not essential, the researcher had the opportunity to learn and use NVIVO and it was thought use of NVIVO might aid the systematic analysis of a large dataset. Furthermore, trialling out methods of analysis was an important experience for the researcher. NVIVO version 9 software was used to organise the data during the analysis.

5.2.10.1 Patient demographics

The patient population was characterised by using a descriptive analysis (date of birth, gender, ethnicity, living alone, and type of glaucoma).

5.2.10.2 Calculation of adherence from TDA data

The calculation of the percentage adherence rate was derived from the number of doses administered over the monitoring period, as recorded by the TDA, using the adjusted adherence calculator[105, 227] as described in Chapter 3.3.5.

Introduction and warm-up

1. Why did you decide to participate in this study?
   - Try to expand on general themes emerging where appropriate.

General feelings about using eye drops

2. Think back to the first time you used your eye drops.
   What were your first impressions?
3. What has using eye drops been like for you?
4. What do you feel about the eye drops you are currently taking?
   How do you feel about the dosage?
   What do you like most about the drops you use?
   What do you like least about the eye drops you use?
   What drawbacks/side effects, if any, are there to using eye drops?

Motivation

5. Would you say there is anything that has motivated you to take your eye drops?
   In what way does this motivate you?
   How often does it motivate you?

TDA/bottle comparison

6. What was it like using your eye drops **without** the Travalert?
7. What was it like using your eye drops **with** the Travalert?
8. Which did you prefer?
   Try to expand on reasons for this.
9. The TDA recorded each time you used your travoprost. What are your thoughts about this? If you had the choice, would you continue to use the Travalert or not?
   Why is that?

Adherence

10. I know it can be quite difficult to use eye drops every day. Can you remember how many times you did not use them in the past month?
    Can you think back to the days that you missed a dose and what happened or what you thought led to you missing a dose?
    Do you think this was the same for both the month you used the Travalert and the month you used the bottle?
11. Review adherence data collected with the TDA device with the participant.

Summary

12. Summarise the discussion and check if there is anything else the participant would like to add.

Figure 5.3 The topic guide used in the participant interviews

5.3 Findings

The study recruited seven participants. One participant had to be withdrawn because they suffered side effects to their eye drops during the observation phase. Thus, six participants were interviewed, three in their home and three at NNUH, and the data analysed. Of the six participants interviewed, one participant did not return their TDA so the data could not be extracted as they had misunderstood the instructions about returning it. On review of the themes emerging from the six interviews, it was felt that the data had provided varied evidence with repeating themes, so the decision was taken not to proceed with any further interviews.

The characteristics of both groups are displayed in Table 5.1. Only one participant had less than 80% adherence and he reported that this was due to running out of medication.

Table 5.1 Characteristics for each participant

ID/ Group	Gender	Age	Diagnosis	% Adherence measured by TDA (duration of use)	Participant preferred application method
1/A	Female	51	Ocular hypertension	100% (28 days)	Travalert
2/B	Female	72	Glaucoma	100% (28 days)	Travalert
3/A	Male	87	Glaucoma	78% (27 days)	Travalert
4/B	Female	74	Glaucoma	TDA not returned	Travalert
5/A	Female	81	Glaucoma	Withdrawn – side effects to drops	
6/B	Male	56	Glaucoma suspect	91% (23 days)	Travalert
7/A	Male	55	Glaucoma suspect	93% (28 days)	Bottle

5.3.1 Summary of analysis

Six overarching themes were identified and applied to the data; (1) Initial experiences of diagnosis and initiating treatment, (2) motivations to use eye drops, (3) reasons for taking part in the study, (4) administration of eye drops, (5) experiences of monitored adherence and (6) differences between administrating eye drops with the TDA and the bottle. Only the themes that were felt to be

relevant to the study aims and objectives have been reported in this chapter. The themes were brought together under four main headings that highlighted potential reactivity biases which could have affected patient behaviour.

5.3.1.1 Study participation motivates use of eye drops

Commonly, participants reported that protecting their eye-sight was their main motivation to use eye drops.

> *Because I need my eyesight, I mean that is the biggest thing isn't it, there is no way you can function without your eyes properly.* ***(01, female)***

However, taking part in the study was also described as a motivator to use treatment and additional information provided as part of the informed consent procedure reinforced the necessity to use eye drops.

> *…well you told me that was what you were going to do and so… it is quite a good motivator.* ***(01, female)***

> *It was just something I knew that when I came up here and first spoke to you and found out what was the matter, I knew I had to keep doing it and after talking to you, you said set a time and der, der, der… that's what I tried to do.* ***(07, male)***

There was also evidence that the novelty of the TDA itself was a motivation to use eye drops.

> *Well, If I hadn't met you [referring to moderator] I would have carried on using the bottle, I wouldn't have known no different would I? I love it, I've never known anyone use anything like this before.* ***(02, female)***

5.3.1.2 Use of the TDA makes administration of eye drops easier

Some participants reported that using eye drops was problematic particularly initially. Trying to find the correct position to hold the bottle to avoid the eye drops running down the cheeks was difficult.

When I first started using the bottle, because I was looking in the mirror and I was trying to put in, but because it was just going down there wasn't it [refers to rolling down cheeks]. ***(02, female)***

However, the application of eye drops was felt to get easier over time.

Yeah it took some time to get used to, get the sort of right position, you know, a couple of times it went out, at first, but now I am so used to it. ***(04, female)***

Most participants reported that the TDA was easier to use than the bottle alone. The lever was easy to use which was better than trying to squeeze the bottle and the device was bigger and thus easier to hold and precisely apply the drop into the eye than the small bottle on its own.

I can sort of press it [the lever] and you get a drop straight away. Otherwise, with the bottle you had to sort of struggle, you don't know how much pressure you should put in whether you get too much sort of drop, bigger drop than normal. ***(04, female)***

The lever was quite handy rather than having to squeeze the bottle, definitely. ***(01, female****)*

But that machine [referring to TDA] was good because it is bigger and as I say you can get that over your eye and err, and you stand more of a chance of hitting the bulls-eye! ***(03, male)***

I think Travalert would be better because, you can, it is easier to hold in your hand. ***(04, female)***

If I do use it, if my wife wasn't there to put the eye drops in, I probably would use the little machine more. I feel that I would probably get a, if I was doing it myself, a more accurate shot. ***(03, male)***

Only one participant chose not to keep the TDA after the study. He preferred to control the pressure on the bottle himself as he felt he could get the right amount of liquid out of the bottle, which he could not do with the TDA.

5.3.1.3 Use of TDA makes administration of eye drops easier to remember

Remembering to use eye drops was reported to be easy if it was part of a daily routine. However, participants did report that the TDA was a visible reminder to use drops, which aided the memory.

> *Because it's your routine, I mean, it's not 10 o'clock every night it's between 10 and I say 11.30, 12 o'clock but its every time I go to bed there is it is sitting there and you just go click and its in that's done it's not a problem at all.* ***(06, male)***

> *But once the machine [Travalert] went back I thought well I just ain't going to remember, you know I'm sort of not forgetful but I just need that little nudge to make me remember I've got to do it at 9 o'clock…I set my phone so I know what I've got to do at 9….****(07, male)***

> *Yeah, it does remind you, being the container there [referring to Travalert]….****(04, female)***

> *I knew it was there and I knew I had to use it because it was you know it is quite large thing well, it's a nice handy size…****(07, male)***

The TDA also had a tear drop symbol, which flashes on the display screen when it was time to apply drops in the evening, and flashes continually until the dose has been taken. Some participants commented on how helpful the flashing was and actually prevented them from forgetting to use their drops.

> *The times when I am out of the routine is the times when I sometimes actually get my head down and think, oh, I haven't done my eye drops. Urm so that you know as you turn the light off you saw it flashing****…(01, female)***

> *[moderator asks "do you think there was a time that you missed your drops]… definitely not with the Travalert because that did flash at you, possibility once I might have done it without with the Travalert.* ***(01, female)***

5.3.1.4 Monitoring adherence

The majority of participants reported that they were more aware of their eye drop use when their adherence was being monitored. They felt that they would be "discovered" if they had not administered them and this made them feel more conscious of the need to use their drops.

> *even though I was routined, it did make me, I mean there was occasions its gone passed certain times like, it did make me think about doing it a lot more because you don't want to miss it, I don't want to be in a position where it is like four days I've missed it you know.* ***(06, male)***

> *well I suppose that would make you, well, knowing full well that I mentioned to you that you can't get away with nothing, yes, then you do get on with it because you say you've not used it!* ***(03, male)***

> *I was conscious, it's like your phone, I'm conscious it is there so whatever I'm doing every now and again I'm looking, I wasn't looking at the time, I was looking to see if the tear drop had turned up…and all of sudden I think to myself "how long has that been on there".* ***(07, male)***

> *…plus the alert thing… that really does get you going. Yes a couple of times as I have said when I've come home later or something it has been flashing at me, you know, and I think oh yeah, that is definitely… whereas you think yeah, I must do that.* ***(01, female)***

5.4 Discussion

There were equal numbers of males and females interviewed in the study and representation from the range of ages expected of the glaucomatous population at the recruiting site.

Largely, participants acknowledged being highly motivated to use their eye drops. The fundamental reason given for good adherence with their drops was to preserve their sight, which is consistent with previous findings in a qualitative study undertaken with the same patient population in 2008.[42] All participants discussed some form of routine to help ensure they were able to use their eye drops as prescribed which was also consistent with previous research.[42, 228] As expected from motivated and routine driven participants, their adherence measured by the TDA was high; only one participant had less than 80% adherence reportedly caused by running out of eye drops.

Participants gave insightful accounts of their experiences during the study period, which gave a better understanding of patient behaviours not only when participants use the TDA but also when participating in a study.

One modification made to the TDA used in the present study was leaving visual cue window on display rather than being covered with a sticker in NAGS. Whilst this might have reduced the amount of 'tampering' with the device, since participants were not curious to see what was being concealed, some participants did reflect on the usefulness of the 'tear drop' appearing when it was time take a dose and that it reminded them whether they had used their drops that evening. Such a modification was felt necessary to reduce over interest in the workings of the TDA but did introduce another potential reactivity effect that was not present in NAGS.

Overall, the findings evidenced possible reactivity effects which could have caused a study bias during NAGS; awareness of monitoring adherence, the novelty of using the TDA together with participating in a study changed motivation to be adherent to medication as well as inflating expectations of using drops in comparison to standard use of the bottle. The researcher also acted as a promoter of good adherence through the information given during the informed consent process, study visits and general interaction during the course of the study, which patients would not normally have received through standard care.

5.5 Methodological critique

It is widely accepted that participants who take part in research are more motivated individuals than those who decline and may be more likely to be focussed to use their medication. If study participation is a motivator, a fundamental positive sampling bias might have been introduced and patients prone to non-adherence may have been missing from the sample.

The interviews and framework approach to analysis successfully unearthed participant experiences of using the TDA in a study setting. The sample of only six interviews was relatively small but the range and consistency of the data collected was good with a wide representation of ages, even mix of male and females, those with POAG or OH/GS and equal numbers from groups A and B. The interviews revealed that the participants were also from a range of social backgrounds. The data was rich in terms of examples used and details given by participants. The emerging themes were repeated by the latter interviews with no new evidence emerging and therefore data saturation was reached in six interviews.

Because non-adherence is felt to be a socially unacceptable behaviour, participants may have felt uneasy about admitting non-adherence with the researcher even though anonymity in the research process was guaranteed. However, review of the data showed evidence of a good rapport with the researcher and participants' freely discussing evidence of instances of non-adherence. Some participants thanked the researcher for including them in the study because it had given them the opportunity to discuss their experiences. The transcripts suggested that participants were very willing to share their experiences and there was ease in the conversation without signs of embarrassment when disclosing information about their adherence.

However, as described in Section 4.1, as the main the researcher in the NAGS study, and the main author on the exploring reactivity study, the fact that I undertook the analysis in isolation could be criticised. Building rapport and creating a discussion with participants may have altered the topics that were discussed and the information that was shared with me. Certainly, embarking on the research in the first instance was influenced by the need to find out what individuals felt about using the TDA and without a vested interest in the NAGS study the projected would never have been conducted. However, during the study

I was very much aware of these potential influences and am confident that I was able to explore all the data collected impartially.

Carrying out the interviews in participants own homes was an enlightening experience for the researcher. Some participants wanted to actually show the researcher where they physically kept their medication or pointed or made suggestive movements about elements of their environment to help them illustrate the point they wanted to convey. Compared to the interviews that were carried out in the eye clinic, this made the interview feel more real and brought the conversation to life. Furthermore, when analysing the data it was easier to remember parts of interviews that had taken place in people's homes, the surroundings, noises, interruptions in some cases, all added to a sense of reality and was overall was considered a helpful method.

Creating themes and topic coding was efficient with the use of NVIVO and retrieving themes and particular phrases was made much easier. The initial training was a two-day workshop followed by a few sessions getting more familiar with the software, but it was a relatively easy process to learn. There were many more additional functions that the software could have performed if more time had been spent learning these but with only 6 interviews to analyse, the quantitative functions of NVIVO were not considered valid and were not utilised.

5.6 Conclusions

Whilst the focus groups described in Chapter 4 confirmed that the NAGS study had been well received, the study methods could have introduced various reactivity effects. Further exploration of the use of the TDA described in Chapter 5 also highlighted the specific reactivity effects caused by the TDA. Further research was required to ascertain the effect size caused by these reactivity effects in order to establish a reliable measure of behaviour change. The contribution of such a study would provide an estimate of the extent to which research procedures cause an underestimate of the true magnitude of patient non-adherence to medication. Even if the effects were subtle, they would still be important to the conclusions drawn from adherence intervention studies in an area of research lacking empirical evidence and where bias is inadvertently introduced by experimental design errors. If the effects were negligible it could be argued that the methods used in NAGS remain valid and could be recommended for future intervention studies, thus suggesting that the majority of patients do not require additional support to obtain good adherence with use of eye drops. However, significant changes in behaviour caused by the reactivity effects might suggest that the intervention used in NAGS holds some credibility and that better methods to measure adherence are required.

Section 3. Establishing Patient and Public Opinion of a Modified Consent Procedure

Presentations resulting from this section:

Cate H, Bhattacharya D, Clark A and Broadway DC. Attitudes towards the use of a modified consent procedure in a study to measure adherence to glaucoma therapy (oral). UK Society of Behavioural Medicine, Newcastle, 2015. *Winner of a High Scoring Presentation Award.*

Chapter 6. Consultation with patients

6.1 Introduction

Previous evidence has suggested that reactivity effects have a minimal effect on study outcomes,[208] but the follow-up work to NAGS discussed in Chapter 4, 'Exploring the user experiences of the NAGS study' and Chapter 5, 'Exploring study reactivity bias', identified multiple reactivity effects. The magnitude of the effect size could have been further amplified if a synergistic relationship occurred between these different reactivity effects; a hypothesis with limited prior reporting, evidence or investigation. Deciding to explore the extent to which reactivity effects could cause changes in behaviour was not only important to improve our understanding of the NAGS methodology but also for the wider research community in order to comprehend patient behaviour when involved in interventional studies more generally. If a reactivity effect could be observed and quantified, then all future studies that monitor behaviour could either modify their study method to control for these biases or apply a corrective calculation value to outcome data to account for such biases.

A study was designed to measure the change in behaviour when participants were exposed to simulated reactivity effects. Two designs were considered; an independent group RCT, or a cross-over study. The 'reactivity stimuli' was awareness of participating in a study and measuring adherence to medication using a TDA and questionnaires. The RCT was designed to compare the medication adherence behaviour between two independent groups, one group subjected to the 'reactivity stimuli' and one group assigned as a control arm, which would not receive the 'reactivity stimuli'. The cross-over study would first measure medication adherence behaviour in a control phase when participants were <u>not</u> aware that they were taking part in a study and that their adherence to eye drops was being monitored, compared to the experimental phase when participants were exposed to the 'reactivity stimuli'. Whichever study design was selected, participants would need to remain masked to the fact that they were taking part in a study and that their adherence was being monitored when participating in the control arm of the study. Withholding such information and not taking consent

prior to participation in a study is rarely considered acceptable, such practice having important ethical implications.

6.1.1 The ethical debate

The arguments for and against obtaining informed consent or use of deceit in medical studies are discussed in a series of articles in the British Medical Journal (McLean, Dennis,[229] Kale, Bhagwanjee *et al.,*[230] and Seedat[230]). Over many decades the move towards fully informed consent for all participants in clinical trials has been formalised in various guidelines.

The British Psychological Society (BPS) have published ethical guidelines for good research practice.[231] The use of deception is discouraged due to the potential to cause distress and harm and make recipients cynical about research activities. However, because behaviour can be modified if individuals are aware that they are being studied, it is recognised that in some cases deception is necessary. If research does need to involve deception then it should be designed in such a way that it protects the dignity of the participants and that the objectives have strong scientific and medical justification and appropriate risk management.[231]

The declaration of Helsinki and International Conference on Harmonisation for Good Clinical Practice offer no guidance on the use of deception, but the Council for International Organizations of Medical Sciences / World Health Organization,[232] and The Royal College of Physicians (2007) acknowledge that some research, must deliberately misinform subjects to ensure participants do not modify their behaviour in response to knowledge of the study protocol.[233]

The NHS National Research Ethics Service (NRES) undertook a shared ethical debate exercise involving 20 Research Ethics Committees in 2009.[233] The NRES debate reviewed the issues, guidance and evidence for use of deception in medical research specifically and determined that ethical review committees should ensure that the proposed research:

- is such that the deception only poses minimal risk
- is indispensable to the methods of the study
- is planned after considering that no other research method would suffice
- will lead or is likely to result in advances in knowledge, and

- follows wide consultation undertaken at the protocol design stage.

The evidence suggests that there are legitimate cases which advocate the need for the nature, purpose and duration of the experiment (including the method and means, hazards and inconveniences expected, effects on health or person which may result from participation in the study) to be provided to avoid “force, fraud, deceit, duress or coercion” of participants in research.[234] However, others insist that good reasons not to seek such consent often exist, one of those being where methodological reasons would exclude this.[229, 230, 234-237]

A study investigating the effectiveness of stroke care after discharge from hospital provides a case example of a modified informed consent procedure.[235] Patients in the intervention group could not be informed that they were taking part in a study to examine the effectiveness of outreach stroke-care since they needed to remain masked to their allocation strategy in order to avoid this introducing bias in participant responses to the evaluation of their own care. After six months in the care programme, researchers sent a letter to all 102 participants informing them that they had participated in a study and the reasons for the study. An ethics committee approved the study on the basis that there was no risk to patients and the reason for the study was clarified retrospectively. The participants were interviewed two weeks after their participation in the study had been revealed to them, in order to evaluate the effects of withholding study information. The results revealed that trust in doctors did not decrease because information had been withheld; only one patient said that their willingness to participate in future studies had decreased, and two participants had negative feelings after finding out the information had been withheld from them. The majority reported not feeling any sense of negativity because the information was unimportant, the patient understood the reason why the information was withheld, or it was acceptable that the information was withheld. The results suggested that a modified procedure to withhold information deserves consideration when patients need to be masked to study outcomes and if this entails no risk to the participant.

6.1.2 Adherence studies using deception

There are examples of glaucoma studies that have used deception to conceal the monitoring devices that monitor the eye drop use. The studies by Kass *et al*.[122, 225]

used a monitoring device hidden within eye drop bottles. Participants were told that the bottles were "free samples" and that it was important to return the "free sample" at the next visit since the pharmaceutical company would provide additional medication to the clinic when empty bottles were collected. The study conducted by Rossi *et al.,*[47] provided patients with a TDA during routine follow-up and used retrospective consent. Patients were therefore unaware both of study participation and monitoring of their adherence. In the studies by Hermann *et al*.[183, 226] not all patients were explicitly told that their adherence was being monitored, instead they were told that the monitoring device attached to their eye drops measured the temperature of the medication. However, these studies were not carried out in the UK and different countries follow different guidelines for ethical research practice.

However, two examples of general adherence studies undertaken in the UK have been published. In a study carried out in 1995, 102 patients with asthma were provided with terbutaline and budesonide turbohalers[238] that were fitted with turbohaler inhalation computers to measure adherence, these being concealed from the patient. The turbohaler study aimed to examine psychological factors such as patient attitudes to asthma and its treatment, as well as anxiety and depression as possible reasons for non-adherence. On the basis that masked observation was required in order to obtain an accurate picture of "normal" behaviour, ethical approval was given by the United Medical and Dental Schools Ethics Committee. However, the authors did not describe how the study was conducted, if any form of consent was taken from participants, or any follow-up work to assess the effect that masking had on participants.

The second UK adherence study aimed to determine factors associated with adherence and persistence to bisphosphonate therapy in osteoporosis, but the researchers concealed the purpose of the study from participants, informing them instead that they were gathering information on their experience of osteoporosis and its treatment.[239] Participants were recruited through advertisements placed in the UK National Osteoporosis Society magazine. A telephone interview was undertaken and participant responses were used to assess self-reported adherence. In this cohort of patients with osteoporosis, self-reported non-adherence was unexpectedly high with 52% of participants reporting that they were non-adherent. Participants are often thought to underestimate true non-

adherence, which is attributed to both the social desirability to be adherent resulting in reporting and memory bias. However, the results of the osteoporosis study support the hypothesis that when people are not aware that their adherence to medication is under scrutiny they are more likely to behave naturally and respondents may have felt at ease to report their true non-adherence to medication demonstrating that 'reactivity to monitoring effects' can exist.

6.1.3 Conclusions

Whilst the use of modified consent and deception in research had been used in previous research practice, there are clear signs that many issues still remained unresolved. How patients might feel if they were to be involved in a study using modified consent methods required further exploration involving consultation with patients and individuals who share the same social and cultural background as to those who might become participants in such studies.

6.2 A mixed method study to elicit views of a modified consent method

6.2.1 Aim

A study was designed to elicit opinion from patients and members of the public regarding the use of a modified consent procedure, specifically an initial withholding of information and use of a later, retrospective, consent method process. The aim was to use opinion captured from this population to shape the design of a subsequent study to observe patient adherence to glaucoma eye drops and determine if such a study design would be acceptable to participants.

6.2.2 Objectives

The objectives of the initial study were to consult with members of the public, and patients with glaucoma, as representatives of the population affected by glaucomatous disease:

1. to capture opinion about the use of modified informed consent procedure
2. to measure acceptability of using a modified consent method and quantify factors that might change opinion of acceptability
3. to understand the concerns that may arise when using a modified consent method in order to design a study which minimised these fears.

6.2.3 Study pathway

The Norfolk Patient and Public Involvement in Research (PPIRes) group provide support to the local research community and ensure that public and patient perspectives inform the design, delivery and dissemination of research. The PPIREs panel are 'informed volunteers' from a range of backgrounds and thus, they were an obvious place to start the consultation process. The researcher gave a short presentation at the start of a group meeting to set the scene and give background information from which a discussion was encouraged. One of the members had previously worked on the NAGS Steering Group Committee and was aware of the TDA and the complexity of measuring adherence. It was clear from the initial discussion with the PPIRes group that opinions would be wide-

ranging and a discussion template was drawn from this preliminary work as presented in Table 7.1, to be used with subsequent focus group meetings.

As individuals are ‘products of their environment’ and are influenced by the people that surround them all of the time, the majority of opinions are not formed in isolation.[240] Thus, focus groups were chosen as an ideal method for examining the reality of the modified consent subject, since a group dynamic encourages the social interaction that can develop ideas between individuals.[241] For complex topics, a small sample size of 5 to 7 people per focus group is ideal and allows for the moderator to probe the key concepts using ‘structured’ and ‘free’ probes.[240] The focus group methodology and findings are discussed in Chapter 7. A qualitative approach enabled patient and public views about this complex topic to be explored and a fresh perspective to be understood rather than the researcher making assumptions about the likely opinions and feelings that withholding information were likely to elicit.

The qualitative phase informed the design of a questionnaire that would enable engagement with a wider population of patients and members of the public, from which quantitative data could be drawn to provide a measure of what people thought. The design of the questionnaire is discussed in detail in Chapter 8.

Chapter 9 describes the evaluation of the questionnaire design which was required before use. Focus groups were not a suitable forum for evaluating the design of a questionnaire, since members within groups can tend to speculate about what other individuals might do when answering survey questions as opposed to reporting how they would react themselves.[241] Thus a panel of researchers with previous experience of designing questionnaires and the local PPIRes group members independently reviewed the design and content of the questionnaire and made revisions. Further testing of the questionnaire was undertaken using cognitive interviewing techniques to evaluate the questionnaire for reliability and validity with a sample of patients with glaucoma and the general public.

Chapter 10 describes how the questionnaire was used to consult with patients with glaucoma and the general public visiting a general out-patient hospital, together with an examination of the results.

6.2.4 Ethical and Research Governance approvals

The mixed method study to elicit views of a modified consent method received ethical approval from the Southampton B Ethics Committee (appendix 13) and research governance approval from the Norfolk and Norwich University Hospital (appendix 14).

Chapter 7. Focus groups to elicit views of a modified consent method

7.1 Method

7.1.1 Identification and recruitment

A poster advertisement in the eye clinic of the NNUH was used to invite people with glaucoma to attend the focus groups (appendix 15). Patients interested in participating in a focus group either approached the researcher via the reception staff in the eye clinic, by telephone or email to request further information. Additional posters were displayed at a patient glaucoma education meeting organised by and held at the NNUH. A participant information sheet was provided with a consent form, which patients returned to the researcher if they wished to participate. In addition, participants received a written information sheet about the research process and how ethics committees operate in the UK (appendix 16). Once consent was received, the following information was collected to inform sampling: age, sex, ethnicity, employment and marital status.

7.1.2 Participant selection

Five to six participants were required for each focus group. Factors that may influence perceptions regarding the acceptability of modified informed consent procedures were not found during the review of the literature. Thus, participants were purposively sampled to represent the widest range of demographic characteristics possible.

Participants were contacted by email or telephone to confirm the meeting dates. However, once selected and contacted to confirm their attendance, some participants were unable to attend meetings on dates offered. Therefore, all participants who had registered an initial interest were invited, irrespective of any sampling methodology to ensure adequate numbers for the planned focus groups.

7.1.3 Focus group interview guide and scenarios

The initial PPIRes consultation group held in March 2012 described in Chapter 6.2 helped to design a topic guide for two planned focus groups described in Figure 7.1. The focus group topic guide was designed to address the following:

- patient expectations of the informed consent procedure
- opinion of research designed to withhold information
- opinion of research which deceives participants
- opinion of the role of an ethical committee in research

Two vignettes were used during the focus groups. Vignettes are short scenarios in written or pictorial form, intended to elicit perceptions, opinions, beliefs and attitudes from responses to the circumstances described.[242] In qualitative research, participants are usually asked to respond to a particular situation by stating what they would do, or how they might imagine a third person would react to certain situations and often entail some form of moral dilemma. Vignettes can be used with individuals or within focus groups, although little has been written about the latter,[243] and are often used as ice-breakers to engage participants in the topic and encourage dialogue within a group. Vignettes may reflect what individuals believe and how they respond in reality and therefore, the discourse that emerges helps researchers to make links between beliefs and actions. However, not enough is known about the relationship between vignettes and real life responses to be able to draw parallels between the two.[244]

When using vignettes, the stories must appear plausible and real to participants. Thus, the vignettes featured a research situation about a glaucoma study to enable the participants to engage with a scenario that related to their own medical condition and experiences of attending the eye department. Sufficient context was provided to ensure respondents had enough understanding of the situation being depicted, but vague enough to 'force' participants to discuss any arising additional factors that might have influenced their decisions. Some ambiguity in scenarios can be advantageous to the researcher, since it leaves space for participants to define the situation in their own terms.[245]

Introduction: Introduce yourself and tell us if you have taken part in any research before.

1. Review experiences of participation in research.
2. Would anyone consider taking part in clinical study?
   Review opinion, if so why / or why not?
   Would this be for glaucoma / other medical conditions or both?

Check that participants are sufficiently briefed on the information contained in the patient information sheet regarding the research process, what is an ethics committee, what is informed consent, and the research process.

3. What would they expect when taking part in a clinical trial?
   Review opinion and ideas and where these originate from.
4. Do you think it is ever right for researchers to withhold information about a study?
   Review ideas.
   Specific areas to drill down to:
   Is this the same for any research topic or specific to glaucoma studies?
   Would you feel that you weren't being treated with respect?
   Would you feel negatively about research to the point you would never take part in research again?
   Would it reduce your trust in all doctors?
5. What if there was a good scientific reason to withhold information?
6. How do you think you would feel if you took part in a glaucoma study and some information was withheld from you?
   If you had taken part in a study that you were not aware of would you like to know about this at the end of the study and have this explained to you?
7. How would you feel about being deliberately being deceived about a study you were taking part in?
   Is withholding information and deceit different?
8. How would you feel if you your clinician were collecting information about your glaucoma to use in a study without your permission? (Audit work)
   Is this ever right? Why or why not?
9. Do you think you would feel differently if you knew that the study had been reviewed by an ethics committee?
   Is it reassuring to know that a study has been reviewed in this way?
   Review ideas.
10. What do you think are the most important aspects for researchers to consider when taking consent and informing patients about research?
11. Is there anything else you would like to add or think I may have missed that you wish to discuss?

Scenarios: I will read you a scenario followed by 5 options to choose from. The scenario describes a hypothetical glaucoma studies Please try and imagine yourself in the situation then chose which option best describes your opinion. When everyone has made a decision I will ask you all to hold up the card with your chosen option (cards provided to each participant) to display to the group. We will then take a moment to discuss the reasons behind your decisions.

1. There is a new eye drop available for the treatment of glaucoma and your clinicians would like to test if it is better than your existing eye drops for treatment of your glaucoma. Your clinician is going to do a study where patients will be asked to use either their existing treatment or the new treatment for comparison, but the bottles will look exactly the same so patients will not know what they have

	been asked to use. You have a 50/50 chance of using the new eye drops or using your own current drops (this method is used frequently in these types of study already). You will be reviewed more frequently during the study to ensure that your condition is not deteriorating, however, your clinician does not want to tell you anything about the new drops or its side effects in case it changes the way in which you use the drops or what to expect when you start to use them.
A	You give your consent to take part as long as you are fully informed after the study has finished about what the drops were and their side effects.
B	You would consent to take part if you were fully informed at the end of the study about the drops and their side effects, and could withdraw your consent to your results being used if I did not agree with the new treatment.
C	You consent to taking part and would not need to be fully informed after the study, as you trust clinicians/researchers/and ethical committees enough to ensure your safety is not compromised.
D	You don't think patients should need to give consent or be fully informed about the study as clinicians should be allowed to test new treatments as they see fit.
E	You would not consider taking part in this study. Please consider and state your reason why.
2.	Your clinician would like to undertake a study to see if patients use their eye drops as prescribed. Your clinician knows how difficult it is for patients to use drops and to remember to use them every day. He would like to try and find out if this is a significant problem for glaucoma patients. He is going to use an eye dropper aid that helps patients administer an eye drop into the eye, but electronically keeps a record of the time and date that the dropper aid has been used. The electronic recording device is held within a plastic sleeve that fits around a bottle of eye drops and so it is not possible to tell that it is actually recording the use of eye drops. The clinician is aware that patients might be more inclined to use their eye drops differently if they know they are taking part in a study and being monitored for eye drops use, so decides not to tell you anything about the study and just asks you to use the device to see if it helps you administer the eye drops (he does not mention that it is measuring every time you use your eye drops). The clinician feels this is acceptable because there is no risk to you taking part in the study, your eye drops and glaucoma care continues just the same, and yet he will collect some very important data about the way in which you use your drops.
A	I agree that as there is minimal risk and it makes no difference to my glaucoma care. The clinician is right to carry out a study like this.
B	I agree that a study like this is useful, but the clinician should still ask me if I would like to take part even if I do change my behaviour because of it.
C	I agree that a study like this is useful and the clinician should tell me after the study has finished exactly what he was doing and why, and ask me if I will consent to him using this information.
D	I don't think patients should need to give consent or be fully informed about the study as clinicians should be allowed to test as they see fit.
E	I don't think clinicians should ever deceive patients, or do research without patient consent under any circumstances.

Figure 7.1 Focus group discussion template

7.1.4 Analysis

Both focus group discussions were digitally recorded and transcribed by an independent transcriber. The collected focus group data were analysed by the researcher using a framework approach, as described in Chapter 4.2.7. NVIVO version 9 software was used to organise the data during the analysis.

7.2 Findings

The characteristics of both focus groups are displayed in Table 7.2. There were more females than males and all participants were white British. The groups were comprised of people largely of retirement age which accounted for the high rate of unemployment.

Table 7.1 Participant demographics

		Total n=9	Group 1 n=5	Group 2 n=4
Age (years)	Median (IQ)	66 (63, 78)	66 (63, 79)	68 (57, 76)
Male	No. (%)	3 (33)	2 (40)	1 (25)
Employed	No. (%)	1 (11)	1 (20)	0 (0)
British	No. (%)	9 (100)	5 (100)	4 (100)
Living alone	No. (%)	2 (22)	5 (100)	2 (50)

7.2.1 Experience of research

One member of group 1 (1M) had previously been involved in a glaucoma clinical research placebo/control research study within the eye clinic at NNUH. '1M' spent time describing his experiences of taking part in the study; he had not known if he had used placebo or active treatment for his glaucoma, but regardless of this he had found taking part to be a very positive experience.

Two members of group 2 described different experiences of their previous involvement in research. Participant '2F' had taken part in a large cancer study for about 10 years, undertaking various fitness tests. '2F' explained that whilst she had not suffered with cancer herself, it was important to volunteer for something that might help others in the future. When the study had finished she received a letter thanking and updating her on the outcome of the study, which had made her feel very proud to have been involved in something positive. Participant '3F' had also taken part in a clinical trial because she "had a medical condition which caused her body to produce cancerous cells". However, her experience had been rather negative because she felt that she had not received enough information and

had not received any feedback from the study in which she had participated making her feel unappreciated.

7.2.2 Behavioural levers affecting research participation

All focus group participants considered that they would take part in a clinical trial or research [the term was used interchangeably throughout the dialogue] not only for their own personal benefit but to help their family and future generations as well.

> *I think the idea of research is a positive thing, we are never going to progress with problems are we, unless people do look into it and research for future answers.* ***4M, group 2.***

> *"My father had ordinary glaucoma and my son's pressure is slightly raised, so I would be very interested if it helps people."* ***5F, group 1.***

Participant 'KR', who had participated in a previous glaucoma study, described how he had consistent contact with his clinician and members of the research team during the course of the study from which he had benefited. During the study other health issues had been identified and reported to his GP that might otherwise have gone unnoticed. Other participants felt that taking part in a research study meant that they would see a consultant more regularly and have greater reassurance in the continuity of care and additional tests.

> *Being horribly cynical, as the situation is at the moment we come once a year if we are lucky, I have never actually seen my consultant,… I have only ever seen a registrar at the most, mostly nurses, which might indicate that my condition is not very serious, but if you took part in something like this [referring to a research study], then presumably you would get to see the big man himself quite frequently!* ***6M, group 2.***

> *Yes, I only saw [consultant name] once in the eighteen months, and I thought when you said what you were doing, I thought that, arrghh, perhaps I will see him more often.* ***2F, group 2.***

However, participants also discussed their perceived risks associated with research. Some participants used examples of clinical trials involving eye drops.

Eyesight was felt to be “extremely precious” and all participants agreed that they would consider taking part in future eye research, despite the significant perceived potential risk associated with this. Participant ‘7F’ discussed how she was willing to participate in eye research but stated that she would not want to take part in a study which used a placebo eye drop as she knew this would put her eyesight at risk of further damage from high eye pressure. Both groups agreed that participation in research was about evaluating the risks involved and comparisons where made between which type of research would hold the greatest amount of risk.

> *Oh yes, well obviously with drugs trials there is a certain amount of risk to patients isn’t there? Well, I mean, not just necessarily to their overall health but it might make them feel very unwell, you know, but obviously, a group like this [referring to the focus group]... you know... well, there is no risk is there?* ***6M, group 2.***

Group 1 participants referred to studies where physical harm had been caused; Northwick Park in 2006 and the lack of ethical oversight that led to the distribution of thalidomide in the 1960s. After much discussion, the group concluded that research within the NHS did now have a reliable system of testing drugs through different phases of trials, so that if something adverse was going to happen, it would have done so in an earlier phase of the trial. Thus, the phase of the study would be used by patients to help guide them in making a decision about what risks might be involved should they have to decide if they felt taking part a study was acceptable.

7.2.3 Ethical committees

Participants felt reassured by the presence of the NHS ethical review system. The differences between different types of research studies, such as observational, interviews and clinical trials, were discussed and most agreed that all studies should undergo the same ethical review processes regardless of the type of study. Some participants were surprised to learn that all research underwent a rigorous ethical review process even if relating to a study not involving an investigational drug.

Participants felt that involvement from an Ethics Committee gave reassurances to patients that the potential risks had been considered before a study would be given approval and that an Ethics Committee would be in control during the whole study process.

> *With the ethics committees being there at every step you have to assume that things are going along alright.* ***7F, group 1.***

> *You have to have trust in the ethics committees I suppose don't you. You are putting your fate as it were in their hands, they have agreed that it is ok.* ***5F, group 1.***

In general it was felt that the current system used to ensure good ethical conduct gives research credibility and reassurances to participants. The focus group participants felt that patients diagnosed with the health condition under investigation can act as representatives of that patient population in order to give their opinion about the study design and that these opinions should inform the ethical review process on a systematically, particularly with studies that contain a degree risk or specific ethical concerns.

> *...especially if something is particularly controversial or slightly dangerous or that could help you know...yes, I have proof here that, you know, several people I have spoken to who have got it, and would like this to go ahead as it could help.* ***5F, group 1****.*

> *Possibly have someone from the patient group on the ethics committee to be able to put their view across.* ***3F, group 2.***

Another issue that arose in the focus group meeting related to feedback. It was felt that participants of research would find it beneficial to be able to provide feedback to an ethics committee about researcher conduct, whether they felt that they had received enough information during the study and how they had been treated during the research study. Focus group members felt that the ability to offer feedback would help research participants to feel more empowered and that an ethics committee could learn valuable lessons about researcher conduct and research standards.

So would they want feedback from us and how we felt, we had been treated within this trial, within this research, if there was a feedback form to say, yes we enjoyed it, yes we were kept informed, no we didn't like this part of it, yes we think this. Is there feedback to the ethics committee to say that your research was worthwhile and it was beneficial? ***3F, group 2***

7.2.4 Ensuring patient confidentiality when collecting data for research purposes

Some participants from both focus groups had fears relating to data protection and confidentiality of their information. Because participants are aware that large amounts of information are stored electronically it was felt that this could be more easily 'lost' in error. Participants also shared their experiences of doctors and health workers breaching confidentiality by discussing patient details in public areas and that pharmaceutical companies could corrupt NHS employees in order to get access to confidential information.

And confidentiality, I think that is important, even though this [details about your eyes] isn't you know terribly personal, as it were, you wouldn't want other people to know… ***5F, group1.***

And it isn't just doctors. I can remember going for my lunch one day in a pub… and there were two social workers there talking about one of their clients on the ward and I was sitting three tables away and I suddenly thought, you can't do that, I'm beginning to know who you are talking about and I think that everyone else does too... ***8F, group 1.***

...think about pharmaceutical companies that charge such exorbitant fees for medicines, you know, to the National Health. They like to get hold of all sorts of information you know. So they could use someone in the hospital couldn't they. ***2F, group 2.***

Some participants felt that better safeguarding systems were required to protect patient information and thought that researchers should be respectful of the information they have access to since it belongs to the patient. Access to patient hospital records should only be granted to researchers if the study is worthwhile

and beneficial to patients. The ethics committee was seen to be a suitable governing body that could oversee these safeguarding systems and give access to information where it was appropriate based upon the competence of the researcher to review, extract and store patient data appropriately.

However, there were mixed opinions among the groups when determining what was felt to be an acceptable level of data extraction for researchers to carry out without consent from the patient. There were those who felt that researchers should always seek consent from patients before gathering data from medical records. Conversely there was those who felt the practice of data extraction from notes was acceptable without patient consent providing that the research had been agreed by an ethics committee.

> *I suppose it is different if you have something you don't want people to know about, AIDS or HIV or something like that, urm but for something like glaucoma I don't think anybody would mind anybody knowing.* ***5F, group1***

> *My daughter is a hospital pharmacist and she is always having to be involved in doing audits on this that and the other, and again selecting information anonymously has got to be done… How else are they going to get the information?* ***9F, group 1****.*

> *I think the principle needs to be approved… It should be part of the parameters you're working with presenting your, your urm sort of rationale for your research project…****7F, group 1***

> *I think that ought to be as well, that they would ask, not just go through random batches of files. It is personal without, and unfortunately in this day and age the way that things are going, it is so easily abused with the technology. And I think that is a frightening aspect, quite frankly.* ***4M, group 2***

> *I suppose really, all our information is there for anybody to look at anyway, how many people have looked at it in the first place … so I think it can all be quite academic at the end of the day.* ***3F, group 2***

7.2.5 Withholding information from participants

Providing information to participants during all stages of the research process was felt to be important namely at the time of consent, during the study participation phase and after the study, when it was felt the conclusions should be shared with research participants. However, there were mixed views as to the level of information that should be given to participants in research studies. Some participants felt that as much information as possible should be given at every opportunity, whilst others acknowledged that there may be circumstances when this may not be possible or even necessary. Discussions focused on the fact that not all participants may require the same level of information from researchers; this being dependent upon literacy levels, personal need for information and ability to understand complex information. Participants also acknowledged that too much information might actually change the way that patients might react and feel about a study if trying to please the researcher.

> *I can see that there would be occasions when subjects [referring to participants] of the research might colour their findings to basically be nice to the researcher.* ***6M, group 2.***

Participants suggested that information should always be given in layman's terms, a brief synopsis of the research project should always be given and on-going communication throughout the study should be provided so that if a patient's condition were to change or new information becomes available, participants should have the reassurance that this will be communicated with them. As patients have the freedom to choose to opt out of research at any point, if they feel that the new information changes their willingness to continue with the study they may withdraw their consent. It was agreed that the specific important information that should always be shared with participants are the possible risks associated with a study, such examples discussed were side effects and first-in-human drug trials.

The idea of researchers deliberately withholding information from participants was discussed within the focus groups. Participants from both groups chose to discuss the topic in terms of the physical risks that participants may unknowingly be agreeing to. No definitive answer could be given as to whether it was right or wrong to withhold information, since it was felt that this was dependent upon the

merits of each individual study. The participants felt it was important that there should be a legitimate reason for withholding information and the information that was going to be withheld should be evaluated by an ethics committee, along with the type of patient safety strategies that would ensure that participants would be kept from any harm.

> *If it was something like 'a cold' then, so be it. But if they know that it is likely to cause blindness, to go to the extreme, then I would damn well want to know. Then I'm afraid that my answer would be no, I would not take part.* ***9F, group 1***

> *Because there are different types of research, so there's just paper, and a consensus of information or a consensus of knowledge or whatever you want to call it, others it is going to be more in depth. And I think the more in depth it goes, then I think you would have to ask the question, 'well why would you need to keep that information to yourself'. Why would you not share that with me? If I'm prepared to take part in a drug trial, why have you withheld information from me?* ***3F, group 2.***

The guidelines followed by ethical committees in order to protect participants from feelings that they have not been treated with respect, which would have a negative effect on future research, or cause a loss of trust in their doctors were not referred to during the focus group discussions. When probed specifically on the subject, only one person suggested that they might not be able to trust a doctor who had been involved in deceiving them.

Neither of the two participants who had previously had negative experiences of research (3F and 6M) felt that this experience would change their opinion in considering participation in future research studies.

Participants also discussed what they felt was the difference between 'withholding information' and 'deception'. There was total agreement that it was not permissible to use deliberate deception whereas withholding information would be acceptable in certain circumstances. Examples given of deliberate deception were not telling somebody they might be using a placebo or giving false information to patients.

I think there has to be a distinction between the two. I don't think you could ever condone deliberate deceit and deliberate misleading, but um, as I say, if the information is just not offered and the patient doesn't ask, then I can't see that there is too much of a problem. ***6M, group 2.***

…you might well want to do a similar sort of thing in any trial and that's withholding information, that is perfectly acceptable. But to deceive somebody by saying oh we have had no problems with this or something and they have actually been having problems obviously that would be perhaps a step too far. ***7F, group 1.***

7.2.6 Scenarios

The scenarios are presented in Figure 7.1.

Scenario 1

All participants reported that they would give their consent to taking part in the study described in the first scenario. Eight participants chose option 'A'; to give their consent to take part as long as they were fully informed after the study had finished about what the drops were and their side effects. One participant chose option 'C'; to give consent to take part but would not need to be fully informed about the study, since they trusted in clinicians/researchers/ethical committees enough to ensure their safety was not compromised.

Before making their choice, participants in focus group 2 discussed the risks associated with the study and the fact that information about the eye drops was being withheld. Together the group defined the situation and decided a course of action to overcome the perceived risks. The main elements of concern appeared to rest upon the perceived physical risk from the use of eye drops, not the fact that researchers were deliberately withholding information from participants. Once the degree of risk had been established, it was felt that the risk would be minimised because research clinicians would monitor patients more closely. Furthermore, it was felt that if a participant did have a problem with the use of eye drops and they were able to stop using the eye drops, participation would be satisfactory.

But as long as I am informed beforehand of what why and when and as long as I know I am going to be monitored throughout, so if I thought they were going to affect my eye in anyway or myself personally, then yep I would actually say, "I don't think I want to carry on with that" or the doctor would say, "no, I think you need to come off these drops" you know." ***3F, group 2.***

Scenario 2

Scenario 2 was of particular significance as it was based upon the future planned study to investigate research reactivity effects. All participants agreed that they would take part; 5 participants chose option 'C' to have the study explained and retrospective consent obtained at the end of the study, 3 participants chose option 'A' because they felt that as there would be no change to their glaucoma care and that it involved no risk, the study could be carried out without consent, although 1 participant felt that regardless of possible changes to behaviour, consent should still be obtained at the beginning of the study.

In general participants felt that because the study would be reviewed by an ethics committee and because it would not change their way or life, or their medication, that the study was acceptable. Participant 3F had previously been adamant that all information about research should be discussed with participants prior to participation. However, when considering this scenario, she felt differently:

I think because of, it's just monitoring how you are using your drops or not, so it is not going to change my way of life, you know the tablets or drops are not going to change me in anyway shape or form in the research, but as long as I know it has been through an Ethics Committee, obviously it has had permission to go through the research, but as long as I know afterwards, they say, "well look, we wanted to monitor you because now we are going to try and do a new type or dropper, or a new way of reminding somebody to use their drops and we needed to know who is at risk, and how they are going to use it. ***3F, group 2.***

Option 'C' appeared to have been favoured because participants felt the need to have information about research in which they had participated. Those who chose

option ‘A’ felt that it would be absurd to go through a whole study only to decline consent right at the end.

> *It just seems to be silly that you would go through the whole procedure and then say “no, you can’t use my results”. It’s just, it just seems daft!* ***6M, group 2.***

However, the participant who chose option ‘B’ was completely adamant that participants have a right to information, and consent should be taken regardless of the perceived benefits of the study.

> *From my point of view that negates my earlier thing, that we ought to be told, we have got a right, and I would like to be told…* ***4M, group 2.***

Many of the participants discussed the merits of such a study and felt it would really help clinicians to understand patients and potentially stop prescribing stronger drops that might not actually be necessary. It was felt that there would be no other way of collecting this information without changing the consent procedure. Participants did not consider the study described in scenario 2 to be classed as deception.

As far as I can say that is a brilliant idea. ***8F, group 1.***

I don’t feel in this case it is deception as such,… if you told people what the survey was then it would actually skew the results. I can’t see any other way of getting the information without tweaking it. ***9F, group 1.***

… in this particular scenario it must help the clinician to understand why your condition isn’t responding to the eye drops if you are not regularly taking them ...I think it is a win win situation. ***5F, group 1****.*

7.3 Discussion

The results from the focus groups used to elicit views of a modified consent method suggested that there were behavioural levers that would either increase or reduce the likelihood of patient participation in research. Focus group participants predominantly based their initial decision as to whether they would participate in research on the perceived risks of any study, a common factor cited in other survey studies.[246-248] The findings confirmed the established standards that research participants should be given information about the research and that this should be in understandable layman's terms and clearly identify any associated risks with participation in the research. However, when patients need to be masked to study the fact that they are taking part in research, it appeared that use of a modified consent procedure and at least the initial withholding of information might be acceptable to participants, should this entail no, or minimal, risk. Interestingly, previous research by Boter et al., has shown that only a small minority of participants had negative feelings after finding out that information had been withheld from them when involved in research.[235]

An ethics committee has an important role in the research process and is trusted by patients to represent them and make decisions on their behalf. However, the focus group participants felt that additional consultation with representative patient groups would be ideal before approval is given to research. Furthermore, it was felt that research participants should be given the opportunity to give feedback to an ethical committee about the conduct of the research once a study was completed. Focus group participants also stated that for studies that collect information from patient medical records there should be close regulation to ensure that the research is worthwhile, that researchers have the required competency to complete the task and that they would safeguard patient confidentiality. In certain circumstances, particularly if a study where to involve the collection of highly sensitive data, the focus group participants agreed that consent should be sought from patients before data collection.

An important conclusion that was made in the focus groups was that an ethics committee should work in conjunction with patient groups to decide when the use of a modified consent procedure was justifiable and ensure that such studies would not cause harm, distress or hold additional perceived risks to participants.

In the mock scenarios, the focus group participants tended to agree that they would take part in a study that withheld information from patients. When the mock study was specifically aimed to assess patient behaviour towards medication adherence, all but one participant agreed they would be happy to participate without giving prior consent. In general, participants favoured the idea of debriefing participants that may have taken part in a study without their knowledge, but stated that a formal retrospective consent process was not always entirely necessary.

The findings from the focus group meetings suggested that designing a study using a retrospective consent design was justifiable and would be be acceptable in a local glaucoma patient population for the specific purposes of monitoring adherence to medication. However, it was felt that consultation with a wider patient population was required to show the generalisability of these opinions. Building on the knowledge gathered from this preliminary work, Chapter 8 describes the body of work that was undertaken in order to design and implement a questionnaire that could seek opinion from a wider population of both patients and members of the public.

7.4 Methodological critique

The focus groups involved the use of hypothetical questions where respondents were asked to make predictions about their future behaviour. Such questions may reveal intention or a state of mind at the time of asking, but have often been found to be poor predictors of actual future behaviour.[249] Furthermore, often in a hypothetical situation there is not enough relevant information given to the respondent in order for them to make a judgement.[241] Use of hypothetical questions could therefore be considered an unsuitable method for collection of participant opinions and attitudes. However, the researcher was careful to use this type of questioning in the context of a study scenario that gave specific information in which respondents were able to identify with, which may have negated some of these misgivings.

The focus group identified that participants found it difficult to express their explicit opinion about the acceptability of research due to the range and complexity of different types of research. Participants needed to know more information about the reasons for a study and exactly what was involved, including the potential risks and benefits to patients. Thus, the use of two scenarios enabled participants to clearly identify and discuss their opinions in context and were better able to give specific examples and explain their judgements in context. More importantly, the scenarios gave a systematic comparison of individual responses to different behaviours. However, use of scenarios can involve subjective interpretations so respondents may distort the information given through recall error and report based on their selective perceptions. In addition, participants may have been keen to provide a socially desirable response. However, in the probing session, participants maintained their initial response and gave good evidence to support their opinions.

By virtue of the fact that the participants taking part in the focus groups had willingly volunteered to take part, they were likely to represent the characteristics held by more motivated individuals and therefore those more likely to be willing to volunteer for research generally. Therefore, in order to seek opinion from a wider range of individual characteristics, a follow-up questionnaire survey was considered to be beneficial.

Chapter 8. Questionnaire Design

A questionnaire method was chosen for use in the collection of standardised responses from a large population and assess whether the opinions elicited from small focus groups could be verified. The questionnaire had to be designed in such a way as to yield reliable, valid, sensitive, unbiased and complete data to ensure the differences recorded were not due to artefact, or variances in the way the data were collected. [250] Literature on the principles of questionnaire design aided the design of the questionnaire and is discussed in this chapter.

8.1 Questionnaire specification

The primary outcome variable was designed to measure respondents' opinion of taking part in a research study that used a modified consent method. The focus groups described in Chapter 7 had revealed the core concepts that were interwoven with the primary outcome variable and these had to be measured by the questionnaire. The extracted themes from the focus groups were categorised into three main domains; experiences, opinions, and attitudes. Table 8.1 summarises these core concepts derived from the focus group study, separated into their respective domains and how these were matched to questionnaire outcome variables. Demographic information, previous experiences of research, experience of health services and diagnosis or knowledge of glaucoma parameters were also collected to establish variances in primary outcome due to these variables, this being a benefit of using a questionnaire method with a large cohort.

Table 8.1 The matrix of core concepts with their respective questionnaire outcome variables

Domain	Core Concepts	Question objective
Opinions	Concerns about taking part in research.	Describe the concerns participants have about taking part in research. Identify whether there is an association between previously taking part in a research study (attitude) and opinion about possible concerns when taking part in research?
	Expectation about information provision and advice about the possible risks when taking part in research?	Report the percentage of respondents that would expect to receive information about the possible risks associated with taking part in research.
	Is it acceptable for researchers to withhold information from participants?	Report the percentage of respondents that feel it is acceptable to withhold information from participants. Describe opinion about the main concerns and report if this has any association with the main outcome variable.
	Is it acceptable for researchers to omit participant consent before entering a study?	Report the percentage of respondents that feel it is acceptable not to take consent before entering a study and any association with the main outcome variable.
	Satisfaction with services provided at the eye clinic.	Describe experiences of the eye clinic and any association with the main outcome variable.
	Does taking part in research improve satisfaction with health care received?	Report the percentage of participants that would expect an improvement with their health care when taking part in research and any association with the main outcome variable.

Domain	Core Concepts	Question objective
Experiences	Previous experience of research.	Report the percentage of the cohort which had previously taken part in research and any association with the main outcome variable.
	Positive or negative experience of research.	Describe experiences and any association with main outcome variable.
	Type of research participants have taken part in previously.	Report the percentage of respondents who have previously taken part in and any association with the main outcome variable.
Attitudes	Reasons why participants do not value research.	Open question for participants to report any reasons why they did not value the research they participated in.
	Willingness to participate in research.	Report the willingness of participants to take part in research and any association with the main outcome variable.
	Concerns associated with information being withheld when taking part in research?	Describe the main concerns when information is going to be withheld from participants.
	What are the main concerns with consent not being taken before entering a study?	Describe the main concerns associated with consent is not being obtained before entering a study.
Demographics	Do demographic variables influence the main outcome variable?	Describe patient demographics and any association with the main outcome variable.

8.2 Questionnaire Construction

8.2.1 Presentation

The presentation of a questionnaire is important to enhance readability, understanding of the questions and response options and encourage successful completion. The recommended format is to print questionnaires as booklets to give greater ease in reading and turning pages, reduction of the risk of losing pages and facilitate the use of a double page format.[251] The placement of the questions on the page must ensure that respondents do not accidentally skip questions or need to turn a page mid-question since this is more likely to result in response errors. Splitting response categories over two pages may also introduce a subtle form of loading, as respondents may not read or give less consideration to items on the second page.[252]

Questions should not be crowded onto the page in order to make the questionnaire look shorter; it is argued that a longer questionnaire, which is less cramped and has more “white space”, looks easier to complete, generally resulting in higher response rates and less errors. Sufficient space should be available for responses to open-ended questions, particularly as the amount of space available is likely to act as an indication of the level of detail required by the respondent. It has been shown that using lines for open-ended questions, makes the questionnaire look more crowded and should only be used with short answers of one or two words or a number.[253] A font size of 12 points is considered sufficient but a minimum 14 point san serif font should be used if respondents are likely to have visual impairment.[254]

There is a paucity of evidence for the suggested use of colour in questionnaires and its impact on response rates and errors.[254] The paper upon which any questionnaire is printed has been recommend to be white or off-white[252] and the contrast between the type and the paper is important for legibility; black on a white or yellow background has been shown to give the best contrast.[255] The use of thicker paper has been recommended to reduce print showing through from the previous page.[256]

Graphic non-verbal language such as achieved with spatial arrangement of information and other visual phenomena such as colour and brightness should be considered. There is a need for consistency in the brightness, colour, shape and

location in order to define the desired navigational path for respondents to follow when answering a questionnaire.[254] Questions should also be numbered to minimise the risk of skipping questions and to facilitate cross referencing in data processing.[251]

The layout of the questionnaire was designed using the above recommendations to maximise the response rate. An envelope with a bright design was chosen to attract initial attention to the questionnaire. A pen was enclosed in the envelope for respondents to use to complete the questionnaire whilst attending their appointment at the hospital if they chose too. A booklet style of high quality paper was chosen in order to look professional and make the questionnaire easier to complete without a desk.

8.2.2 Response alternatives

A list of suggested responses from which respondents can select their most appropriate answer(s) to questions are termed 'response alternatives'. Response alternatives can clarify the intended meaning of a question and direct the respondent as to what is important to the researcher or what is expected. A question may state, "What have you done today?" Such a broad question can be interpreted in multiple ways and only when respondents are given a list of options might they know what was intended by the question for example, "had a shower", "drove to work", "drank a cup of tea", or the question could have intended to search activity based responses such as "went to work", "took part in a leisure activity", "did the cleaning". However, listing items in this way reduces the likelihood that respondents report other activities that have not been suggested.[253] Whilst response alternatives can be used to frame intention of the question, the subtle unintentional influences that they can introduce may change the meaning of a question, an issue that is frequently overlooked when designing a questionnaire[257] and a problem which is discussed again when considering the order of questions in paragraph 8.2.4.

Questions such as "Did you ever do…?" are straightforward, with the respondent searching through their own memories for a suitable example. However, if a respondent does not have a suitable answer stored in their memory, the judgement they make will be strongly affected by the context and question cues.[253]

Using the same posed question “What have you done today?”, if the respondent is aware that the questionnaire is about driving to work, they might automatically offer this as a sensible answer and not give any thought to the other activities that they have carried out that day, since their memory recall is focused on thinking about driving to work.

When providing respondents with a list of multiple-choice answers, ordinal biases may occur as people tend to choose figures that are near the average or middle of a series. Therefore, the sequence order of the response options can be randomised into different orders during piloting, presenting different answer sequences to different groups to gain a measure of the ordinal bias and make allowances for it.[249]

8.2.3 Type of questions

Questions can be divided into two classes; those which are verifiable, for example behavioural and factual information, or psychological states and attitudes which are non-verifiable.

Attitude questions/statements deal with awareness, perceptions, opinions or beliefs, and essentially the state of mind of the respondent. An attitude or belief is likely to be more complex and multi-faceted than a question of fact and may therefore need to be approached from a number of angles rather than relying on a single question to gather this type of information. In such cases, multiple questions using ‘scaling’ approaches can be used. Scaled ‘attitude statements’ consist of approximately eight statements that have been selected and put together from much larger sets of statements. The traditional method used to compose scaled attitude measures is a complex process requiring extensive piloting and statistical analyses. The resulting attitude scales are not designed to yield subtle insights into individual cases, but give estimates of attitudes of broad groups and how these attitudes may relate to other variables within the survey. ‘Attitude statements’ are usually single sentences that express a point of view, belief or judgement, and are phrased so that the respondent can either agree or disagree; these require careful composition in order to encourage the respondent to express their response in their own way. Thus, using double questions, double negatives and statements which are too long should be avoided.[249]

The majority of respondents were unlikely to have taken part in previous research and thus would not be able to draw on previous experiences in order to answer questions on this topic. Therefore, the vignette about a glaucoma research study that had been successfully used by participants in the focus groups described in Chapter 7 was modified for use within the questionnaire. In this way, respondents were able to engage themselves in a scenario that could be applicable to them and provided the context from which to base their responses to the questions.

Classification questions about personal information, used for stratifying the sample, (for example, age, sex, marital status, income and education) were placed at the end of the questionnaire and preceded with an explanation for their necessity. Reassuring the respondent that the inquiry was genuine and for a good reason has been suggested to avoid any offence to be caused by questions that could be regarded as sensitive.[249]

Questions that could be considered threatening or sensitive to a respondent required careful construction to avoid potential negative response effects or under reporting. By deliberately loading questions and acknowledging that certain behaviours that are perceived as 'socially undesirable' are commonplace, or citing authority to justify the behaviour, for example "Many doctors say…", it has been shown that responses can be optimised.[254] Thus, an explicit statement to confirm confidentiality was used to overcome any possible apprehension that respondents might have felt about completing a 'health questionnaire'. The introduction page to the questionnaire explained why the respondent had been 'chosen', with endorsement from two 'sponsors' (UEA and NNUH) to give further reassurance to respondents who might have been sceptical about completing questionnaires.

8.2.4 Ordering of questions

Questionnaires can become unpleasant for a respondent if the ordering and phrasing of the questions are not synthesised correctly. Care must be taken to ensure that questions work from the easiest through to the more difficult in a logical sequence, with one question setting the context for later questions, or conversely that earlier questions do not influence later questions, since the order of questions may affect the overall semantics of any given question which can influence participant response rates. 'Order effects' caused by the context of a

question can be set deliberately to clarify the meaning of a question, or encourage respondents to consider an issue in the context that is of interest to the researcher and aids the respondent to retrieve information. Unfortunately, the context is sometimes set unintentionally and this leads to adverse 'response effects' or 'response errors'.[253] Thus, researchers need to evaluate the design of the questionnaire so that as far as possible, context effects are deliberate rather than unanticipated.

Estimations of order effects can be quantified using statistical models. If the bias cannot be treated statistically, then randomising question order across participants can be implemented. In this case the researcher produces different questionnaires, with random ordering of relevant items.[249, 254, 258, 259] Unless there is some natural ordering required, randomising response alternatives will not eliminate context effects, but will ensure that conclusions do not reflect on the specific order of response alternatives.[253] General or ambiguous questions will increase context effects, although the context effects will be much smaller or may vanish completely if the respondent already has a judgment or substantial amounts of relevant information accessible in memory.

Leading questions can suggest what an answer should be, in the opinion of the researchers, or indicate the researchers' points of view. Loaded questions or words may also suggest feelings of approval or disapproval. Furthermore, certain words may be more or less neutral in one context or group than in another and careful consideration of words and piloting has been shown to help control for these dangers.[249]

The preliminary work with the focus groups described in Chapter 7 highlighted that the context of the questionnaire would be important to the way that respondents interpreted the questions and that additional background information was required to help respondents answer the questions in the correct context. Therefore, additional information was provided between questions in order to clarify why researchers would wish to use a 'modified consent procedure'. The order of the questions was purposefully executed to encourage respondents to consider the issues in the context of the research study scenario from the outset. However, it was possible that in setting the context, responses to the main outcome variable may have been altered if respondents had felt led to answer either positively or negatively by these 'context setting' exercises.

Therefore, two versions of the questionnaires were produced. Version 1 had the main outcome variable positioned near the end of questionnaire whilst Version 2 was configured to present the main outcome variable at the beginning of the questionnaire to determine whether the responses to the main outcome variable could be collected without bias or order effects.

However, two main concerns with the Version 2 configuration were considered. Firstly, respondents might not have understood the context within which to answer the questions and secondly, respondents might have returned to the beginning of the questionnaire and changed their response once they had read subsequent questions that set the context.

To test these context effects and to see if question order had an effect on responses, ten non-clinical colleagues from the UEA and NNUH, naïve to the research aims, were asked to complete a pilot version of the questionnaire and give feedback to the researcher. Five colleagues completed Version 1, and five colleagues completed Version 2. Feedback was recorded from each colleague using probing questions and open dialogue:

- What were your experiences of completing the questionnaire? (i.e. difficult, easy, hard to read, too much to read, too many questions etc.)?
- Were there any improvements that you would suggest?
- How did you find the order of the questions?
- Were you tempted to go back and change any of the answers you had given to previous questions at any stage?
- Do you have any other comments?

The responses were analysed qualitatively to look for context effects and to decide which questionnaire would provide the best format to be taken forward for further testing; Tables 8.2 and 8.3 summarises the feedback and summary of suggested changes for Versions 1 and 2 respectively. There were no notable differences with respect to the order of the questions between the two versions, thus order effects were not thought to be significant. However, there was still a possibility that the justifications given within the questionnaire may have had an effect on the main outcome variable. To overcome the potential bias, the main outcome measure was presented both at the beginning of the questionnaire, before any

justification for using such a methodology was given, and again at the end of the questionnaire.

Table 8.2 Feedback from Version 1 of the questionnaire

ID no.	Feedback question	Summary of outcome or Changes implemented
	What were your experiences of completing the questionnaire?	
11	Did not take longer than 20 mins and was OK to complete	No overall changes made to the length and readability of the questionnaire as it was well accepted by respondents.
12	Not too difficult or too long	
13	Took 11 minutes. Easy to follow and read. Liked the scenario.	
14	Easy to read. A little daunting at first as the booklet seems big, but doesn't take long to complete.	
15	Easy to read	
	Where there any improvements you would make?	
11	Did not think 'value' was the right word, for experiences of research question, and think 'enjoy' would be better.	To be tested in the cognitive interviewing pilots.
12	Wanted to be able to tick more than one box in the scenario question.	Response options were revised.
12	Highlight within the text that the difference between the withholding information question and not gaining permission.	Withholding information and consent issues, now combined into one question.
12	Felt it was difficult to answer questions about how you might 'feel' and was uncertain about 'feelings' on the subject.	Questions about 'feelings' removed.
13	Did not read bold headers at top of page, so could be clearer.	Could not improve.
	How did you find the order of the questions?	
11	No problem	Respondents were happy with the order of questions. The questions relating to the research example should follow on directly rather than being split.
12	No problem	
13	No problem	
14	Question about the research example should come directly after the research example, not at the end.	
15	No problem	
	Where you tempted to go back and change any answers?	
11	No	No respondents reported being tempted to and change their answers.
12	No	
13	No	
14	No	
15	No	
	Other	
12	The scenario box needs to be made bolder with a darker box or symbol 'I' to indicate information.	The scenario box was redesigned to be more 'highlighted'.
12	Introduction too long and does not need an explanation about glaucoma or 'a glaucoma patient has tested this questionnaire'.	The introduction was made more succinct.
14	Found it difficult to just pick one opinion for the final scenario question.	The response options have been revised.

Table 8.3 Feedback from Version 2 of the questionnaire

ID	Feedback question	Summary of outcome or Changes implemented
	What were your experiences of completing the questionnaire?	
1	Easy to complete and understand.	No overall changes to be made to the length and readability of the questionnaire as it was well accepted by respondents. One comment about scenario being part of the questionnaire was addressed by making the scenario clearer within the text.
2	Difficult to read the first page and understand the scenario was part of the questionnaire.	
4	Well written and did not feel too long.	
5	Not too long and no problems answering the questions.	
	Where there any improvements you would make?	
2	Clearly label 'The example' as such.	The scenario was given an additional heading: 'The Example'
3	Introduction was too long and wordy.	The introduction was re-written introduction to be more succinct.
3	The questions were repetitive.	Questionnaire was made shorter to be more succinct.
4	Felt repetitive.	
5	Grammatical problems with question 5 once ticked box 'c'.	Question 5 has been removed.
5	The introduction was too long and felt that you needed to be a glaucoma patient to answer the questionnaire.	Introduction was re-worded to avoid this.
	How did you find the order of the questions?	
1	No problem.	Added more information to the introduction to set the context better from the outset. Respondents were happy with the order of the questions.
2	Needed to read the whole of the questionnaire to understand the reason for the scenario and question that followed.	
3	No problem.	
4	No problem.	
5	Helpful to have the question about the scenario directly following it (has dyslexia).	
	Where you tempted to go back and change any answers?	
1	No	No respondents reported being tempted to and change their answers.
2	Did review the questions first.	
3	No	
4	No	
5	No	
	Other	
2	Gave two answers to the scenario instead of one because she could not choose only one.	Changed response options to the scenario question.
3	Withholding information question – was not able to only give one answer.	Changed response options to the scenario question.
3	Withholding information question "depends on type of research", is too open.	This response option was removed.
3	Would like to have the questions linked to a particular scenario as had to tick 'would depend on research'.	All questions revised to be linked to the scenario.
4	Would like to have the questions linked to a particular scenario as had to tick 'would depend on research'.	
4	Question 'Withholding information' needs to add a response about risk to patients.	The response options were revised.

8.2.5 Reliability and validity

The aim of questionnaire design is to give a valid and reliable measure of a particular construct; reliability referring to the probability of obtaining the same results again should the measure be duplicated and validity referring to whether the question measured what it intended to measure.[241, 249]

Evaluation of reliability can be measured in terms of scale consistency using a Cronbach's alpha, or a test-retest method.[241, 260] Questionnaires using such methods to test for reliability must contain multiple measures which can be correlated with each other. For example, to test reliability of factual questions, asking the same question twice with slightly different phasing can identify errors in question wording, serial or contextual effects and is therefore a measure of internal validity.[249, 261]

Content validity cannot be properly quantified since it refers to how representative the measure is to the specific construct. Preliminary work on the questionnaire design confirmed the validity of the content to ensure that all of the aspects of the concept informing the research question had been captured within the questionnaire. Interviews and focus groups enabled a "feel for the problem" and generated a pool of questions to meet this aim.[260]

Measurement error can in principle be verified in reports about behaviours or events, but this is not possible with attitude or non-factual topics, which deal with state of mind.[253] Questionnaires reporting subjective evaluative judgements are much more difficult to measure and validate than questions of fact, due to the lack of criterion groups to compare with the questionnaire. Furthermore, non-factual questions are more open to bias caused by wording, response sets, leading questions, social desirability and contextual effects. In general, the more difficult it becomes to find a suitable external criterion, the more researchers will concentrate of content validity to ensure the questionnaires are a well-balanced sample of the content domain to be measured.[249]

Construct validity offers a measure of external consistency by comparing the new scale or questionnaire to another independent measure of the same variable and ensures the content of the questionnaire measures the intended construct.[249] However, in the case of a questionnaire designed to evaluate opinions on modified consent for adherence research, there were no comparable criteria available. The

questionnaire was designed to feature mainly non-factual data relating to each of the respondent's own opinions. Furthermore, with no previous evidence to suggest what factors might determine behaviour decisions regarding use of a modified consent procedure together with no previous measures for comparison, testing validity and reliability involving correlation of test items was not deemed possible; instead, the focus remained upon determining good content validity and context effects.

Face validity, confirms the extent to which a measure appears to measure what it is supposed to measure. A questionnaire that seems relevant to the lay person is said to have "face validity".[262] Face validity was sought from non-clinical hospital staff and university staff reviewing the questionnaire. Following these preliminary checks, a focus group with PPIRes group members reviewed different ideas for the design and wording used in the questionnaire. Seven PhD students from the Medicines Management Group at the UEA with experience of questionnaire design were also asked to critique the design and content of the questionnaires. Minor revisions to the wording, design and content used in pilot questionnaires were made based upon their recommendations. With endorsement from these lay and experienced representatives the first full version of the questionnaire was drawn together resulting in questionnaire version 3 shown in appendix 17. However, further piloting was required before the questionnaire could be considered complete. Chapter 9 describes the cognitive interviewing approach[263] used to gain further face validity.

Chapter 9. Cognitive interviewing

9.1 Introduction

Before using the questionnaire designed to determine the acceptability of an adherence study involving modified consent, it was considered necessary to test the questionnaire using a cognitive interviewing technique. Cognitive interviewing was considered an ideal technique to reduce measurement error due to poor content validity or context effects and to identify problems relating to format and interpretation of the questions.

There is complexity in the thinking processes that are involved in answering a question. In general, it is known that respondents will do their best to answer all questions put to them in a questionnaire and they are likely to modify the question in their own mind, if they have to, in order to answer them. Particular questions that are prone to modification are questions that call for mental calculations for example, 'how much do you use per month?', questions that do not apply directly to the respondent, issues that they do not have any experience of and general questions or questions with conflicting parts.[264]

Several proposed models have defined the sequence of cognitive processes that occurs when respondents are asked a survey question. In its simplest form, there are four actions that respondents must complete in order to answer a question. Firstly, a respondent must comprehend the question, and then retrieve the necessary information from their long-term memory. A respondent must then make a judgement about the information needed to answer the question and then respond to the question. However, the process is probably more complex than this simple linear model would suggest involving numerous interactions between the different phases.[250] Figure 5.1 illustrates a task-focused 'question-and-answer' model. The model can help to identify the cause of measurement errors and identify whether the problem is connected to comprehension of the questions, process or communication errors.[250]

- Comprehension - the key concern is that respondents understand the question in the manner that the researcher intended. Interpretation of the

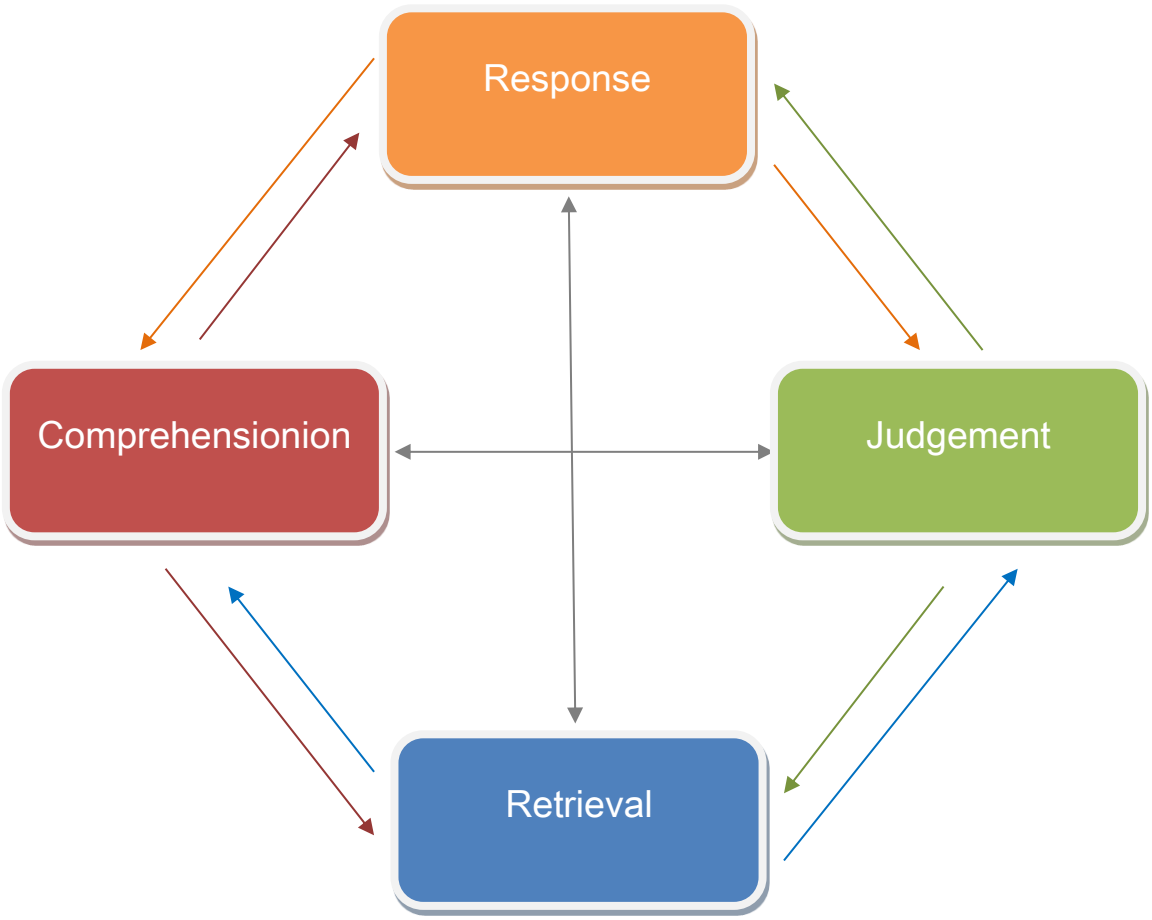
question is often based upon the respondents background stock of knowledge and what the questionnaire requires.[253] Literally understanding the words will not enable the respondent to answer the question, they will need to draw upon their knowledge and background information to interpret the text to give a meaningful answer; these two intertwined processes must work together to provide a semantic understanding of the question with a pragmatic meaning.[265]

- Retrieval of information - information retrieved from the long-term memory will either be factual (current of historical) or attitudinal. If the retrieval context is different to the original encoding context, then the respondent many not be able to recognise that the event took place or be able to recall the correct event. The rarer and more distinctive the event was, the more likely a respondent is to remember it, so that commonly occurring events will be harder to distinguish and recall individually. There are several processes involved in retrieval that might result in respondents being unable to recall an event, or recall it accurately. Giving context to the question may help respondents to use their own recall strategies[250] and behavioural questions are more likely to be accessible to respondents if the behaviour is of personal importance to them. When designing questions, it is also important to assess how easily respondents will be able to retrieve the information required and to what level of detail.

- Judgement - judgement is very important in the question-and-answer process since information is often difficult to recall accurately, may be incomplete, or the question requests a view or opinion on something which may not have been thought about for some time or in that context.[253] A respondent must first consider if they understand the question in relation to their situation and determine if they have access to the information requested. Following this, the respondent will modify their answer to meet the perceived needs of the question in terms of detail and accuracy. In addition, judgemental heuristics will affect a respondent's ability to answer frequency questions. People tend to estimate the frequency, likelihood or typicality of events by the ease with which they can bring relevant examples to mind.[250, 253]

- Response - having formed a judgement, a respondent must format the response in accordance with any pre-defined answers on the questionnaire. Thus, the choice of response method originally chosen by the researcher, may affect the way the respondent decides to answer the question and, therefore, the results. Likewise, the response alternatives, may also affect the interpretation of the question and thus the recall and judgement strategies used. Respondents may also wish to edit their answers before communicating them in order to conform to social desirability. However, this is normally limited to sensitive and potentially threatening questions.

Figure 9.1 Question and answer model



To reduce measurement error due to the respondent question-and-answer process, the cognitive processes known to influence respondent behaviour must be considered in questionnaire design. For this reason, it is recommended that questionnaires undergo extensive pre-testing with focus groups and cognitive

experts, followed by cognitive interviewing with the intended population of respondents, in order to identify problems relating to format and interpretation.[253]

9.1.1 Cognitive interviewing

Cognitive interviewing is a tool for pre-testing survey instruments uniquely sourcing information about the cognitive process. Collecting verbal reports has become a standard method of research in many applied areas; accounting, management of learning disabilities, development of survey questions, validation of multiple-choice questions and user testing of computer products.[263] The use of verbal reports focuses on the mental processes involved with answering questions; question comprehension, retrieval of information from memory, judgement processes and response processes.

The use of verbal probing is the basic technique of giving “probes” to a questionnaire respondent in order to gain an insight into specific information relevant to a question or an answer given by a respondent.[241] The probing is either carried out during the task (concurrent), or once the questionnaire has been completed (retrospectively).[250] Whether probing is done concurrently or retrospectively, probes will either be scripted prior to the interview, or spontaneously ‘thought up’ during the interview by an interviewer. The "spontaneous" approach to probing may be less scientific, but the most interesting and productive forms of probing often develop through the course of an interview, as a product of the particular relationship between the interviewer, respondent and questionnaire. One of the key underlying assumptions of the cognitive interviewing approach is that these developments often cannot be anticipated in advance of the interview. Further, a subject’s answer to a particular probe may well lead the interviewer to use other probes and to follow-up on the issues that emerge as the most interesting or important.[241]

Probing methodologies tend to lead a respondent to report their thought processes in a coherent and intelligent dialogue with the interviewer. A respondent has time to rationalise their behaviour before reporting their thoughts to the interviewer. Probing during a questionnaire task itself may reduce the time respondents have to ‘smooth over’ their answers, but interrupts the thought process of completing the questionnaire.

The think-aloud method, was largely developed by Simon, Newell and Ericsson[263] and first used in the 1990s as a method for piloting questionnaires. The concurrent think-aloud method asks a respondent to keep talking about whatever thoughts come to mind, whilst completing the questionnaire. No interruptions or suggestive prompts, or questions are required, as a respondent gives a concurrent account of their thoughts. Because all conscious effort is directed at solving a problem, a respondent has no room left for reflecting on the task and therefore talking aloud does not interfere with the task as can happen using probing techniques.[263]

For most individuals, expressing their thoughts by talking out aloud becomes a routine within a few minutes and most respondents immediately forget the presence of a recording device or interviewer.[253] The data gathered by cognitive interviewing is also very direct since there is no delay in relaying thoughts. However, because there is no interpretation by the respondent, the think-aloud protocols are not necessarily complete since the respondent may only verbalize part of their thoughts. Therefore, the structuring of the information gathered by cognitive interviewing is left to the person analysing the protocol. Furthermore, the information collected may be less detailed and may miss some problems with the questionnaire.[266]

However, a retrospective think-aloud method allows an interviewer to ask questions about completion of the questionnaire at suitable intervals during the process, perhaps after a question, or at a section break. More detailed data is obtained using the retrospective method compared to concurrent think-aloud and the interview probes may encourage quieter respondents to talk. However, interviewer probes could cause equal contamination of any results by interrupting the task process. If a respondent is particularly quiet and prompting or probing is required by an interviewer, this could potentially change what was intended as a concurrent think-aloud method into a retrospective think-aloud method, thus ‘muddying the water’ between the two.[253]

Neither concurrent nor retrospective think-aloud methods change the kinds of strategies used by respondents to retrieve information. The only possible effect is that think-aloud methods may spur respondents to make greater cognitive efforts to retrieve information.[267] Most respondents are ‘cognitive misers’, doing just enough retrieval to come up with an answer that they think is acceptable.

Questioning the processes that a respondent uses may increase this level of effort, a possible Hawthorne effect in its own right, but studies to test this have been inconclusive.[253]

Practitioners of cognitive interviewing techniques often mix think-aloud and probing techniques into the same interview. In fact, procedural flexibility, as opposed to rigid adherence to one dogmatic approach, has been often viewed as one of the most attractive features of the cognitive interviewing approach.[241]

Think-aloud protocols and probing methods are qualitative in nature and whilst they might indicate the existence of a problem, they cannot provide quantitative information on its extent or with respect to the size of effect. Furthermore, the method relies upon the skill of the respondent to verbalise their thought processes which discriminate against less articulate respondents.[250]

Despite the reservations and limitations outlined, cognitive methods have greatly improved our understanding of sources of measurement error in questionnaires and survey methodology and should be seen as a component of the assessment process of questionnaire design. Cognitive interviewing techniques are used by several research groups working within healthcare fields. The use of cognitive interviewing in questionnaire development, however, has gone unreported in many publications, possibly because of the space constraints for the methods sections of published papers, particularly with respect to piloting components.[268]

9.1.2 Sample size

For the successful use of cognitive interviewing in questionnaire design, determining the number of interviews requires judgement by an interviewer. If it becomes obvious after several interviews that there are major problems to be rectified, then there is little benefit in conducting more interviews before modifications are made to the questionnaire. In the very early stages of questionnaire development, as few as four interviews may be sufficient to make improvements to an initial draft questionnaire. An advantage of the cognitive approach is that, if the basis for the failure of a particular question is understood, a resolution to the problem may be apparent. After the questionnaire has been revised, a new round of interviewing can be conducted to test the changes.

However, such small sample sizes have been criticised.[269] More important than sample size when using cognitive interviewing, are the characteristics of the study participants. Participants need the skill to verbalise their thinking processes as previously discussed.[250, 266, 270] Furthermore, researchers expect that the sample will be representative of the population of investigation and will reveal all the dimensions of a research question.[271]

In general, due to the small samples involved in cognitive interviewing, a researcher's judgment is required, in determining the implications of any findings. For example, a particular interview may have been uncharacteristic, and could be ignored. Alternatively, it may be found that a set of subjects tested were more highly educated, on average, than the population to be surveyed, such that only a small number of interviews would be necessary to achieve significant improvements.

9.1.3 Processing data from cognitive interviews

There are a variety of methods used for compiling the results from cognitive interviewing. In early work, protocols of subjects' thinking-aloud consisted of the researchers' notes summarising the vocalisations of respondents rather than direct transcriptions of actual words. Until tape recorders became available (1945) there was no practicable means to record verbalisations.[263] However, from written transcripts, a researcher can obtain almost instant access to all the verbalizations corresponding to a given process and coding reliability can be addressed by several coders with the same raw transcription.

Some researchers listen carefully to the recording of each interview, whereas others will work only from written notes. Many researchers will make a report for each interview conducted, whereas others may produce one written report encompassing the results from all interviews. Sometimes it is necessary to compile the exact responses from respondents whereas, in some circumstances, the response data is less relevant, since the qualitative element is of much greater importance.

Some researchers prefer to rely on standardised analysis of recordings of interviews; however, this is a time-consuming activity and the appropriateness

depends on the nature of the testing. When revisions are required quickly, it is not often possible to devote the resources necessary to transcribe and analyse recorded interviews; in this case, reliance on written outcome notes alone may be sufficient. Recording is still valuable where project staff or a sponsor/client may want to listen to a recording to get a first-hand impression of how a questionnaire is working.

There has been debate about whether formal or informal analysis of cognitive interviews is most useful. In a study by Murtagh et al[268] formal analysis consisting of transcription and content analysis of the interviews was undertaken. However, for the present study it was felt unnecessary to go to these lengths of analysis since it was considered straightforward to identify the difficulties and those questions that worked well. In addition, complex and intensive coding has been shown to be ineffective in diagnosing problems that require expert judgement, such a faulty question ordering. Thus subjective interpretation remains key to analysis and a reasonable trade-off between completeness and timeliness is recommended.[241]

9.2 Method

In order to reduce measurement error due to poor content validity, context effects, and to identify problems relating to format and interpretation of questions, cognitive interviewing was used to test the questionnaires that had been designed to assess the acceptability of an adherence study involving modified consent.

9.2.1 Participant identification and recruitment

An invitation to participate in a cognitive interview was sent to all hospital staff at the NNUH via the weekly electronic intranet newsletter. An e-mail was also sent to patients who had previously registered an interest in current adherence research whilst recruiting focus group participants. Individuals interested in participation were provided with a copy of the participant information sheet and consent form either sent electronically or posted as requested. After reading the participant information sheet, those willing to volunteer were asked to contact the Glaucoma Research Unit to register their interest and arrange a date for their interview. The written consent was taken at the time of their interview. Interview appointments were arranged to suit the participant and took place in the NNUH Glaucoma Research Unit office or in participants' own homes, as preferred.

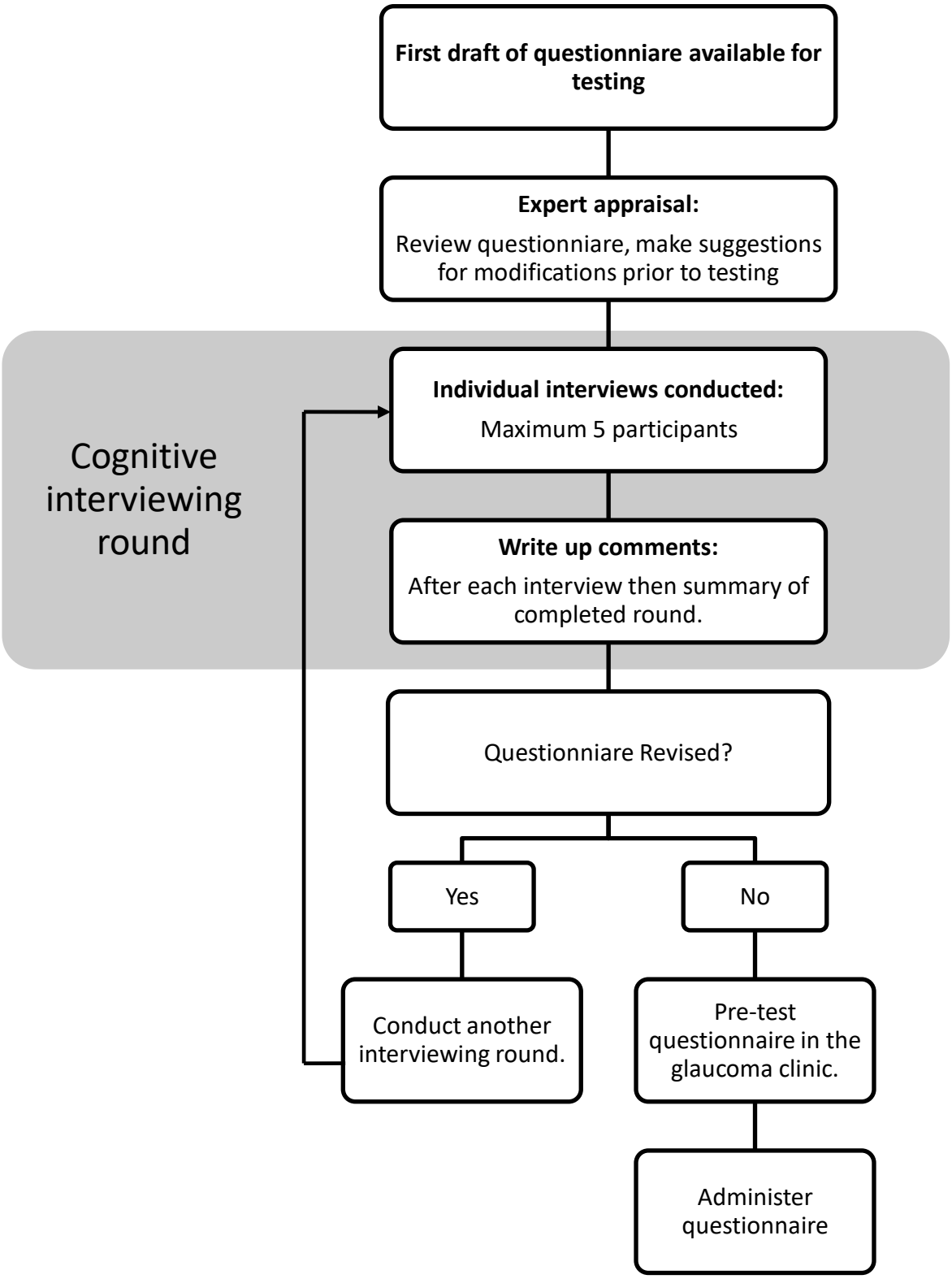


Figure 9.2. Flow diagram of questionnaire development using cognitive interviewing techniques

9.2.2 The cognitive interviewing task

During each participant session, the researcher guided the participant to use a think-aloud procedure, audio recorded the participants' voice, observed the participant and took notes. Based on evidence from Sudman *et al.* (1996)[253] and Van Den Haak *et al.* (2003)[270] the following procedure was undertaken:

Upon arriving, each participant had the opportunity to ask questions about the task. If still agreeable to participation, each interviewee was asked to complete the consent form and demographic collection form. The demographic information (age, sex, ethnicity, employment and marital status) was collected to enable a description of the population.

The interviewer taught the participant how to perform the think-aloud procedure. The training generally involved practicing at the start of the interview. An example think-aloud exercise would start with the interviewer saying

"Try to visualise the place where you live, and think about how many windows there are in that place. As you count up the windows, tell me what you are seeing and thinking about."

Depending on how well a subject responded to this exercise, further training was carried out, prior to beginning the core part of the interview as suggested by Willis in 2005.[241]

The following instructions were read out verbatim to ensure consistency:

"Think-aloud while completing the questionnaire. Please pretend that I am not here, so do not ask for assistance. If you fall silent for a while, I will remind you to keep thinking aloud. Of course, if you feel uncomfortable at any stage, please just tell me you would like to stop. Finally, remember that it is the questionnaire, and not you, that is being tested. Do you have any questions before we start?"

The researcher sat out sight of each participant to minimise the influence of the researcher presence, although this was not always possible when the interview took place in a participants' home. When not possible to sit out of site, the researcher would tell the participant *"I am not watching what you are writing in your questionnaire, just listening to what you say".* Once participants began completing the questionnaire, they were not interrupted, unless they fell silent for

about 10 seconds, in which case they were instructed to "*keep talking"* or probing was instigated.

When each participant had finished their questionnaire, or if they were struggling with the think-aloud method, probes were used to try and gain further information. Examples of probes used:

- What did you think you needed to do in order to answer that question?
- What were you thinking about when you answered that question?
- I noticed that you hesitated before you answered that question. Why was that?
- Can you repeat the question in your own words?
- What does that word mean to you?

When the interview was complete, participants were thanked for their help and asked if they had any additional feedback. Feedback helped to elicit patterns appearing across users that might have inferred a significant problem that might otherwise have been missed if individuals had not been given the freedom to report any other thoughts.

Figure 9.2 demonstrates how the cognitive interviewing process continued until no more revisions of the questionnaire was required.

9.2.3 Data analysis of cognitive interviewing task

The number of interviews required in each round was determined by the researcher and ranged between 2 and 5 interviews.

The think-aloud protocols were scanned for verbal or observed indicators of problems experienced: referring to doubt, task difficulty and incomprehensibility (adapted process from Cannell, Fowler and Marquis, 1968).[272]

The types of problems encountered were defined and categorised. There was no standard list available, but the likely categories were based upon the study by Van Den Haak *et al.* (2003):[270]

- Layout problems: the participant fails to spot particular instructions within the questionnaire.
- Terminology problems: The participant does not comprehend part(s) of the terminology used in the questionnaire.
- Data entry problems: The participant does not know how to reply to a question.
- Comprehensiveness problems: The questionnaire lacks the information necessary to use it effectively.
- Feedback problems: The questionnaire fails to give sufficient data entry options or free text.

After each round of interviews were completed, the researcher summarised the findings on a question-by-question basis.[241]

- Feedback requested at the end of the think-aloud session was collated and analysed.
- The outcome of the 'probing' was then included along with the question-specific comments on a question-by question basis.
- Comments were further aggregated, for a complete review of the questionnaire.
- A cognitive interviewing outcome report was written which contained the final annotated questionnaire with an overall written summary of the most significant problems that were found and how these were overcome.
- The renewed questionnaire entered the next round of 'interviewing' until no further revisions were required as described in Figure 9.2.

9.2.4 Pre-study pilot survey

As a final test of the questionnaire, a small pilot study was carried out to ensure that the questionnaires were completed as expected when not being tested under 'experimental conditions'. Fifteen questionnaires were distributed to patients and members of the public attending the eye clinic at the Cromer hospital in order to emulate the main study conditions. Errors from respondents or missing data were reviewed, to ensure usability of the questionnaires; this enabled any errors to be rectified and improvements made to the questionnaire should that have been necessary.

A population from the Cromer hospital (a satellite hospital to the NNUH) was chosen to avoid patients who had previously taken part in NAGS at NNUH and who would already know about the TDA and could have induced a response bias.

The data from the completed questionnaires were entered into the data collection tool, to ensure usability and reliability in the data entry method. The research assistant entered the data and this was verified by the researcher.

9.2.5 Review of question objectives

Although not considered crucial to the cognitive methods, reviewing the question objectives is well within its scope and was the final stage of the cognitive interviewing and piloting process. A respondent may be able to answer a question, but it must still be a meaningful outcome measure.[241] All questions that had presented difficulty and had to be changed to improve their understand-ability were reviewed to assess their utility as a measure.

9.3 Findings

Four cognitive interviewing rounds were required with a total of 17 participants; the results from each round with a review of the changes made to the questionnaire are detailed in Tables 9.1 to 9.4.

Following the round 2 interviews, it was apparent that participants were finding it difficult to make a decision as to whether the study used an acceptable consent method or not. Forcing respondents to answer either 'yes' or 'no' may have led to a response bias and thus their report would not truly reflect their real attitude towards the use of modified consent method for proposed study. Therefore, a visual analogue scale (VAS) was designed to replace the 'yes/no' answer, which it was predicted would reduce the chance of the question not being answered and provide an assessment of the level of acceptability.

The VAS is a psychometric response instrument used to measure subjective characteristics or attitudes that cannot be directly measured in questionnaires. When responding to a VAS item, respondents specify their level of agreement to a statement by indicating a position along a continuous line between two end-points. The continuous aspect of a VAS differentiates it from discrete scales associated with the Likert scale or dichotomised responses. There is evidence showing that a VAS has superior metrical characteristics than discrete scales, thus a wider range of statistical methods can be applied to the measurements.[273]

However, question 2 of the questionnaire, as shown in appendix 18, still gave the option for respondents to specifically state if they felt the doctor should not carry out the study under any circumstances, thus acting as an alternative measure of acceptability using a yes/no option.

Table 9.1 Final report for round 1 cognitive interviewing

4 Participants - All white British, not living alone and in paid work	
1	Male, 43 years old, IT technician at NNUH with an interest in questionnaire design
	This participant managed the think aloud task well. He approached it methodically from a design perspective rather than a personal perspective which enabled him to complete the questionnaire quickly as he did not take long to consider and answer the questions.
The remaining participants all took a lot of time to consider each question and at times even showed some angst when having to make a decision.	
2	Female, 58 years old, glaucoma patient and secretary at NNUH.
	The participant struggled with the fact she was being recorded and was a 'guinea pig' and even reported this during the interview as she felt she was not doing very well. She felt that this had hindered how she would normally have completed the questionnaire. She found the think aloud technique difficult and so the think aloud task was abandoned in favour of probing on completion of the questionnaire. She felt very strongly that participants should be informed about a study, but could also understand why it was important to do a study like this. She therefore found it difficult to complete the questions, and spent a long time thinking about her answers because she felt it was difficult to justify her reasons.
3	Male, 63 years old, glaucoma patient and health records clerk at NNUH
	The participant completed the think aloud task very well and entered into the task whole-heartedly. He said afterwards that he had found it very difficult to complete the task whilst also trying to answer the questions within the questionnaire. During the probing session on reviewing his responses he felt that he wanted to change some of his answers as he had time to reflect on it and had changed his opinion.
4	Female,55 years old, consultant, at NNUH
	The participant did not complete the think aloud task very well. However a combination of probing during the completion of the questionnaire and at the end of the task was carried out instead. She found it very difficult to put her clinical knowledge and thinking aside in order to answer the questionnaire with her own thoughts and opinions. She was considering her patients rather than her own views. As a patient she would not mind taking part in this study at all, but with her 'clinical hat' she knew it probably was not ethical and therefore found it hard to distinguish between the two.
Time taken to complete questionnaire	
1	5 minutes
2	13 minutes
3	17 minutes
4	14 minutes
Review of each element of the questionnaire	
Envelope	The envelope and instructions were acceptable. People liked the fact that there was a free post envelope that gave responders the option of when and where to complete the questionnaire. All liked the idea of free pen. One participant commented on how much the questionnaires must have cost to produce as they were of very good quality and in colour. She worked for NHS and so was aware that the NHS did not allow the use colour printing.

Introduction	They liked the fact that it should only take 10 minutes to complete the questionnaire and introduction was a good setting for the whole questionnaire. The introduction also let people decide if they want to commit to completing the questionnaire or not.
Scenario	The scenario was easy to read and understand. None of the participants thought this could have been a real study, they really did think it was just a scenario. Only one participant was curious and asked about the device at the end of the questionnaire. However one participant felt that the wording could be changed to the research 'case' as 'example' made him feel that we were just providing an example of what was to follow during the questionnaire, rather than it being part of the questionnaire itself. Changes made: Second sentence changed to make it clearer that the example research project forms part of the questionnaire: "Although we use an example of a research project…" changed to "We will use an example of a research project…"
Question 1	This proved a problem for one participant who felt that the question was fine but answered 'yes, the research is acceptable' and also 'that participants should not be told the information upfront'. This is a contradiction. During probing, it became apparent, that he meant, 'yes the research concept is acceptable', but not the method of withholding information and retrospective consent'. Changes were made to the questionnaire to make it clear it referred to the research study, not just the concept. Changes made: The final paragraph was shortened and the text added to the introduction to question 1 so that the questions flowed more easily from the scenario. Question 1 was also re-phrased in order to ensure that the reader was clear that we are referring the "example" rather than the research idea in general.
Question 2	There are so many options for participants to choose from that they couldn't process them all. In addition, it was too difficult to select just one answer. There were too many 'yes' options and the no option was too harsh in comparison that respondents felt that they should not tick it. Changes made: The number of options was reduced and the question re-phrased so that participants could choose however many options was applicable to them.
Question 3	Two participants answered this incorrectly as they had mis-read the question. They felt the error was probably just because of the pressure of doing the 'think aloud' and could not really explain why they had done it wrong. Changes made: This question was changed to use the same format as question 2 so as to avoid any misinterpretation of the instructions.
Question 4	No comments
Question 5	One participant had no concerns so did not tick a response box, but would have preferred to have ticked something, just to ensure this was reflected and not simply look like she had forgotten to answer the question. Changes made: An additional box added for "I have no concerns" was added.
Question 6	No comments
Question 7	No comments requiring action.

Table 9.2 Final report for round 2 cognitive interviewing

5 Participants - All white British, not living alone, 5 retired, and 1 in paid work.	
5	Female, 60 years old, previously seen in the glaucoma clinic as had been referred by her optician with suspected glaucoma.
	She did not complete the think aloud task very well and therefore probing at the end of the questionnaire was used to good success.
6	Female, 58 years old and a current glaucoma patient with suspected glaucoma.
	This participant completed the think aloud task very well and added insight into the reason for her answers as she went along. She is a retired mental health nurse and referred to her training and experiences of this as she went along, commenting what she knew was not ethical from a patient perspective and how personally she felt differently to this. She had to make a real effort to answer the questionnaire from her own personal perspective rather than as an ex-professional.
7	Female, 54 years old, working at NNUH and patient with glaucoma.
	This participant was very good at the think aloud task explaining her reasons as she went through the questionnaire with great success. She had previously taken part in a study using the TDA described in the scenario and drew upon these experiences during the completion of the questionnaire.
8	Male, 72 years old, patiet with glaucoma.
	This participant struggled with the think aloud, so probing during and after the questionnaire completion was used. He had heard of the TDA described in the scenario after attending a lecture at NNUH.
9	Male, 65 years old, patient with glaucoma.
	The participant was dyslexic and therefore requested his wife to join him to help him with the questionnaire. This made it problematic to do a think aloud, but a realistic example of how the questionnaire might be completed in real life so we went ahead and I used probing throughout and after the questionnaire was completed.
Review of each element of the questionnaire	
Envelope	One participant felt the freepost envelope gave freedom for respondents to decode as to whether they would like to take part in the questionnaire and when to do this. If completing the questionnaire whilst at the hospital was not appropriate then the questionnaire could be taken home to complete when they are able to concentrate on it, or get help to answer the questions if they found reading it difficult.
Intro	Easy to read.
Scenario	The scenario was easy to read and understood.
Question 1	Participant 5 found this difficult to answer and felt it was a 50/50 decision but decided that overall the doctor should ask permission before starting the research. Participant 6 answered this question without any problems, and immediately felt that it was important to know why you are doing research and what it is all about and permission should be asked. Participant 7 took a lot of time to consider her answer but decided that patients should be told about the research and that it is unacceptable to withhold information. “Patients should know that they are going to be tested for their usage of eye drops.” Participants 8 and 9 answered ‘yes’ straight away. Points to consider and changes to be made:

	Overall opinion on this question is mixed. If participants ticked 'no' it was always followed by ticking 'participants should be informed about participation'. It was possible that this question could be removed from the questionnaire, particularly as there were no response options related to ticking 'yes'. The impression was that patients felt uneasy about answering the question and that it was difficult to make a decision. Forcing a participant to make a decision of either 'yes' or 'no' may lead to a response bias and the answer will not truly reflect the real attitude towards use of modified consent method for this study. Therefore, a visual analogue scale was more appropriate in order to assess level of acceptability.
Question 2	After the justification in the introduction to question 2, participant 5 changed her mind and ticked 'yes,' that the research example was acceptable. Participant 6 also changed her mind, but it took her a long time to get to that conclusion, stating she could see both sides of the argument. She knew that people do act differently when they are being observed so could understand the justification, but also felt that patients should really know that they are taking part in research and why they are being observed. Although she felt forced to make a decision, she understood why, and did not feel uncomfortable about this. Participant 7 also changed her mind as she considered that patients would change their behaviour, and therefore the study would need to withhold that information from patients. However, she went onto to state that she would not tick statement C 'participants are told the real reason for the research project at the end' because she felt that patients should be told at the beginning of the study, not at the end, so the question needed rephrasing. Participants 8 and 9 were the only ones to answer 'no' to this question because they thought patients should be given information, however, they answered 'yes' to the first question and so contradicted themselves with no reason for this. Points to consider and changes to be made: It was important to ensure that participants realised that this question was still in relation to the scenario, and changes were made to the text to ensure this was clear. A visual analogue scale was more appropriate in order to assess level of acceptability towards use of modified consent method for the study instead of a 'yes' or 'no' answer. One participant misread the instruction to only tick the statements if answered 'yes', so the instruction was made bold.
Question 3	Participants seemed happy to choose which statements applied to them with ease. Participant 6 acknowledged that she had contradicted herself in saying that she would not be concerned about taking part in this research, but then stated that she would like to know if she were taking part in research. She felt it was more about the risk, and if the risk is low and the benefit high, then it was OK. Participant 8 wanted the question to give a fuller explanation of exactly what information would be given. The concern is that this makes the

	question too lengthy, so the question was changed to state 'fully informed' in order to add clarity.
Question 4	The initial question 'Have you ever taken part in any health research' has caused some confusion because of the response options are 'Yes', 'No', or 'Don't know'. The 'don't know' option makes participants feel that in the past they may have been deceived about participation in research and therefore have to answer 'don't know'. This response option will be changed to 'don't remember'.
Question 5	No changes.
Question 6	Participants 5 and 6 found it easy to answer 'yes' after reading the justifications. Participant 7 struggled to come to a decision about this question and so started to draw on her previous experiences. After she had finished the questionnaire she went on to say how difficult it was to make a decision because it was not clear cut, even though the questionnaire may suggest that such a decision was clear cut. Participant 8 answered 'yes' easily, and had maintained it was acceptable to undertake this study all the way through the questionnaire. Participant 9 answered 'yes' easily which was a contradiction to what had been answered in question 2. When asked directly they said it would not really bother them whether they knew about the study or not, but then went on to say that they would feel abused if they had not been told about the study. It was impossible to get an answer from them to convince me as to whether they were happy with the scenario or not. Points to consider and changes to be made: With all the interviews undertaken in this round, I felt that the participants understood why the study should be undertaken and agreed that it should be carried out, but they found it difficult to decide if it was acceptable to withhold information from patients and not take consent. This clearly showed the complexity of the subject and that weighing up whether it is acceptable or not is problematic. Forcing a participant to make a decision of either 'yes' or 'no' may lead to a response bias and the answer will not truly reflect the real attitude towards use of modified consent method for this study. Therefore, a visual analogue scale may be more appropriate in order to assess level of acceptability. One participant had become a bit confused as to whether she was supposed to be ticking each justification statement to indicate whether she agreed with it or not because the questionnaire states "please think about the example again" which made her feel that she was being asked a question about the statements. This has been made clearer in the wording.
Question 7	Participant 5 found it hard to answer all the questions as there was no option to describe that she had been discharged from the glaucoma clinic. Participant 8 could not indicate that he attended a private hospital. These response options were modified accordingly. Participant 6 would have liked an additional box for 'I do not find the doctor approachable' rather than have to write it in the free text box. This list has been modified to include this. The final question "do you think that taking part in a research study in the

	glaucoma clinic would change the experiences you have described above" appears too difficult to answer because respondents feel the question is too open. Participant 6 did not like the question or know how to answer it. Other participants misinterpreted the question believing it to mean that research in general might improve the experiences of patients due to advances in knowledge, rather than the intended meaning. Due to possible confusion and the fact that question 7 had little potential as an outcome measure it was removed.

Table 9.3 Final report for round 3 cognitive interviewing

6 Participants - All white, 1 of South-African origin, 1 living alone, and six in paid work.	
10	Male, 62 years old, and from South-Africa originally, glaucoma patient seen annually in the glaucoma clinic.
	This participant was extremely interested in the topic because he has glaucoma. He produces teaching materials for 'group learning education', and so was particularly interested in the cognitive aspects of completing a questionnaire. He was very 'pro' glaucoma research and was disappointed he had never taken part in research before.
11	Male, 47 years old. Glaucoma patient and using eye drops and seen annually in the glaucoma clinic.
	This participant was interested in the topic because he has glaucoma. He works in the hospital in the technical team and does not have contact with patients. He undertook the think aloud well, but I used concurrent probing during the interview as well to try and understand some of his comments a bit better. This approach worked well as he was good at explaining himself and providing as much information about what was informing his beliefs or thoughts. However, completion of the questionnaire became more of an open dialogue between us, rather than him completing the questionnaire without assistance.
12	Female, 48 years old, not a glaucoma patient but likes to participate in research.
	This participant worked in the hospital pharmacy. She did not have any personal or family experience of glaucoma and came the questionnaire completely open minded in that respect. She was able to use think aloud successfully and we carried out some retrospective probing at the end.
13	Male, 47 years old, glaucoma suspect.
	This participant was interested in the topic area as he is a glaucoma suspect. He works in the Diabetic Eye Screening service with patients and therefore found it difficult to detach his own opinions from what he thought patients might feel. A combination of think aloud and concurrent probing was used.
14	Female, 56 years old, family history of glaucoma.
	This participant was interested in the topic area as she enjoys taking part in research and has a family history of glaucoma. She was thinking about the perspective of her mother and father and other people, rather than giving her own opinion and what she was able to read and understand herself. I felt in this case, she was giving an opinion of what others might feel, rather than just reporting her own perspective.
15	Female, 40 years old, glaucoma suspect.
	This participant was interest in the topic as she is a glaucoma suspect. She works in hospital governance and has a background in nursing. No concurrent probing or think aloud was used, just retrospective probing.
Review of each element of the questionnaire	
Front cover	Participant 11 felt that the front cover needed to be more eye catching and to 'sell' the questionnaire to potential respondents. He felt that the word research would draw people in. Participant 14 agreed with this and thought the current title was ideal.
Intro	Easy to read.
Scenario	Participant 11 may have misunderstood the reason for the research and was trying to establish how it helped people who needed to use eye

	drops. From this, he felt that it was unnecessary to give the device to everyone, as someone like him, knew how to use drops. The scenario needed to make clearer the reason for the research? Participant 12 may also have misunderstood the reason for the research in the same way as participant 11. She thought that if the drops were to help patients use eye drops by telling how many drops they had used, then this information should not be kept from patients who might need this information to help them. Participant 14 thought it was hard 'for others' to take the information in and that it may need pictures or be spaced out further. Participant 15 thought the scenario was a bit stilted and patronising. Changes to be made: The scenario has been updated to make the reason for the research clearer and read easier with a little more spacing.
Question 1	No problems using the scale to report opinion of acceptability.
Question 2	Participant 10 had to check why the question was exactly the same as question 1 and could not understand why. An immediate modification was made. Participant 11 had to check if he should answer the response options because he had answered unacceptable. He thought they were good questions, and therefore should be 'allowed' to answer them. Participant 15 also wanted to be able to answer the response options. Participant 13 thought that response option A was too difficult to understand. He did understand it but had to read it several times and thought the term 'patient representative' was too difficult to understand and could be misinterpreted. Points to consider and changes to be made: Wording changed immediately after participant 10 (before the following participants had completed questionnaire) as immediate resolution was required: "Does this change your opinion of the research example? Please indicate your opinion on the line below, whether it is the same as your answer to question 1, or different now." The response options were made available for everyone to answer regardless of whether they responded acceptable or unacceptable and additional response option B added. The response option A was made easier to understand.
Question 3	Participant 13 was initially concerned about the research example because of the ethical issues that might surround such research. Therefore he felt there should be another response option that bridged the gap between option A – 'I have no concerns' to options B-E which are too extreme. Points to consider and changes to be made: Add another response option: "I might be initially concerned, but not once the research had been fully explained."
Question 4	No problems.
Question 5	No problems.
Question 6	No problems. Participants did not mind being asked the same question for a 3rd time and understood why we might want to do this.

Question 7	Participant 10 struggled with the response options relating to his satisfaction with the clinic. He did not like the word 'reassuring' as that is not the right word. A participant in the last round also mentioned this, so an immediate change was made. Participant 11 could not answer how often he was seen in the Glaucoma Clinic as he was seen about once every 18 months – 2 years. Changes to be made: An immediate change was made after participant 10 (before the following participants) as immediate resolution was required. And changes to the response options made. Need to add "I attend a Glaucoma Clinic about once every one – two years" to capture those whose appointments who fall 18 monthly.

Table 9.4 Final report for round 4 cognitive interviewing

2 Participants – Both white, living with others, and in paid work.	
16	Female, 61 years old, family history of glaucoma
	This participant was interested in the topic area as she enjoys taking part in research. She has a family history of glaucoma. She did the think aloud task well combined with retrospective probing.
17	Female, 53, years old, glaucoma patent using eye drops.
	This participant was interested in the topic because she has glaucoma. We used retrospective probing.
Review of each element of the questionnaire which was problematic	
Justification section	Participant 16 felt that the justification needed to be clearer to impress upon respondents that we know that patient do change their behaviour when taking part in research rather than using 'may' and 'might'. This paragraph was changed to reflect this.
Question 2	Even though response option A has been re-worded many times to try and make this understood both participants still did not understand this, and it actually distracted participant 17 from answering correctly, because when we discussed it, she had totally missed response option D, which would have been the response she needed to select, but missed it as she was confused about response option C. The response was removed from this section, as it has not been possible to make this option acceptable to all users, during each round of testing. Added an additional instruction before the response options: "Read the statements from the list below then tick all which might apply."
Question 3	Added an additional instruction before the response options: "Read the statements from the list below then tick all which might apply."
Final Comments	Apart from a few further refinements, the questionnaire was completed by both under 10 minutes, with no further discussion about problems encountered, other than those addressed above, which have been remedied easily. The questionnaire is felt suitable for pilot testing with the study population. 10 questionnaires should be collected to ensure they are completed fully and the collection technique works as expected.

9.3.1 Review of question objectives

Each question was reviewed to ensure it could be analysed in order to meet its outcome objective. The results of the review are shown in Table 9.5.

Table 9.5 Review of question objectives

	Question	Issue
1.	Is the research example acceptable?	What is felt about a research study which withholds information from participants and does not take consent? Baseline measure.
	Free text comments	Identify any areas of concern or additional information.
2.	Now what do you feel about the research example?	What is felt about withholding information and not taking consent after a justification has been given for doing this.
	If you do think this is acceptable, would any of the following be important to you?	Identify the important issues for respondents who would be willing to take part in research.
3.	If you had taken part in the research example without your knowledge, please consider how you would feel once you had been fully informed about the research.	Explore further issues: Feelings of not being treated with respect? Reduce trust in doctors? Would they not take part in research again?
	Other, please describe.	Identify any other concerns about taking part in this research.
4.	Have you ever taken part in any health research e.g. at a GP surgery or hospital.	Does previously taking part in research affect opinion?
	How would you describe your overall experience?	Does positive or negative experiences of research affect opinion?
	Please describe why you did or did not value the experience	Identify any other reasons for not valuing research.
	Please describe what sort of research it was	Understand the types of research people have taken part in before.
5.	Would you ever consider taking part in research undertaken by a Hospital or GP surgery?	Does being willing to take part in research affect opinion?
	Do you feel any of the statements below describe concerns you might have about taking part in research?	Do perceived 'risks' associated with research affect opinion?
	Are there any other issues or concerns that you feel could affect you if you were involved in research.	Collect other concerns that could affect people taking part in research.
	Would you expect to receive information about the possible risks of taking part in a research study if there were any?	Would information about the possible risks of participation be expected?
6.	Would you think the research example is acceptable?	What is felt about withholding information and not taking consent after a justification has been given for doing this.
		Does strength of conviction about acceptability change with increased justification for the study.
7.	Demographic information:	Does gender or age affect opinion?
	Type of patient or member of public	Does the type of glaucoma patient or member of the public affect opinion?
	Glaucoma patient information:	Do patient experiences affect opinion?

9.3.2 Pre-survey test

Pilot questionnaires were given to 15 patients or members of the public for completion. Eight questionnaires were returned using a reply envelope, which confirmed that instructions for return of the questionnaires were understood. Only one question failed to be completed by one participant and the heading of this questions was emboldened to highlight that question continued overleaf, in case that was the reason for the question being overlooked. A relatively high, 53% response rate, with only one item of missing data, confirmed that the questionnaire was both suitable and usable within the patient and public population intended.

The data collection spread sheet was tested for ease of data entry and small modifications made to improve usability.

9.4 Discussion

Volunteers for cognitive interviews are to some extent self-selected and are not likely, therefore, to be representative of a survey population as a whole. Most importantly, these volunteers may tend to be higher in their level of educational attainment, in comparison with an average survey respondent, with the potential to overlook problems that occur in 'real life' and 'interview' findings might, therefore, underestimate the severity of problems. However, the participants recruited from NNUH ranged from a variety of working backgrounds, from a filing clerk to a health practitioner; it was felt, therefore, that individuals with an adequate range of educational attainment were consulted.

The environment in which the questionnaire was completed during cognitive interviews might have placed the responder under greater pressure to think about and answer the questions than would be expected of a respondent not undertaking a think-aloud process. However, the type of questions administered where mainly testing comprehension processes which do not appear to differ greatly between the experimental setting and that of real life; for example, if someone does not know the location of his or her abdomen, it is doubtful that they would know this wherever the test was executed. Retrieval processes, may be different since the 'home environment' may provide different cues that affect recall of thoughts. Furthermore, opinions may have been altered if the respondent had been trying to please the researcher during the interview. Thus, a small pilot survey was appropriate to assess that the questionnaire was effective in 'real life' circumstances and to explore any unexpected results or failure to complete the questionnaire. In addition, whilst the cognitive interview could not test the likely response rate, since no-one declined to answer any part of the questionnaire, the pilot study found that not all participants who received the questionnaire responded. However, those that were returned gave full and complete responses, which confirmed that the questionnaire was accessible and understood by those within the pilot cohort.

Some might argue that a cognitive interviewing approach was deficient, because the samples used were too small to make reasonable conclusions. However, the purpose of the interviews was not for statistical estimation, but to gain the opportunity to interview a variety of individuals' representative of the sample population. Furthermore, the qualitative aspect of the interview ensured that the

problems occurring were evaluated and immediately addressed, rather than simply counting the number of interviews in which a problem occurred. The qualitative nature of the process also meant that a finding could be based on just one interview and did not need to be verified by a large number of other individuals with the same reported problem.

Cognitive interviewing was an effective means of identifying potential problems, *before* the problems were encountered repeatedly in the 'field'. With no previous evidence on which to base this questionnaire, the entire process of building the questionnaire starting from focus group feedback, moving to questionnaire design and then using cognitive interviewing not only established a reliable measure, but provided a comprehensive overview of the subject area. Each cognitive interview led to a conversation about respondents' own thoughts on the subject area beyond that of the questionnaire data. The willingness for respondents to share their opinions was a profitable process in terms of gaining a greater understanding of the subject area for the researcher.

Cognitive interviewing was not so useful for assessing issues of question burden; participants in cognitive interviews have been reported to be more patient and attentive, relative to respondents in the field. Thus, piloting the questionnaire was essential to test for any burden effects not detected during the cognitive interviewing process.

9.5. Methodological critique

Running a cognitive interview is largely a social encounter and the notion that it is purely a programmed exchange is unrealistic. There are two facets to cognitive interviewer behaviour that must be balanced and co-ordinated for maximum effect; technical ability and interpersonal skills.[241] Although not trained in cognitive interviewing specifically, a wide breadth of clinical and social research had previously been undertaken by the researcher. In addition, the researcher benefitted from the previous experience of having dealt with the type of patients inherently involved in the interviews. Of particular importance, the researcher was aware of bias and context effects, was familiar with the questionnaire design process and was, therefore, well suited to appraise the questionnaire.

Previous exposure to cognitive interviews and the opportunity to observe experienced interviewers would have been beneficial, but without such an opportunity, additional reading of the subject area and potential pitfalls was vitally important. In particular, knowledge of the Cognitive Aspects of Survey Methodology approach was obtained.[253] The researcher also undertook a practice session, before embarking on the first test case.

Each interview was different with respect to the social exchange required for each individual, but the instructions given and initial think aloud training remained largely the same; this confirmed a consistency in the ability of the researcher to interact and give instructions to each participant successfully and the extent of probing and discussion was flexible according to the needs of each interview.

Since there was only one researcher working on the project, it was not necessary to control for different approaches and evaluations of the interview, which is required when using multiple interviewers.

Chapter 10. Questionnaire data collection

10.1 Method

After extensive testing of the questionnaire through cognitive interviewing and piloting, the questionnaire (appendix 19) was ready for distribution among the sample population and ethical approval for use of the revised questionnaire was sought.

10.1.1 Participant identification and recruitment

A hospital setting was felt to be the best location to capture responses compared to any other arbitrary public area. Thus, questionnaires were given to all adults entering the Cromer hospital out-patient department. The entrance to the glaucoma clinic was just inside the main entrance of the hospital. Therefore, respondents were likely to be a mix of people who were either attending the glaucoma clinic and would therefore have experience of glaucoma care, or those attending other out-patient services within the hospital, these representing individuals found in the general population with less knowledge about glaucoma.

Respondents had the option of completing the questionnaire whilst waiting for their consultation with their clinician and returning it to the collection box before leaving the hospital, or to take the questionnaire home for completion and return it in a freepost reply envelope. Respondents who declined to participate had no further involvement.

10.1.2 Data processing

On collection of each completed questionnaire, a case number was assigned, for identification purposes. Pre-coded question data was entered into the database by the coder (assistant researcher) and then verified by the researcher. Responses to open questions were transcribed verbatim.

The data were checked for internal consistency to pick up any inconsistencies in the filter questions. A review of missing data was undertaken to decide if list-wise or pair-wise deletion should be undertaken.

Respondents were asked to mark their attitude towards the use of a modified consent procedure using the VAS. The number nearest the participant mark on the scale was used to give a metrical characteristic of attitude. Marks exactly between the division lines were rounded up.

10.1.3 Sample size for questionnaire study

Without a similar study for comparison of expected range of opinion and because the population criterion was undefined, a sample size calculation was not possible. However, the aim was to collect responses from 200 people to give a 95% confidence interval and ± 5% margin of error for a population of 500 people. The pilot test achieved described in Chapter 53% response rate, and therefore 400 questionnaires were prepared to achieve approximately 200 responses.

10.1.4 Analysis of the questionnaires

Table 10.1 describes how each question within the questionnaire was used to meet the objectives of the study.

The study scenario (appendix 19) was presented to the respondent at the beginning of the questionnaire. Perceived acceptability of the study scenario was then measured at three different points during the questionnaire (Attitude 1, 2 and 3). The first measure of acceptability was directly after the scenario had been presented in order to capture the respondents' initial reaction to it (Attitude 1). The next section of the questionnaire informed respondents about behaviour changes likely to occur when patients take part in research. A justification for use of the study scenario was then presented to the respondent and their reaction to the acceptability of the study scenario was measured again (Attitude 2). The questionnaire then went on to examine the wider attitudes towards research; if respondents would consider taking part in research, and respondents' previous experiences of research. Finally, further justifications for using the study scenario were given and acceptability of the study scenario was measured for the final time (Attitude 3). Changes in attitude between the Attitude 1 and Attitude 3 could be explored and in this way used to determine if justifications for use of the study scenario influenced attitudes.

The median score of acceptability of using a modified consent procedure was calculated for each VAS (Attitude 1, Attitude 2 and Attitude 3) and a Wilcoxon signed rank test used to compare results at each of the three test points during the questionnaire to establish changes in attitude.

Median scores were also categorised into three groups; responses measuring 1-4 on the VAS indicated a mild to strong opinion that the study scenario was unacceptable, whilst scores 6-9 depicted a mild to strong opinion that the study scenario was acceptable and a response of 5 indicated no opinion.

The median scores of acceptability were compared using the attitudes of 'patients who attend a glaucoma clinic' to assess if experience of glaucoma care had any effect on attitude to participating in the study scenario using an independent samples Mann-Whitney U test at all three test points (Attitude 1, Attitude 2 and Attitude 3).

Logistic regression was used to identify predictors of respondents likely to participate in a glaucoma study using a modified consent procedure. Explanatory factors were entered into a univariate model by estimating the odds ratio of the study scenario being acceptable at Attitude 3 along with the corresponding 95% confidence interval and p-value. Statistically significant independent factors were manually selected to construct a multivariate model.

Cross tabulation of results over the three test points (Attitude 1, Attitude 2 and Attitude 3) was used to establish if respondents changed their opinion during the course of the study.

Logistic regression was used to identify any predictors of respondents most likely to change their opinion of the acceptability of the study scenario, throughout the exercise. Explanatory factors were entered into a univariate model by estimating the odds ratio of the study scenario being acceptable at Attitude 3 along with the corresponding 95% confidence interval and p-value. Statistically significant independent factors were manually selected to construct a multivariate model.

Descriptive statistics were used to report what respondents thought were important factors to consider if using the study scenario and what they would have felt if they had taken part in the study scenario, experiences of previous research and if they would take part in research in the future.

The respondent population was characterised using descriptive statistics.

Table 10.1 Description of outcome measures

Question		Question Outcome	Secondary outcomes
1.	Is the example research study acceptable?	Describe opinion of the cohort: % who felt the study is acceptable (1-4) % who felt the study is unacceptable (6-9) % undecided (5)	None
	Free text comments	Qualitative analysis – report different reasons and quantify if possible.	None
2.	Now what do you feel about the example research study?	Describe opinion of the cohort: % who felt the study is acceptable (1-4) % who felt the study is unacceptable (6-10) % undecided (5)	Does attitude to acceptability change when the justification for the study is stated.
	If the example research study is acceptable, would any of the following be important to you?	Describe what the cohort thinks is important if information is withheld. % as long as there is no risk to participants % participants should be told at the end of the study.	.
	Should the doctor carry out the study?	Primary Outcome: % of the cohort that think the doctor should not carry out the study either way	Yes/No option of acceptability of the research example
3.	If you had taken part in the example research study without your knowledge, please consider how you would feel once you had been fully informed about the research.	Describe what the cohort might feel if they had taken part in this research. % it would not concern me at all % would feel initially concerned % would feel they had not been treated with respect % would feel it would break rapport with their doctor % would not trust doctors or researchers in the future % would not take part in research again % who thinks research should not have been undertaken	Enter into logistic regression models: 1. Factors that may influence acceptability of the study scenario 2. Factors that may influence a change in opinion.
	Other, please describe	Qualitative analysis – report different reasons and quantify.	None
4.	Have you ever taken part in any health research e.g. at a GP surgery or hospital	Describe cohort: % have taken part in research % have not taken part in research % don't remember	Enter into logistic regression models
	How would you describe your overall experience?	Of those who took part in research: % found the study interesting % given enough information % valued the experience % found the study dull % was not given enough information % did not value the experience	Enter into logistic regression models
	Please describe why you did or did not value the experience	Qualitative analysis – report different reasons and quantify.	None
	Please describe what sort of research it was	Qualitative analysis – report research experience of the cohort.	None

5.	Would you ever consider taking part in research undertaken by a Hospital or GP surgery?	Describe cohort: % consider taking part in research % not consider taking part in research % depend on the type of research % don't know	Enter into logistic regression models
	Do you feel any of the statements below describe concerns you might have about taking part in research?	Describe concerns about research: % concerned about confidentiality % concerned information might be withheld % there could be risks to health and wellbeing % that have no concerns	Enter into logistic regression models
	Are there any other issues or concerns that you feel could affect you if you were involved in research	Qualitative analysis – report different concerns and quantify	Enter into logistic regression models
	Would you expect to receive information about the possible risks of taking part in a research study if there were any?	Describe cohort % would expect to receive information about risks % would not expect to receive information about risks % don't know	None
6.	Would you think the research example is acceptable?	Primary Outcome: Describe opinion of the cohort: % who felt the study is acceptable (1-4) % who felt the study is unacceptable (6-9) % undecided (5)	Describe differences between attitudes of acceptability at different points throughout the questionnaire.
7.	Demographic information	% Male % Female	Enter into logistic regression models
		% 39 under % 40-64 % 65+	Enter into logistic regression models
		% Patient % carer/friend/relative visiting hospital % Other – qualitative analysis Other – qualitative analysis	Enter into logistic regression models
	Glaucoma patient information	% First visit % once a year % more than once a year	Enter into logistic regression models
		% have used eye drops before % have not used eye drops before % don't know	Enter into logistic regression models
		% satisfactory experience of eye clinic % not satisfactory experience of eye clinic % no opinion	Enter into logistic regression models
		Reasons for opinion about eye clinic: % travelling % waiting times % tests % Don't like seeing a different doctor % questions % approachable % other – qualitative analysis	Enter into logistic regression models

10.2 Results

In March 2013, a questionnaire was offered to every person entering the main hospital entrance at the Cromer hospital, over three consecutive mornings. Four hundred questionnaire packs were distributed and within 5 weeks of distribution, 208 questionnaires had been returned, a response rate of 52%. Missing data was minimal from the returned questionnaires; of the 1456 expected responses, only 22 questions had an answer been omitted (1.5%) and most omissions occurred from questions relating to personal demographic information (32%). Therefore, no techniques were required to handle the missing data to avoid bias.

Table 10.2 describes the respondent demographics. A greater number of responses were received from females than males and the largest proportion of responses were from those aged over 65 years. A response rate could not be calculated as the demographic data for those who received the questionnaire was not collected. Most respondents were patients attending the hospital, of which a proportion were patients with glaucoma n=34 (16.4%); of which 16 (47%) were diagnosed with glaucoma, 9 (27%) were diagnosed as a glaucoma suspect and 9 (27%) did not know their diagnosis.

Table 10.2 Respondent demographics and reason for visit to hospital

Demographic characteristic		N	%
Gender	Male	92	44.2
N=208	Female	109	52.4
	Not disclosed	7	3.4
Age	39 under	8	3.8
N=208	40-64	72	34.6
	65+	119	57.7
	Not disclosed	8	3.8
Reason for	Patient	135	65.4
visiting hospital	Carer/friend/relative of a patient	48	23.1
N=208	Other: member of staff (3) / hospital volunteer (4) / visitor (3) / participating in research (1)	11	5.3
	Not disclosed	13	6.3

10.2.1 Primary outcome: Attitude to the use of a modified consent procedure

Respondents' attitudes to the use of the example research study (the study scenario) were measured at three different points during the questionnaire; 'Attitude 1', was determined directly after the scenario had been presented in the introduction, 'Attitude 2' after a justification for using such a study design and 'Attitude 3' after more information about the study and further justifications had been given.

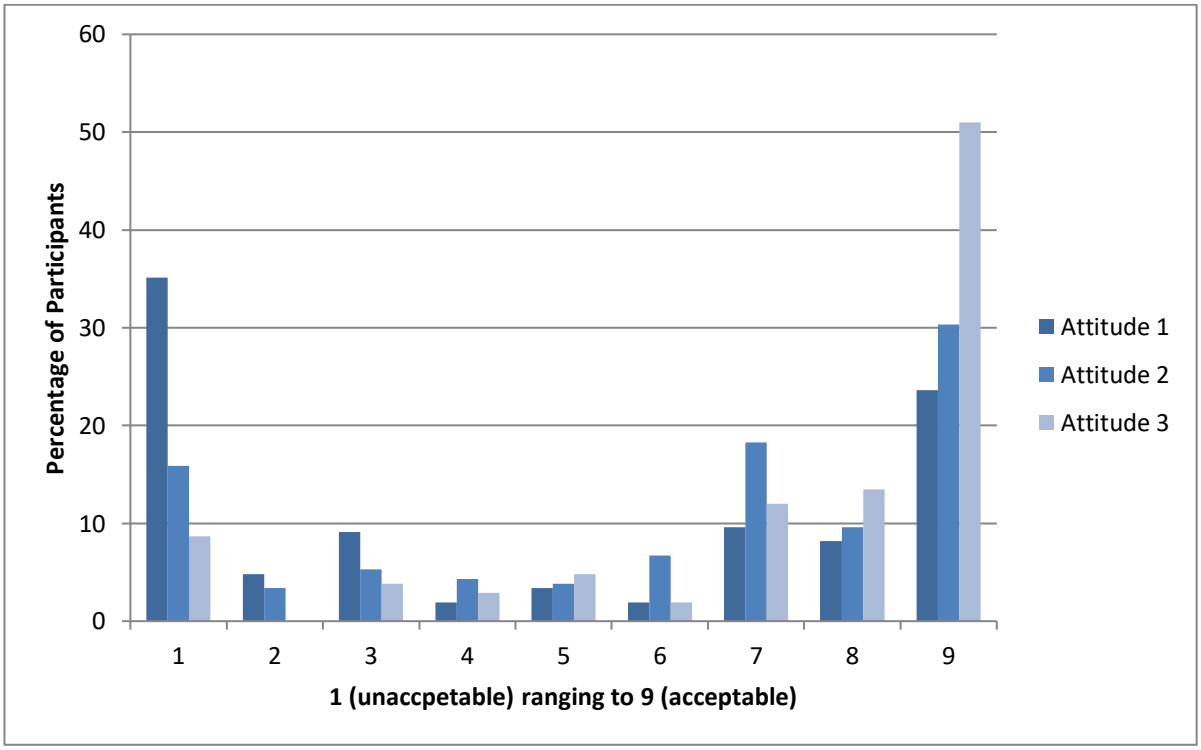


Figure 10.1. Attitudes toward the acceptability of the study scenario measured at 3 points during the questionnaire

Figure 10.1 graphically represents the acceptability of the study scenario at the three different points during the questionnaire. By the time of 'Attitude 3', opinion was strongly polarised with the majority of participants indicating that they felt the study scenario was acceptable. The median attitude score at Attitude 3 was 9 (IQ, 7, 9).

Table 10.3 displays the median scores when the same responses were categorised as ‘unacceptable’, ‘acceptable’ or ‘no opinion’ at the three different points. The majority of respondents felt that the study scenario was acceptable when measured at Attitude 3. Of the 15.7% of participants that responded that the study scenario was unacceptable at Attitude 3 on the VAS, when using a dichotomised ‘yes/no’ response option which asked specifically if the study should not be carried out by researchers (appendix 19, question 2, option c), only (4%) of respondents (n=9) agreed.

Table 10.3 Categorised responses of attitudes to the use of the study scenario

Categorised opinion from VAS scale	**Attitude 1** Initial response to scenario **n (%)** n = 202	**Attitude 2** Reactivity bias described **n (%)** n = 202	**Attitude 3** Final response following justification **n (%)** n = 204
1 – 4 Unacceptable	106 (52.5)	60 (29.7)	32 (15.7)
5 No opinion	7 (3.5)	8 (4.0)	10 (4.9)
6 – 9 Acceptable	89 (44.1)	134 (66.3)	162 (79.4)

10.2.2 Secondary outcomes

10.2.2.1 Changes in Attitude

As shown in Figure 10.1 and Table 10.4, when attitude towards the acceptability of the study scenario was measured initially (Attitude 1), most respondents felt the study was unacceptable. When attitude was measured again (Attitude 2), opinion became more divided but more strongly favoured being acceptable. The final measure of opinion (Attitude 3) found that the majority of respondents felt the study was acceptable. Table 10.4 shows the median attitude score reported at the three measured points and compared them for statistical significance; the opinion

of the study scenario became more acceptable when a justification was given and this change in opinion was statistically significant.

Table 10.4 Attitude scores reported at the three measure points

	Median (IQ range)	Related samples Wilcoxon signed rank		
		Attitude 1 and 2	Attitude 2 and 3	Attitude 1 and 3
Attitude 1 n=203	3.0 (1.0, 8.0)	P <0.001	P<0.001	P<0.001
Attitude 2 n=203	7.0 (3.0, 9.0)			
Attitude 3 n=205	9.0 (7.0, 9.0)			

The cross tabulation in Table 10.5 revealed that of the 202 respondents that responded to all 3 'attitude questions', 57% (n=114) did not change their opinion between 'Attitude 1 and 3', 14% maintained that study was unacceptable and 43% maintained that the study was acceptable. Seventy-two respondents (36%) did change their opinion between 'Attitude 1 and 3'; 35% changed their opinion from being unacceptable at' Attitude 1' to acceptable at 'Attitude 3' and only 1% felt the study scenario was initially acceptable but unacceptable at 'Attitude 3'.

Table 10.5 Change in opinion between Attitude 1 and Attitude 3 using categorised responses.

		Attitude 3			
		Unacceptable	No opinion	Acceptable	Total
Attitude 1	**Unacceptable**	28	7	70	105
	No opinion	1	1	5	7
	Acceptable	2	2	86	90
	Total	31	10	160	202

Further analyses were carried out to establish if any specific factors influenced respondent change of opinion with respect to the study scenario from ‘Attitude 1’ to ‘Attitude 3’ as shown in Table 10.6. Statistically significant factors from the multivariate model revealed that respondents who had previously taken part in research were more likely to change their opinion regarding the acceptability of the scenario once a justification had been given.

Table 10.6 Factors that may influence a change in opinion relating to acceptability of the study scenario

Predictor	Did opinion of the acceptability of the scenario change? No	Yes (%)	Unadjusted OR (95% CI)	p-value	Selected OR (95% CI)	p-value
Gender of respondent						
Female	71	34 (32.4)	1.747 (0.98, 3.13)	0.060	1.428 (0.76, 2.70)	0.273
Male	49	41 (45.6)	1			
Age of respondent						
64 years and under	54	23 (29.9)	1		1	
65 years and over	65	52 (44.4)	1.878 (1.02, 3.45)	0.043	1.592 (0.82, 3.10)	0.171
Reason the respondent was visiting hospital at time of collecting questionnaire						
A patient	80	52 (39.4)	1.202 (0.63, 2.30)	0.576		
A carer/friend/relative/other	37	20 (35.1)	1			
Glaucoma status of the respondent						
Has glaucoma	19	14 (42.4)	1.179 (055, 2.51)	0.670		
Does not have glaucoma	104	65 (38.5)	1			
Would feel that ensuring the research project does not cause risks to participants would Is important						
Yes	107	62 (36.7)	1			
No	15	13 (46.4)	1.496 (0.67, 3.35)	0.328		
Would feel that participants should be told the real reason for the research project upon completion						
Yes	89	61 (40.7)	1.616 (0.80, 3.27)	0.182		
No	33	14 (29.8)	1			
The respondent feels that the research project described in the scenario should not be carried out						
Yes	6	3 (33.3)				
No	116	72 (38.3)	1.241 (0.30, 5.12)	0.765		
If respondent had taken part in the study scenario they would have no concerns						
Yes	39	30 (43.5)	1.314 (0.73, 2.38)	0.368		
No	82	48 (36.9)	1			
If respondent had taken part in the study scenario they may have been initially concerned, but not once explained						
Yes	55	35 (38.9)	1			
No	66	43 (39.4)	1.024 (0.58, 1.81)	0.936		
If respondent had taken part in the study scenario they would feel they had not be treated with respect						
Yes	28	15 (39.4)	1			
No	93	63 (40.4)	1.265 (0.63, 2.56)	0.513		
If respondent had taken part in the study scenario they feel it would break the rapport with their doctor						
Yes	10	9 (47.4)	1.448 (0.56, 3.74	0.445		
No	111	69 (38.3)	1			

Predictor	Did opinion of the acceptability of the scenario change? No	Yes (%)	Unadjusted OR (95% CI)	p-value	Selected OR (95% CI)	p-value
If respondent had taken part in the study scenario they would not trust doctors or researchers in the future						
Yes	6	2 (25.0)	1			
No	115	76 (39.8)	1.983 (0.39, 10.8)	0.409		
If respondent had taken part in the study scenario they may consider whether they would take part in research again						
Yes	17	13 (43.3)	1.224 (0.62, 1.22)	0.615		
No	104	65 (38.5)	1			
Has the respondent taken part in health research before?						
Yes	25	27 (51.9)	2.237 (1.12,4.09)	0.022	1.937 (0.95, 3.95)	0.069
No	91	46 (33.6)	1		1	
If the respondent had taken part in research was this experience interesting?						
Yes	20	18 (47.4)	1			
No	6	8 (57.1)	1.481 (0.431, 5.10)	0.533		
If the respondent had taken part in research were they given enough information about the research?						
Yes	19	15 (45.7)	1			
No	7	10 (58.8)	1.696 (0.53, 5.48)	0.377		
If the respondent had taken part in research did they value the experience?						
Yes	21	19 (47.5)	1			
No	5	7 (58.3)	1.547 (0.42, 5.70)	0.512		
Would the respondent take part in research if asked in the future?						
Yes	50	41 (45.1)	1.511 (0.85, 2.68)	0.157		
No / Would depend	70	38 (35.2)	1			
Would the respondent be concerned that their details may be shared with other people if they took part in research?						
Yes	40	19 (32.2)	1			
No	81	60 (42.6)	1.559 (0.82,2.96)	0.174		
Would the respondent be concerned that your doctor might keep information from them if they took part in research?						
Yes	50	28 (35.9)	1			
No	71	51 (41.8)	1.283 (0.71, 2.31)	0.405		
Would the respondent have any concerns about health risks if they took part in research?						
Yes	50	23 (31.5)	1			
No	71	56 (44.1)	1.715 (0.94, 3.14)	0.081	1.108 (0.49, 2.50)	0.805
Would the respondent have any concerns about taking part research?						
Yes	85	41 (32.5)				
No	36	37 (50.7)	1			

* Using forward selection

10.2.2.2 Attitudes of patients who attend a glaucoma clinic

To determine if attitudes differed between respondents who have a greater awareness of glaucoma treatment and those that did not, the attitudes of respondents who reported previously or currently attending a glaucoma clinic were analysed separately. The median attitude scores are displayed in Table 10.7 and showed that use of the study scenario was more acceptable at Attitude 3 which was statistically significant, there having been an initial statistically significant difference of acceptability between Attitude 1 and 2.

Table 10.7 Median attitude score of respondents who attend a glaucoma clinic, reported at each of three attitude measurement points and compared for statistical significance.

	Median (IQ range)	Related samples Wilcoxon Signed Rank		
		Attitude 1 and 2	Attitude 2 and 3	Attitude 1 and 3
Attitude 1 n=33	4.0 (1.0, 9.0)	p = 0.007	p = 0.076	p = 0.008
Attitude 2 n=33	7.0 (3.0, 9.0)			
Attitude 3 n=34	8.0 (5.0, 9.0)			

Table 10.8 displays the attitudes from the respondents classified as 'the general public' compared to 'patients that had attended a glaucoma clinic'. There was a statistically significant difference at 'Attitude 3', which showed that members of the general public found the study scenario slightly more acceptable than patients who had attended a glaucoma clinic.

Table 10.8 Median score of attitude compared between respondents who 'attend a glaucoma clinic' or are 'members of the public'.

	Median (IQ range)		Independent Samples Mann-Whitney U
	Patients with Glaucoma	General Public	
Attitude 1	4.0 (1.0, 9.0) n=33	3.0 (1.0, 8.0) n=170	p = 0.760
Attitude 2	7.0 (3.0, 9.0) n=33	7.0 (4.0, 9.0) n=170	p = 0.872
Attitude 3	8.0 (5.0, 9.0) n=34	9.0 (7.0, 9.0) n=171	p = 0.043

10.2.2.3 Factors which may influence attitudes

Logistical regression analysis was used to examine if there were other factors that might have affected the likelihood that respondents would react differently to the acceptability of the study scenario. Table 10.9 presents the factors that were entered into a univariate model, from which statistically significant factors were selected to be entered into the multivariate model. The study scenario appeared to be more acceptable to respondents if they had been told the real reason for the study retrospectively and by those who considered themselves to be a carer/relative and therefore not 'a patient with glaucoma' at the time of completing the questionnaire.

Table 10.9 Factors that might influence acceptability of the study scenario

Factor	Was the study scenario considered acceptable		Unadjusted		Selected*	
	No	Yes (%)	OR (95% CI)	p-value	OR (95% CI)	p-value
Gender of respondent						
Female	21	88 (80.7)	1			
Male	18	72 (80.0)	1.048 (0.52, 2.12)	0.897		
Age of respondent						
64 years and under	19	60 (75.9)	1			
65 years and over	20	99 (83.2)	1.567 (0.77, 3.17)	0.211		
Reason the respondent was visiting hospital at time of collecting questionnaire						
A patient	34	101 (74.8)	1			
A carer/friend/relative/other	3	55 (94.8)	6.172 (1.81, 21.02)	0.004	4.082 (1.11, 15.05)	0.035
Glaucoma status of the respondent						
Has glaucoma	9	25 (73.5)	1			
Does not have glaucoma	33	138 (80.7)	1.505 (0.64, 3.53)	0.346		
Of the respondents who have glaucoma how often the glaucoma clinic is attended						
One to two years	5	12 (70.6)	1.200 (0.25, 5.89)	0.822		
More than once a year	4	8 (66.7)	1			
Does the respondent currently use or ever used eye drops for glaucoma?						
Yes	7	21 (75.0)	1			
No	2	8 (80.0)	1.333 (0.23, 7.83)	0.750		
Of the respondents who have glaucoma do they feel their appointments at a glaucoma clinic are satisfactory						
Yes	9	26 (74.3)	1.444 (0.12, 17.90	0.775		
No opinion	1	2 (66.7)	1			
Would feel that ensuring the research project does not cause risks to participants is important						
Yes	31	143 (82.2)	2.563 (1.08, 6.09)	0.033	1.896 (0.57, 6.36)	0.300
No	10	18 (64.3)	1			
Would feel that participants should be told the real reason for the research project upon completion						
Yes	24	131 (84.5)	3.093 (1.48, 6.46)	0.003	2.398 (0.92, 6.22)	0.072
No	17	30 (63.8)	1			
If respondent had taken part in the study scenario they would have no concerns						
Yes	6	64 (91.4)	3.918 (1.56, 9.83)	0.004	2.028 (0.52, 7.97)	0.311
No	36	98 (73.1)	1			
If respondent had taken part in the study scenario they may have been initially concerned, but not once explained						
Yes	11	83 (88.3)	2.961 (1.39, 6.29)	0.005	1.590 (0.47, 5.38)	0.456
No	31	79 (71.8)	1			
If respondent had taken part in the study scenario they would feel they had not be treated with respect						
Yes	23	23 (50.0)	1			
No	19	139 (88.0)	7.316 (3.45, 15.50)	<0.001	2.331 (0.59, 9.16)	0.225

Factor	Was the study scenario considered acceptable		Unadjusted		Selected*	
	No	Yes (%)	OR (95% CI)	p-value	OR (95% CI)	p-value
If respondent had taken part in the study scenario they feel it would break the rapport with their doctor						
Yes	10	12 (54.5)	1			
No	32	150 (82.4)	3.906 (1.55, 9.82)	0.004	1.308 (0.37, 4.68)	0.680
If respondent had taken part in the study scenario they would not trust doctors or researchers in the future						
Yes	7	2 (22.2)	1			
No	35	160 (82.1)	16.000 (3.19, 80.32)	0.001	3.906 (0.62, 24.65)	0.147
If respondent had taken part in the study scenario they may consider whether they would take part in research again						
Yes	15	15 (50.0)	1			
No	27	147 (84.5)	5.444 (2.39, 12.42)	<0.001	1.028 (0.41, 2.59)	0.223
Has the respondent taken part in health research before?						
Yes	10	43 (81.1)	1			
No	26	113 (81.3)	1.011 (0.45, 2.27)	0.979		
If the respondent had taken part in research was this experience interesting?						
Yes	7	33 (82.5)	1.414 (0.31, 6.51)	0.656		
No	3	10 (76.9)	1			
If the respondent had taken part in research were they given enough information?						
Yes	7	30 (81.1)	1			
No	3	13 (81.3)	1.011 (0.23, 4.54)	0.988		
If the respondent had taken part in research did they value the experience?						
Yes	8	34 (81.0)	1			
No	2	9 (81.8)	1.059 (0.19, 5.88)	0.948		
Would the respondent take part in research if asked in the future?						
Yes	14	81 (85.3)	2.025 (0.99, 4.13)	0.052	1.028 (0.41, 2.59)	0.953
No / Would depend	28	80 (74.1)	1			
Would the respondent be concerned that their details may be shared with other people if they took part in research?						
Yes	12	50 (80.6)	1.116 (0.53, 2.36)	0.774		
No	30	112 (78.9)	1			
Would the respondent be concerned that your doctor might keep information from them if they took part in research?						
Yes	22	58 (72.5)	1			
No	20	104 (83.9)	1.972 (0.99, 3.92)	0.052	0.947 (0.36, 2.50)	0.912
Would the respondent have any concerns about health risks if they took part in research?						
Yes	14	62 (81.6)	1.240 (0.61, 2.54)	0.556		
No	28	100 (78.1)	1			
Would the respondent have any concerns about taking part research?						
Yes	12	62 (83.8)	1.566 (0.75, 3.28)	0.236		
No	30	99 (76.7)	1			

10.2.2.4 Supplementary opinions

If they had taken part in any type of research study, the majority of respondents reported that they would expect to be told if there were any possible risks associated with participation (96.5%, 195 of responses). A significant minority (30%, n=62) were concerned that personal details might be shared with other people, 40% (n=82) thought that their doctor/researcher might keep important information about their health from them and 37% (n=76) thought that there could be a risk to their health and wellbeing.

When considering specific participation in the study scenario, 86% (n=173) of respondents felt that it was important to ensure that the study did not cause 'risk' to participants and 76% (n=154) felt that participants should be informed of the real reason for the research upon completion of the study.

From 204 responses, the majority of participants (81%) felt that if they had participated in the study scenario they would not have been concerned or, at least would not have been concerned after the reason for the study had been explained to them. Only 23% reported that they may have felt that they had not been treated with respect by their doctor or the researcher who had kept the information from them; 11% felt that it may break their rapport with their doctor or the researcher that had kept the information from them, 4% felt that they would not trust doctors or researchers in the future and 15% reported that they might consider not taking part in research again.

Respondents were invited to give any other feedback relating to the use of the study scenario. Three responses were positive towards the study scenario:

- *"Anything that furthers medical science is very welcome."*
- *"I would feel pleased that I had taken part in a worthwhile project."*
- *"I consider research into the condition is invaluable."*

Three comments helped define when such a study may not be acceptable:

- *"As long as I wasn't in any danger or at risk."*
- *"It would depend if the doctor was going to gain financially from the research."*
- *"I would ask a solicitor if I could sue if my ID had been disclosed."*

One response was negative towards the use of the study scenario:

- *“I would feel that the doctor/researcher had felt that their cause more important than patients right to knowledge.”*

10.2.2.5 Previous experience of research

Only 26% (n=54) of respondents had previously taken part in research and 28% (n=15) of those had participated in more than one study. The majority of participants had valued their experiences of taking part in research (78%) and found it interesting (74.1%) and had received enough information about the study in which they had participated (69%). Participants’ past experiences of research and intention to take part in research did not have any effect on attitudes towards the use of the study scenario as discovered by the logistic regression analysis summarised in Table 10.8.

10.3 Discussion

The majority of respondents felt that the study scenario was acceptable to some degree or had no opinion either way. Only a small minority felt that a glaucoma related adherence study with modified consent should not be carried out at all.

With respect to withholding information from participants, respondents felt it was important to ensure that there were no risks associated with this and that participants should be told the real reason for the study on completion of their participation. If respondents had taken part in the study themselves, most would not have felt concerned about their participation, or indicated that at least once the reasons for the study had been explained to them, they would not have been concerned.

Only a minority of respondents reported that they might have felt they had not been treated with respect by their doctor, or that their rapport with their doctor may have been broken if they had taken part in the study. The broken trust with their doctor or researcher would make them consider whether they would take part in research again in the future. For respondents who might have had such negative opinions, providing a way of contacting the researcher via telephone, email or letter, might have provided an opportunity for concerns to be discussed sensitively on a one-to-one basis in order to minimise the potential harmful effects described.

Overall, respondents felt that informing participants retrospectively and taking consent after study completion increased acceptability of the study design. Furthermore, assessment of attitudes towards the study scenario at three different time points during the questionnaire gave clear evidence as to how disseminating information about the study and the justification for using such a study design, changed opinion of study acceptability. Thus, providing information that positively validates the justification for the study might help participants to accept the use of a modified consent method and reduce the potential negative responses to having taken part in study without giving prior consent.

Whilst generally a study to investigate reactivity effects in measuring glaucoma therapy adherence with a modified consent process appeared acceptable to the majority of respondents, there were those who held reservations about the use of such a method. Members of the public found the study scenario slightly more acceptable than patients who had or were attending a glaucoma clinic; it could be

considered that members of the public are not so concerned with use of eye drops or participating in research compared to patients who have first-hand experience of these issues and where such matters are of greater concern to them. In conclusion, however, questionnaire development and subsequent usage, highlighted what design aspects should be incorporated into such a study with a modified consent method in order to meet the needs of different individuals.

10.4 Methodological Critique

The study had a good response rate and missing data was minimal which suggested that the advice from the literature and think aloud piloting maximised the design of the questionnaire to increase the response rate and completion of all questions adequately.

Use of a study scenario that mimicked the potential design of the planned future study worked well to set the scene and form a base on which the justification for using retrospective consent methods could be explained to respondents. A good response rate and minimal missing data evidenced that the study scenario and justification was understood by respondents of the questionnaire, assuming that respondents would have failed to complete the questionnaire if they had not understood it.

Using a mix of 'patients with glaucoma' and 'the general public' showed that there were differences in attitude between the two groups and incorporating opinions was important in widening the breadth of opinions sought. Asking respondents to give basic demographic details, previous experiences of research and ophthalmic care enabled confirmation that there was a mix of respondents, providing the ability to examine several factors that might have influenced attitudes to the study scenario. The fact that the majority of respondents were over 65 years of age was considered appropriate for a glaucoma related study, since the condition is very age-related.

The VAS was successful in eliciting responses and overcoming the problems identified in the piloting stages of the questionnaire when using a categorical, dichotomised (yes/no) answer had resulted in missing data.

The initial concerns about how order effects, or introducing information into the questionnaire to give relevance and context to the questions, might bias answers was well founded since attitudes did change over the course of the questionnaire; the methodology used allowed for control of these effects reducing the introduction of any unintentional bias.

10.5 Conclusion

This present section investigated the reasons for, and public opinion of, using a modified consent method. Review of the literature suggested that whilst in some cases deception is necessary, its use can cause distress and harm to participants and they might become cynical of research activities.

Focus group and PPIRes involvement helped inform the design of a questionnaire that was thoroughly validated and piloted before use in a wide consultation with patients and members of the public accessing an NHS facility.

The findings from this exploration of patient and public opinion corroborated, at least to some extent, the guidance and evidence gathered from the 2009 ethical debate exercise undertaken by the NHS National Research Ethics Service (NRES)[274] confirmed that deception should only be used when no other research method would suffice and that research would have a high probability of subsequent advances.

Following the wide consultation that was undertaken to ensure that a project requiring modified consent was appropriate, a research project was designed to investigate the magnitude of reactivity effects in assessing glaucoma therapy adherence, which would minimise harm to participants and follow NRES guidance. Furthermore, it was felt that an application via NRES for ethical approval could be confidently made since the design was founded by evidence and suggestions for additional safeguarding procedures. It was determined that participants should be fully briefed at the end of the study as to the reason for the study. It was determined that the ethical review process itself would likely give further reassurances to participants, since the focus group findings suggested that participants of research trust the ethical review process. As is standard good clinical practice, participants in the planned future study were set to be free to withdraw their data should they disagree with their participation in the study and were to have the opportunity to discuss their participation with the research team should further information or concerns need to be discussed.

Section 4. The React Study; using a modified consent procedure to observe reactivity effects

Presentations resulting from this section:

Cate H, Broadway DC, and Bhattacharya D. Investigating assessment reactivity bias. (Poster) UK Society of Behavioural Medicine, Manchester, 2012.

Cate H, Broadway DC, and Bhattacharya D. Exploring Reactivity Bias: The (haw) Thorny Issue! Investigating assessment reactivity bias (Oral) School of Pharmacy Research Colloquium, 2015. *Winner of Best Oral Presentation.*

Chapter 11. The React Study

11.1 Introduction

Evidence from the NAGS qualitative follow-up study described in Section 2 indicated that study reactivity effects might have altered the measured study findings. Monitoring adherence behaviour, including mere measurement effects originating from completing questionnaires, are thought to activate messages and/or establish ideas to provide information that would not have been available to patients had they not taken part in the study. In particular, the multiple methods used to measure adherence and gather participant opinion might also have changed usual behaviour in addition to the effects caused by participating in research.

Thus, this final section describes the React study, a study designed to measure changes in adherence to medication behaviour when individuals participated in research and were aware that their adherence was being observed, in an attempt to quantify the magnitude of any reactivity effects. As the methods describe, the TDA was used to simulate the effect of measuring adherence just as in NAGS. The 'participation in research', as a factor, was replicated by a consent process which used a participant information leaflet replicating that used in NAGS which explained that participants would have their adherence monitored using the TDA. A questionnaire was used to simulate mere measurement effects.

The React study was designed to replicate NAGS as closely as possible. However, soon after the conception of the React study, latanoprost became the first line treatment for POAG at NNUH instead of travoprost; Xalatan (the trade name for latanoprost) was coming off patent and therefore generic latanoprost became available at a much lower cost and had to be prescribed in the NNUH Eye Department. Therefore, it was not possible to recruit patients that were treatment naïve and about to commence treatment as was the case in NAGS. Instead patients on established travoprost were recruited.

A previous study comparing adherence measured by a MEMS bottle with patient self-reported adherence evaluated using a VAS, concluded that because patients were aware that their adherence was being monitored by the MEMS bottle, there

was a potential for their adherence and their estimations of adherence to be influenced.[94] Thus, collecting self-report data using the 4-item Morisky self-report tool would not only ensure that consistency was maintained by using the same questions as in the NAGS questionnaire, but would also enable a comparison of how awareness of monitoring adherence might affect patient self-report when patients are masked and un-masked to the presence of adherence monitoring.

The NAGS questionnaire also used SIMS to establish the potential barriers to use of medication. However, the NAGS qualitative focus group study found that SIMS was not well received and many responses were left blank, since participants did not feel that the questions were relevant to problems experienced by eye drop users as described in paragraph 4.3.2.4. Therefore, a new tool was sought to replace SIMS to ensure that the questionnaire emulated the same length and type of questioning used in NAGS. The Identification of Medication Adherence Barriers (IMAB) questionnaire is a 30-item questionnaire designed to gauge attitude and decision-making processes in adherence behaviour. Originally designed to assess barriers to adherence to medication for the prevention of cardiovascular disease, statements are given to a respondent to assess attitudes in 10 behaviour domains; 'knowledge', 'skills', 'memory attention and decision making processes', 'social influences', 'environmental constraints', 'emotions', motivation and goals', 'goal conflicts', 'beliefs about capabilities' and 'beliefs about consequences'.[275, 276] Patients are asked to complete the questionnaire by responding to each statement using a 5 point Likert scale ranging from 'strongly agree' to 'strongly disagree'. A response of 'strongly agree' for positively phrased statements would score 1 point and thus indicate a low barrier, whereas a response of 'strongly disagree' would score 5 points and indicate a high barrier to behaviour change. For negatively phrased statements reverse scoring is used so that a response of 'strongly agree' scores 5 points and thus represent a high barrier to behaviour change. Scores from the three statements for each behavioural domain are collated and used to calculate a mean score. The process allows a researcher to clearly see which of the behavioural domains represents the highest barrier to adherence behaviour.

Use of the IMAB in the React study not only fulfilled the need to replicate the NAGS study questionnaire as closely as possible, but had a further function of providing useful evidence for future intervention studies. Identifying individual patient barriers would guide future studies to target individual needs and initiate

behaviour change that improves adherence. It was considered that use of the IMAB questionnaire in a glaucomatous population where self-reported barriers that prevent good medication in conjunction with TDA measured non-adherence, would have the potential to establish if an association exists between measures. An association between the measures of adherence could highlight the IMAB questionnaire as a useful tool for future glaucoma adherence studies and clinical practice.

The design of the study required the use of a modified consent method that withheld information from participants. Section 3 described the work undertaken to establish the acceptability of a modified consent method with patients and members of the public; the majority of which reported that this method would be acceptable. The findings highlighted ways in which participants could be reassured and managed if any potential negative feelings did arise.

11.2 Method

11.2.1 Study aims and objectives

The aim of the React study was to observe the change in TDA measured adherence and self-reported adherence when individuals participated in research in which they were initially unaware and subsequently aware, that their adherence was being observed, during which they completed questionnaires that probed their attitude to adherence behaviour at completion of each phase of the study. The difference in measured adherence determined the magnitude of reactivity effects. The React study also aimed to elicit patient-reported attitudes to adherence to travoprost and its association with measured non-adherence.

The study objectives were to:

A. Determine if there was a difference in adherence to travoprost when participants were un-aware and therefore masked to participation in the study, compared with that of the un-masked period, when participants had agreed to take part in a study in which their adherence was being monitored; Analysis A Figure 11.2.
B. Examine if adherence to travoprost was an attributable factor for individuals declining participation in the un-masked phase; Analysis B Figure 11.2.
C. Establish if there was a difference in self-reported non-adherence when participants were un-aware and therefore masked to participation in the study, compared with that of the un-masked period, when participants had agreed to take part in a study in which their adherence was being monitored.
D. Establish if there was an agreement between self-reported non-adherence and TDA measured adherence in masked and un-masked phases.
E. Establish if opinion of the TDA and perceived usefulness was an attributable factor for adherence to travoprost.
F. Establish if opinion of the TDA and perceived usefulness was an attributable factor for individuals declining participation in either phase of the study.
G. Examine if factors namely, previous problems with eye drops, or satisfaction with information received about diagnosis and eye drops, affected adherence with travoprost in the masked and un-masked phases.

H. Establish if the overall IMAB score or any specific behavioural domain had an association with non-adherence measured by the TDA in the masked and un-masked phases.
I. Examine if age, gender and glaucoma diagnosis, were attributable factors for individuals declining participation in either phase of the study.

11.2.2 Ethical approval

The study received ethical approval from the Norfolk Research Ethics Committee, (appendix 20) and research governance approvals from the East Norfolk and Waveney Research Governance Committee (appendix 21).

11.2.3 Setting, Participants and Recruitment

Patients attending the glaucoma out-patient clinic at NNUH and Spire Hospital (Norwich) meeting the inclusion/exclusion criteria were invited to take part.

Inclusion criteria

- Treated glaucoma patients using travoprost, that, in the opinion of the clinician, was efficacious with no hypersensitivity or other unwanted side effects.*
- Male or female ≥ 18 years of age.
- Patients able to provide a signed informed consent.
- Patients willing and with adequate ability to read and understand English.

Exclusion criteria

- Patients whose drops were applied by care home staff / carers / home-helpers.
- Additional medication required for the treatment of glaucoma.
- Patients who were previously participants in NAGS or the follow-up studies described in Chapter 5 and 7.

*Of the participants from the NAGS study, 7% withdrew due to hypersensitivity or no effect to treatment. By recruiting participants already using established treatment with travoprost the number of early withdrawals was expected to be

reduced significantly. However, patients were withdrawn from the study if they stopped using travoprost for any reason during the study period.

11.2.4 Identification and recruitment

The flow diagram shown in Figure 11.1 shows the identification and recruitment phase, which was followed by the masked phase, intervention and un-masked study phase. The consultant/primary care team identified eligible patients from NNUH and Spire hospital clinics. The patient details were then passed to the specialist NNUH specialist glaucoma nurse. The specialist glaucoma nurse approached the identified patients to ask if they would use the TDA for two months and then complete a questionnaire in order to give their feedback about the usefulness of the TDA using the The React study recruitment script (appendix 22). The patient was informed that their details would be recorded on the contact details form (appendix 23) so that the TDA and instruction leaflet (appendix 13) could initially be sent by post along with all further communication. The identifying clinician/specialist nurse also gathered data about the patient on section B of the contact details form (appendix 23); date of birth, gender, and type of glaucoma diagnosed. Those in contact with the patient specifically avoided using words such as ‘research’ and ‘a study’ or that the TDA measured adherence to ensure that the initial two-month period (56 days) remained a ‘masked phase’.

When patients declined participation in the study, only section B of the data collection form (appendix 23) was completed to ensure that the data passed to the research team remained anonymous. Date of birth, gender and type of glaucoma were used to determine if these variables were significantly different between those who took part in the study and those who declined.

After one week, the patient was telephoned by the specialist glaucoma nurse, or a member of the primary care team, to confirm the use of the TDA and/or to resolve any problems relating to TDA usage. If the patient had decided not to continue using the TDA after one week, a reply envelope was supplied by the primary care team so that the patient could return the TDA.

11.2.5 The study intervention

The study intervention followed the initial two-month masked phase when patients were not aware that their adherence was being monitored or that they were participating in a study. The intervention was designed to simulate the following factors:

- Awareness of the participation in research study objectives - a patient information leaflet and formal consent process, together with discussion with the researcher.
- Effect of measuring adherence – participants aware that the TDA measures adherence
- Questionnaires - mere measurement effects.

11.2.6 The masked phase

Those patients who confirmed they were using the TDA at one week and were intending to continue use of the TDA were then considered to be enrolled into the masked phase for 56 days of monitoring. A 56-day follow-up period was chosen to enable a long enough period for patients to become familiar with the TDA and enter a habitual routine of administering eye drops with the TDA whilst not extending the monitoring period for too long; NAGS found that when the monitoring period was extended beyond 56 days, data retrieval became less reliable, see Table 3.3 in Chapter 3.4.

Upon completion of the masked phase (56 days of monitoring), individuals were sent Questionnaire 1, ‘A review of the Travalert Dosing Aid’ (appendix 24), in the post together with instructions to return their questionnaire and the TDA in a reply envelope provided using ‘end of review phase patient letter (appendix 25). An administrator from the primary care team arranged postage of the questionnaires to ensure that patient details were kept anonymised from the researcher. Questionnaire 1 concluded by asking the patient if they would consider joining a research study which involved using the TDA for a further two months. If the patient declined participation, a letter was sent to them to thank them for reviewing the TDA and to inform them that the data collected from their questionnaire and the TDA would be used for research purposes; however, they could opt out should

they prefer (appendix 26). If patients declined use of their data, the TDA and questionnaire data collected was removed from the analysis. In addition, patients were offered their TDA for future use if they had found that it was a useful aid for administering their eye drops.

11.2.7 The un-masked phase

For patients who were interested in taking part in the React study, a patient information sheet and consent form, with a cover letter, were sent a TDA with fresh batteries to avoid loss of data (appendix 27). The cover letter asked for the consent form to be completed and returned in the postage reply envelope (appendix 28). A one-week follow-up telephone call was made by the researcher to all individuals to ensured that, either they returned their consent form and had started using the TDA, or to resolve any issues about consenting to the study. The researcher ensure the participant understood that their adherence would be monitored by the TDA and that the data would be reviewed when they sent the TDA back to the research at the end of the 56-day monitoring period.

After 56-days of monitoring in the un-masked phase the patient received Questionnaire 2, 'Measuring patient use of travoprost' (appendix 29), a reply envelope to return their TDA and a letter to thank them for taking part in the study (appendix 30).

Receipt of the TDA and Questionnaire 2 by the researcher marked completion of the study. A final letter was sent to them to thank them for taking part in the study and to inform them that the data collected from their questionnaire and the TDA in the initial review phase would be used for research purposes; however, they could opt out should they prefer (appendix 31). Participants were contacted by telephone if they had not returned their final reply envelope. If no contact was made and the data was not retrieved, the patient was considered 'lost-to-follow-up' but a letter was sent to thank them for their involvement in the study and to inform them that the data collected in the masked phase would be used as part of the study (appendix 5). Participants were given the option to opt-out if they specifically requested to do so.

11.2.8 Travalert Dosing Aid

The study used the TDA, which electronically stores the time, date and number of drops administered during the study period as described in 3.3.2.4. The TDA had an alarm feature and visual cue window that displayed a 'tear drop' at a pre-set time to remind the user to administer a dose. During NAGS the alarm feature was disabled and stickers were placed over the visual cue window so these features could not act as an adherence aid. However, as many TDAs used in NAGS were returned with the stickers peeled off and the internal mechanism tampered with, it was felt better in the React study to leave the visual cue window clearly visable to all participants from the outset in order to reduce the desire for curious individuals to remove stickers and explore the internal mechanisms of the TDA. Use of the electronic visual cue window also provided a justified reason for the TDA to have a battery comparment which operated the visual cue window, thus concealing the monitoring function of the TDA. Therefore, in contrast to NAGS that covered the visual reminder with a sticker, the visual cue window was not covered and programmed to appear between 9 pm and 1 am; however, the alarm was deactivated as in NAGS.

11.2.9 Questionnaires

The questionnaires were given at two different time points; after the masked phase Questionnaire 1 called 'The review of the Travalert Dosing Aid' (appendix 23), and after the un-masked phase Questionnaire 2 called 'Measuring patient use of travoprost' (appendix 24). Questionnaires were sent out in the post with a freepost envelope for participants to return to the researcher.

MMAS: The Morisky Measure of Adherence Scale (MMAS)[124] is a commonly used adherence self-report tool and previously used in NAGS, described in Chapter 3.3.5. The MMAS is composed of four yes/no questions (see appendix 8) about past medication use patterns. Participants answering 'yes' to a question scored 1, thus scores ranged from 0-4; 0 indicating perfect adherence and 4 being non-adherent. Minor changes to the wording of the validated questionnaire were made in order to make MMAS relevant to use of eye drops. The questions can be reviewed in appendices 23 and 24, part B.

Usefulness of the TDA: Three 'yes', 'no' or 'no difference' questions were used so that participants could give their feedback about the use of the TDA; 'Do you think the Travalert Dosing Aid… was easier to use than the bottle of eye drops alone?', '…helped you remember using your eye drops?', '…helped you apply your eye drops?' The questions were chosen to gather further information about the perceived use of the TDA and the effect this might have had on adherence to medication. The questions can be reviewed in appendices 23 and 24, part A.

Satisfaction with use of eye drops and information: Three questions were used to assess satisfaction; 1) previous experience of problems using eye drops, 2) satisfaction with information received about their diagnosis and 3) satisfaction with information received about their travoprost. Positively phrased statements, scored 5 points for a response of 'strongly agree' and thus indicated a high satisfaction, whereas a response of 'strongly disagree' scored only 1 point. Negatively phrased statements used reverse scoring so that a response of 'strongly agree' scored 1 point. Findings from NAGS suggested that these topics might have had an effect on the adherence to travoprost. The questions can be reviewed in appendices 23 and 24, page 4.

IMAB: The IMAB questionnaire[275] was modified for use with patients that had glaucoma and were using travoprost eye drops, by changing words referring to 'medication' to 'eye drops' and 'taking medication' to 'applying eye drops'. Since the IMAB questionnaire was combined with other questions relating to the study objectives, the IMAB was shortened from 30 questions to 20, two rather than three from each of the 10 behaviour domains, to avoid respondent fatigue. The 20 questions were chosen to represent the most reported medication barriers from a glaucomatous population. As described in Chapter 11.1 a positively phrased statement, scored 1 point for a response of 'strongly agree' and thus indicated a low barrier, whereas a response of 'strongly disagree' scored 5 points and indicated a high barrier to behaviour change. Negatively phrased statements used the reverse scoring so that a response of 'strongly agree' scored 5 points and thus represented a high barrier to behaviour change.

Assessment of face validity of the questionnaire was sought from the patient and public advisory group (PPIRes) and changes were made to the questionnaire following their recommendations.

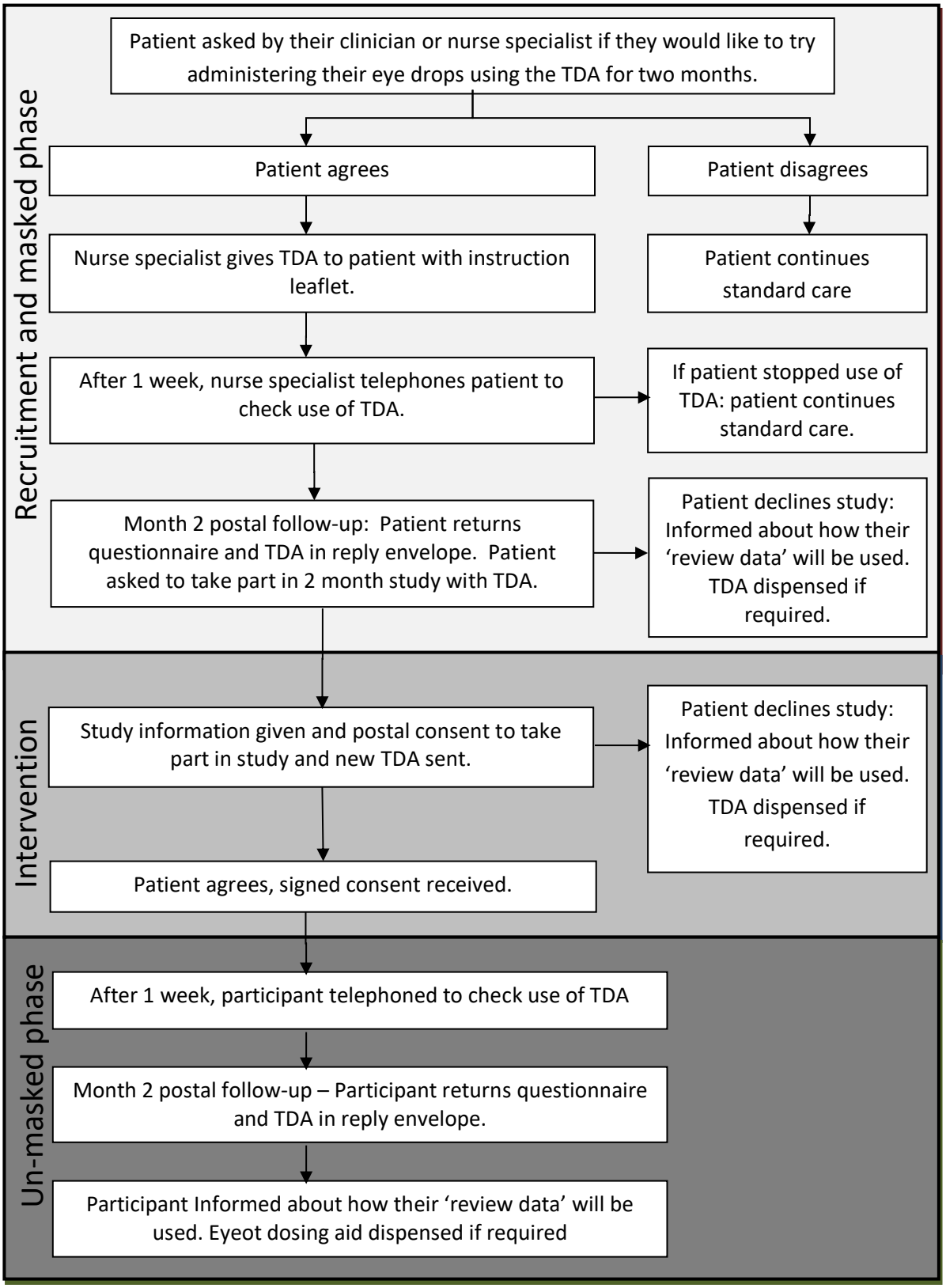


Figure 11.1. Patient flow through 'masked', 'intervention' and 'un-masked' phases

11.2.10 Sample Size

In an oral hygiene study,[215] that compared the measured plaque build-up between a simulated experimental study group of patients compared to a control group, who were not aware that they were participating in a study, the experimental group were found to have 27% less plaque at a 6 month follow-up, than the control group. Thus, the Hawthorne effect of participating in and fulfilling the requirements of a study, altered subject behaviour.

Two previous glaucoma studies using TDAs to measure adherence can be used to estimate the monitoring effects of using the TDA; Rossi *et al.*[47] and Okeke *et al*.[93] The Okeke et al. study masked participants to the fact that their adherence was being monitored for a duration of 12 months (n=196), whilst Rossi et al. monitored participants un-masked for 3 months (n=35). The Okeke *et al.* [93] study had a mean adherence rate of 71%±24% and the Rossi *et al*. study[47] 77%±21% which suggested a 6% difference in measured adherence when comparing a masked and un-masked sample group. However, the difference in measured adherence between the Okeke and Rossi sample groups may not be simply due to reactivity effects; different study methods, sample populations, sample sizes and duration of monitoring may affect measured adherence.

Thus, without any evidence in the literature at the time of designing the React study, using the above studies for guidance only, ten percentage points was chosen to represent a reasonable assumption of expected change in behaviour due to the reactivity effects of study participation monitoring of adherence and mere measurement effects.

Using data from NAGS, which used the same sample population as the proposed study, the difference between the mean adherence at month 2 (74.92%) and month 6 (78.47%) was 2.92 (SD 26.74). Therefore, a sample of 56 participants with complete data from both masked and un-masked phases would give an 80% power to detect a 10 percentage point difference in adherence.

During NAGS, 10% of participants did not complete the study and 25% of TDA data was missing. Thus, an additional 20 participants would be recruited to allow for participants who might withdraw and for missing TDA data in the event of TDA failure. Therefore, 76 participants were required to take part in both the masked and un-masked phases of the React study.

11.2.11 Outcome measures

All the outcome measures were collected at two different time points; after the masked phase and after the un-masked phase.

The percentage adherence score was calculated using the number of adherent doses recorded by the TDA divided by the expected number of doses for the monitoring period using the 'adjusted adherence calculator' described in Chapter 3.3.4. A dichotomised score was also calculated; the proportion of individuals with ≥80% adherence measured by the TDA were dichotomised to the adherent group and those with less than <80% adherence were dichotomised to the non-adherent group.

Secondary outcome measures were:

- MMAS was dichotomised; participants who scored 0 were dichotomised to the adherent group, participants scoring 1-4 were dichotomised to the non-adherent group.
- Self-reported opinion of the usefulness of the TDA was coded into 'yes', 'no' or 'no difference' for each category; 'ease of use', 'help to remember to apply eye drops' and 'help to administer eye drops'.
- IMAB scores were collated as described in Chapter 11.1. Each of the 10 behavioural domains received a score out of 10, a higher score indicating a greater perceived barrier to use of travoprost. The scores for each of the 10 behavioural domains were collated to produce an overall score out of 100.
- Satisfaction with eye drops and information were calculated from participant responses using a scale of 1 to 5 to produce one overall 'satisfaction score'. A higher score indicated a greater satisfaction with use of drops and provision of information.

11.2.12 Statistical analysis

Data were analysed using SPSS version 22. Descriptive statistics were used to characterise the demographics of the study sample. Histograms were visually checked to review the distribution of the data before deciding on the appropriate statistical analysis method.

The primary objective:

Adherence measured by the TDA during the masked phase was compared with the un-masked phase. The distribution of the primary outcome data were reviewed by visual inspection of the histograms and summary statistics reported accordingly. The data in the masked and un-masked phases were skewed but the difference between the individual scores between the two groups was normally distributed. Therefore, a paired t-test was used to test if the mean difference between the adherence scores from the masked and un-masked phases was zero.

Secondary objectives:

Opinion of the TDA and its effect on adherence: Self-reported opinion of the TDA was compared with adherence measured by the TDA to establish if participants who found the TDA useful had improved adherence compared to those who did not find the TDA useful. Adherence was described using median adherence scores and a Chi-squared test was used to compare the dichotomised adherence opinion of the TDA outcome measures.

Individuals who declined participation: To determine if age, gender and type of glaucoma were attributable factors for the self-selected sample, individuals who declined to review the TDA (the masked phase) were compared with individuals who did agree to take part. A Mann Whitney-U test for age was used as the data were from independent groups and not normally distributed, and a Chi-squared test was used to test for independence between gender and glaucoma diagnosis.

In the same way, individuals who had taken part in the masked phase but declined participation in the un-masked phase were compared with those who did take part in the study phase for age, gender and glaucoma diagnosis. In addition, to determine if good adherence measured by the TDA was an attributable factor for individuals choosing to participate in the 'un-masked phase,' the mean average TDA score for the sample who declined to participate in the un-masked phase was compared to the sample who did participate in the un-masked phase using a Student's t-test. To establish if opinion of the usefulness of the TDA was an attributable factor in individuals choosing to participate in the 'un-masked study' a Chi-squared test was used to test for independence in each of the three categories of self-reported opinion of the usefulness of the TDA.

Self-reported adherence: Agreement between the MMAS self-reported adherence and dichotomised adherence measured by the TDA was measured using a Cohen's kappa test. Cohen's kappa measures inter-rater agreement when rating the same object using categorical data and as such established the agreement between the two different methods of measuring adherence for the same individual. The masked and un-masked phase samples were analysed separately to compare any difference between phases.

Responses to the MMAS measure of self-reported adherence in the masked phase and un-masked phase were measured using a Cohen's kappa test of agreement.

Satisfaction with use of eye drops and information: The satisfaction with travoprost and information score was correlated with TDA measured adherence using a Spearman's rank correlation test, since the correlation was non-linear. The masked and un-masked phases were analysed separately and then compared to establish if there was an association between satisfaction and adherence.

Self-reported barriers to adherence: The self-reported barriers to use of medication using the total IMAB score, as well as each behaviour domain score was correlated to mean percentage adherence measured by the TDA in the masked phase and un-masked phase using a Spearman's rank correlation test, since the correlation was non-linear.

Demographics and glaucoma diagnosis: date of birth was used to calculate age at the time of entering the study, gender was dichotomised to either male or female and diagnosis was categorised to either glaucoma suspect, ocular hypertension or primary open angle glaucoma as determined from the patient hospital records.

11.3 Results

11.3.1 Recruitment

The recruitment period was two years; the first eligible patient was enrolled into the masked phase on the 8th January 2014 and the final patient on the 22nd December 2015. At the end of the recruitment period, only 60 participants were recruited to the un-masked phase resulting in 51 individuals with complete paired data for both the masked and un-masked phases. Therefore, the planned sample size had not been achieved. Thus, an interim analysis is reported in this Chapter and recruitment continues in order to achieve the planned study sample of 76 participants.

Figure 11.2 details the number of patients accepting and declining participation in the masked and un-masked study phases and the data attrition rate. Patients from the masked phase were all given the option of declining use of their data during the retrospective consent procedure. No concerns were raised and no patients declined the use of their TDA data.

Objective I: Table 11.1 describes the demographics of the populations that took part in the masked phase and un-masked phase. Age, gender and type of glaucoma were compared between those who refused to take part in the masked phase and those who declined to participate in the un-masked phase. Of the 161 patients who agreed to use the TDA in the masked phase compared to those who refused, there were no statistically significant differences. Of the 110 patients who completed the masked phase, only 60 took agreed to participate in the un-masked phase; there were no statistically significant differences.

Patients refused to use the TDA in the 'review', and therefore the masked phase, because they were already happy with their current routine and use of drops and did not need/want a dosing aid (n = 27), or because they had other health issues that demanded their attention (n = 9). Some people did not want to give a reason (n = 12), were going on holiday for the period of the masked phase (n = 2), or did not like the idea of using a device (n = 3). Reasons for patients refusing to participate in the un-masked phase was not collected as recruitment was by written communication and could not be elicited.

Table 11.1 The demographics of the populations that refused to take part in the React study or took part in the masked and/or un-masked phases. The statistical differences between those who refused to take part in the masked phase and those who declined to participate in the study (and therefore the un-masked phase) are shown.

	Refused (n=53)	Difference between those who refused and those who participated in masked phase ⟷	Masked Phase (n=161)	Difference between those who took part in masked phase but declined un-masked phase ⟷	Un-Masked Phase (n=60)
Gender: Male	26 (49.1%)	p =0.529	71 (45.3%)	p=0.854	27 (45.0%)
Age: Years (Mean)	76.02 (SD 9.6)	p=0.216	74.39 (SD 9.5)	p=0.190	75.7 (SD 9.7)
Type of glaucoma:					
POAG	35 (66.0%)	p=0.307	89 (55.3%)	p=0.172	27 (45.0%)
GS	10 (18.9%)		33 (20.5%)		15 (25.0%)
OH	8 (15.1%)		39 (24.2%)		18 (30.0%)

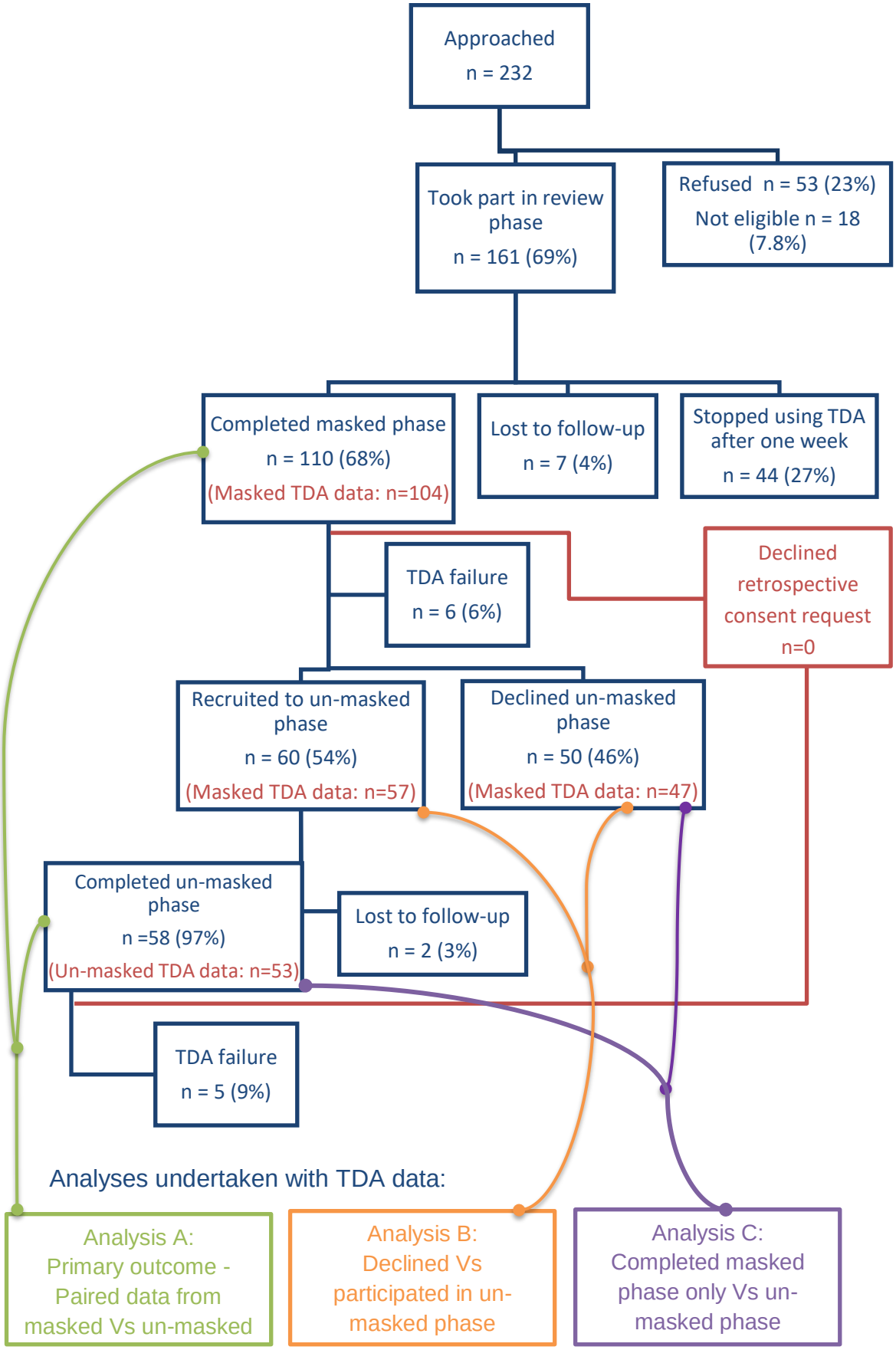


Figure 11.2. Study recruitment flow chart and data attrition; includes details of analyses undertaken A-C

11.3.2 Monitoring period

The monitoring period was 56-days in both phases; masked and un-masked. Participants were advised when to stop using their TDA and return it in the reply envelope provided. Some participants stopped using the TDA before the 56-days was reached and some continued using the TDA for longer. Thus, the period of monitoring time captured by the TDA in the masked phase was a mean of 71 days ranging from 49 to 96 days; 6 participants stopped using their TDA before they reached the planned 56 day monitoring period.

The un-masked phase had a mean follow-up period of 71 days ranging from 43 to 100 days. Four participants stopped using their TDA before they reached the 56 day monitoring period; 1 patient stopped at 43 days because they underwent cataract surgery and no longer required travoprost eye drops, 1 participant advised that they had dropped their TDA and it had subsequently stopped working.

11.3.3 Measured adherence

The mean adherence measured by the TDA during the masked phase was 59.5% (SD, 36.5) and the median was 75.2% (IQR 19.3, 91.4) (n=104). The mean adherence measured by the TDA during the un-masked phase was 82.8% (SD, 21.0) and the median was 91.8% (IQR, 76.5, 96.9) (n=53). The proportion of individuals dichotomised to ≥80% adherence measured by the TDA in the masked phase was 50 (48.1%) and 37 (69.8%) in the un-masked phase (See Figure 11.5).

Histograms are shown in Figure 11.3 showing the distribution of the adherence in both masked and unmasked phases; on visual inspection, there appeared to be more adherent individuals in the un-masked phase compared to the masked phase.

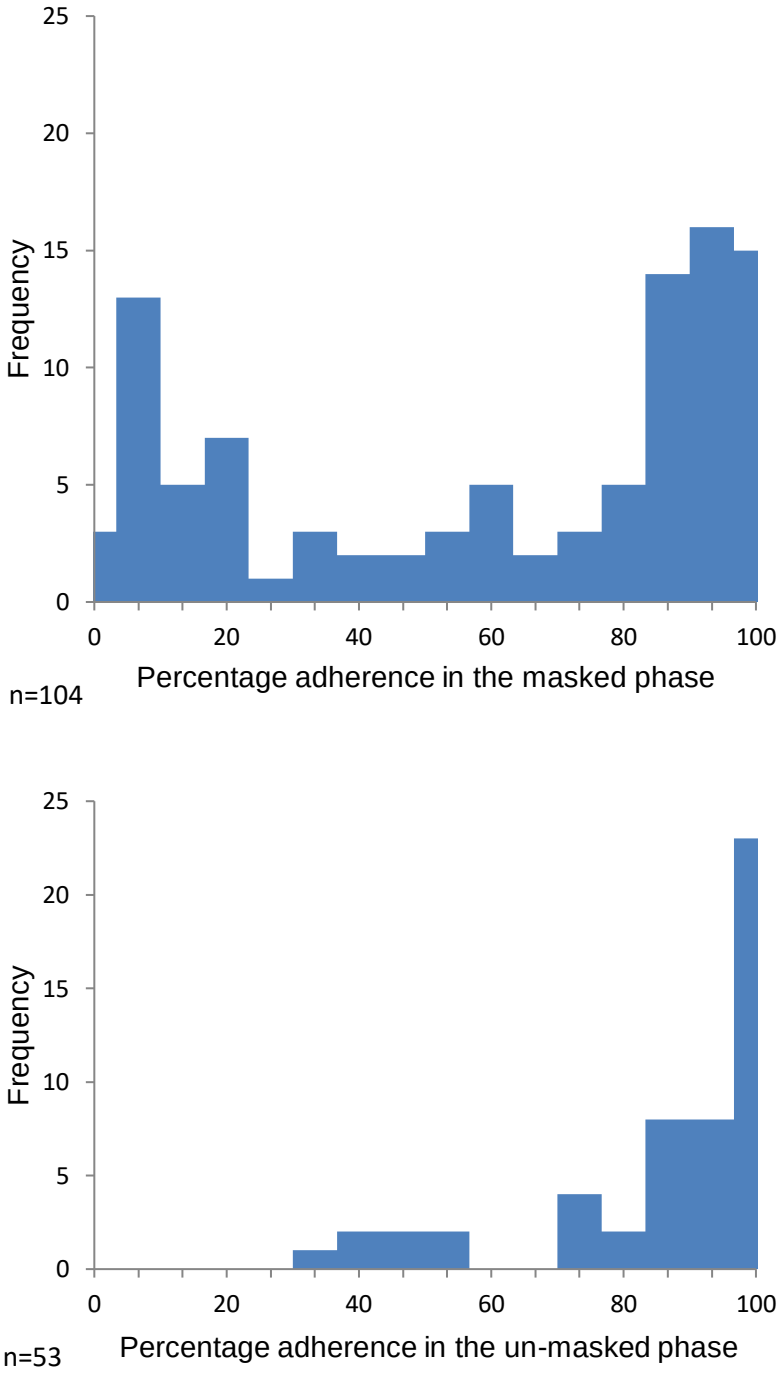


Figure 11.3 Histograms of TDA measured adherence for patients in the masked phase and participants in the un-masked phase

11.3.4 Primary outcome

Objective A (paragraph11.2.1) was achieved by using a matched pairs Students t-test with patients who had complete TDA data from both the masked and un-masked phase (Figure 11.2, Analysis A); mean adherence in the masked phase was 78.1% (SD, 22.2) and the un-masked phase was 82.2% (SD, 21.3) with a mean difference of 4.2% (CI, -2.5, 10.8), a difference that did not reach statistical

significance (p=0.214, n=51). The results are also shown in Figure 11.5. Such a result would lead to not rejecting the null hypothesis, thus implying that there was no difference in adherence behaviour when participants were masked or un-masked. However, as the histogram in Figure 11.4 showed that the majority of individuals had an increase in their adherence when examined visually.

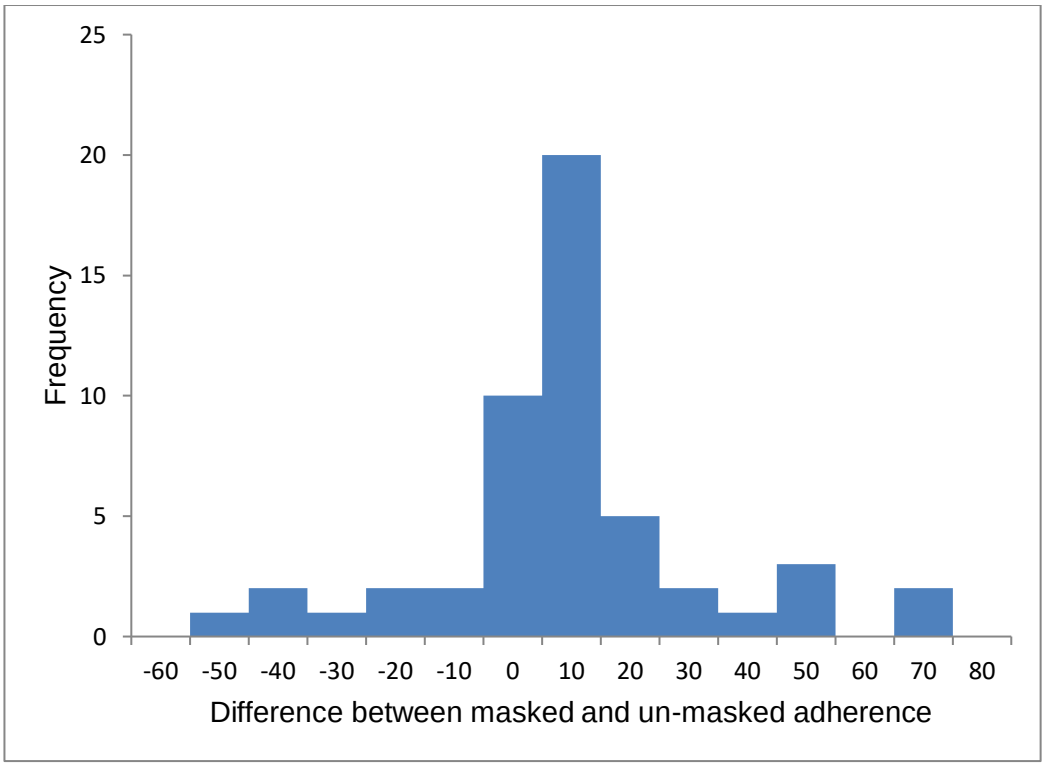


Figure 11.4 Histogram of difference in TDA measured adherence between the paired data for the masked and un-masked phases

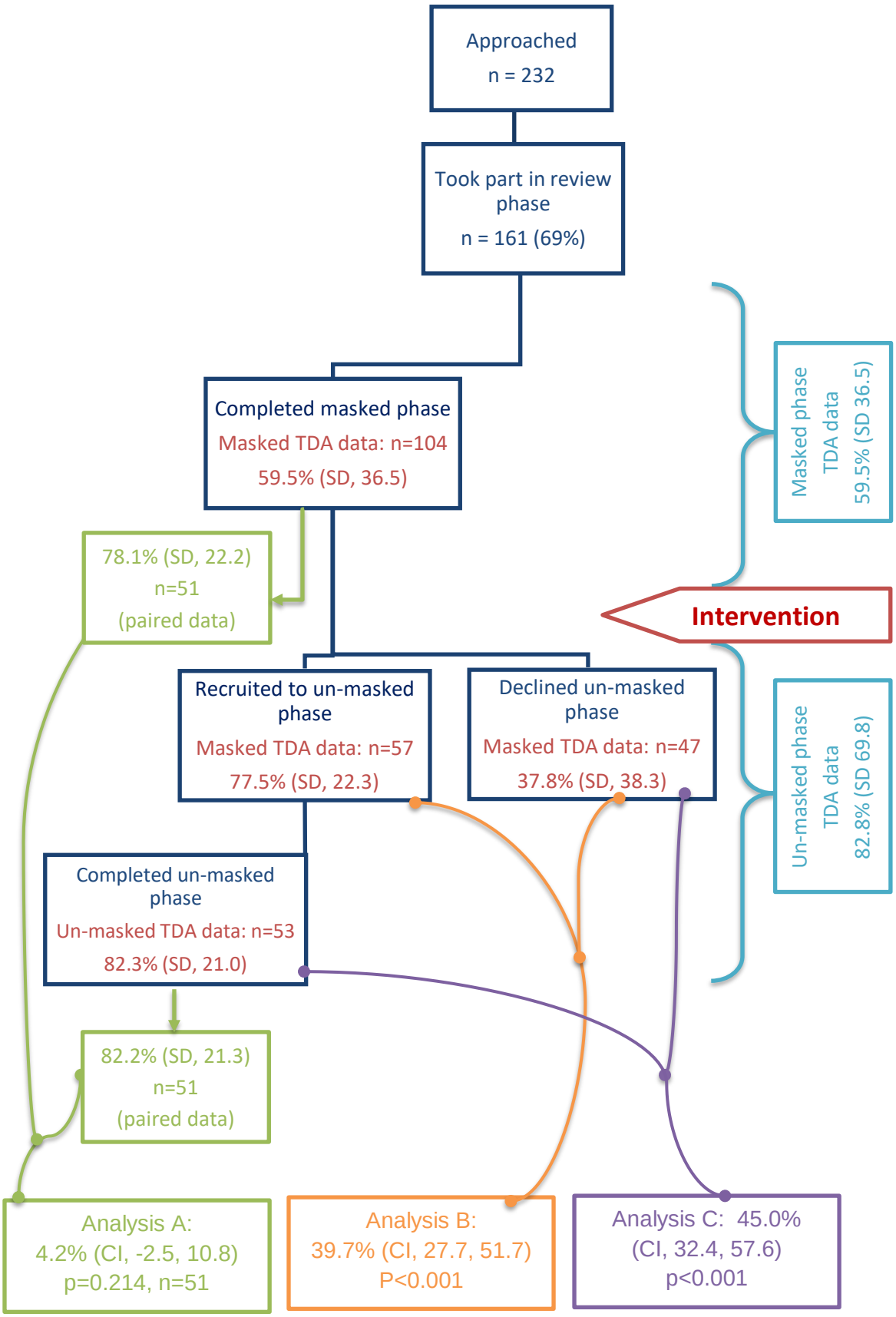


Figure 11.5 Percentage adherence calculated from TDA data are presented to identify the data used for Analysis A, B and C

Objective B (paragraph 11.2.1): TDA measured adherence for those who declined participation in the un-masked phase was significantly different to those who did participate in the un-masked phase (Figure 11.2, Analysis B); mean adherence for the group that declined participation was 37.8% (SD 38.3, n=47) and those agreeing to participate was 77.5% (SD 22.3, n=57) a mean difference of 39.7%(CI 27.7, 51.7, p<0.001) (See Figure 11.5). Therefore, participants with lower adherence measured by the TDA were less likely to participate in the un-masked study phase.

The reported primary outcome analysis matched the adherence score for individuals who had taken part in the masked phase with their adherence score in the un-masked phase; participants who declined participation in the un-masked phase, therefore, did not have an un-masked adherence score and were missing from the paired t-test analysis. Thus, participants with low adherence scores were not included in the final analysis, which may have biased the un-masked sample. In addition, as there is a ceiling effect on measured adherence (adherence cannot be better than 100%), the final analysis was based upon on data with reduced variation.

An unplanned analysis was undertaken to compare the mean of the masked sample group with the mean of the un-masked sample group (Figure 11.2, Analysis C) in an un-paired, before and after intervention, between group analysis. However, the two groups were not independent samples as the individuals who had participated in the un-masked phase had taken part in the masked phase prior. Therefore, the adherence scores of individuals who participated in the un-masked phase were removed from the masked-phase group mean score. The mean adherence of individuals who had only taken part in the masked phase 37.8% (SD 38.3, n=47) were compared to participants that had participated in the un-masked phase (82.8%, SD 21.0, n=53); the mean adherence of the between-group (non-paired) analysis found a statistically significant difference of 45.0% (CI, 32.4, 57.6), p<0.001 (See Figure 11.5).

11.3.5 Self-reported adherence

In the masked phase, the MMAS self-report tool found 89 participants (81.7%) and 42 participants (71.2%) in the un-masked phase to be adherent; less participants

reported being adherent with MMAS in the un-masked phase. Table 11.2 compares the paired self-reported adherence data for individuals who took part in the masked and un-masked phases (Objective C, paragraph 11.2.1); the majority did not alter their self-reported adherence when in the masked phase compared to the un-masked phase and had a moderate Kappa agreement (k= 0.466, p <0.001, n=55).

Table 11.2 Comparison of dichotomised MMAS scores using paired data for individuals with MMAS data in the masked phase and un-masked phase (n=55). Percentages are calculated for the masked phase.

MMAS		Masked phase			Agreement (Kappa)
		Adherent n (%)	Non-adherent n (%)	Total	
Un-masked phase	Adherent	36 (81.8%)	3 (27.3%)	39	(k= 0.466, p <0.001).
	Non-adherent	8 (18.2)	8 (72.7%)	16	
	Total	44	11	55	

However, Table 11.3 shows adherence measured with the TDA and MMAS. In the masked phase most participants reported being adherent with MMAS and there was poor Kappa agreement (k=-0.065, p=0.003, n=101). In the un-masked phase there was slightly more agreement than in the masked phase but this was still poor and not statistically significant (k=0.007, p=0.835, n=51) (Objective D, paragraph 11.2.1).

Table 11.3 Comparison of dichotomised MMAS and TDA scores for individuals in the masked phase and the un-masked phase. Percentages are calculated for MMAS.

		Masked phase MMAS			Un-masked phase MMAS		
		Adherent n (%)	Non-adherent n (%)	Total	Adherent n (%)	Non-adherent n (%)	Total
TDA	Adherent	46 (56.8)	4 (20.0)	50	26 (68.4)	10 (71.4)	36
	Non-adherent	35 (43.2)	16 (80.0)	51	11 (31.6)	4 (28.6)	15
	Total	81	20	101	37	14	51

11.3.6 Perceived usefulness of the TDA

Objective E (paragraph 11.2): Table 11.4 details participant reported opinion of the usefulness of the TDA compared with TDA measured adherence; participants were less adherent if they had not found the TDA easier to use than the bottle alone, helped remember to use eye drops or helped apply eye drops.

Table 11.4 Perceived usefulness of TDA use compared with adherence and participation in the un-masked study.

	Adherence Median (IQR)	Dichotomised Adherent (%)	Chi-squared p-value
Was easier to use than the bottle alone (n = 55)	83.8 (60.0, 93.7)	34 (61.8)	
Was not easier to use than the bottle alone (n = 38)	19.5 (3.5, 83.8)	10 (26.3)	0.002
Made no difference (n = 8)	84.4 (30.4, 95.4)	5 (62.5)	
Helped to remember to use eye drops (n = 31)	83.7 (75,0, 91.4)	21 (67.7)	
Did not help to remember to use eye drops (n = 41)	28.6 (3.6, 89.0)	14 (34.1)	0.018
Made no difference (n = 28)	79.1 (36.7, 94.4)	14 (50.0)	
Helped to apply eye drops (n = 54)	86.2 (71.0, 93.4)	36 (66.7)	
Did not help to apply eye drops (n = 34)	19.5 (3.6, 81.1)	9 (26.5)	0.001
Made no difference (n = 13)	59.7 (18.7, 91.6)	5 (38.5)	

Objective F (paragraph 11.2.1): Perceived usefulness of the TDA was compared with individuals' decision to take part in the un-masked phase. Table 11.5 shows that individuals that found using the TDA easier than using drops from the bottle alone, or helped them to remember to use their drops or helped them to apply their eye drops were more likely to take part in the un-masked phase. The TDA was considered to be least useful at helping individuals remember to use eye drops compared to making use of drops easier or helping to apply eye drops.

Table 11.5 Perceived usefulness of TDA compared with participation in the un-masked study.

	Number of participants that took part in un-masked phase		
	No (%)	Yes (%)	p-value
Was easier	10 (17.5)	47 (82.5)	
Was not easier	33 (78.6)	9 (21.4)	< 0.001
No difference	8 (72.7)	3 (27.3)	
Helped to remember drops	5 (16.1)	26 (83.9)	
Did not help to remember drops	29 (65.9)	15 (34.1)	<0.001
No difference	15 (46.9)	17 (53.1)	
Helped to apply drops	12 (21.1)	45 (78.9)	
Did not help to apply drops	30 (78.9)	8 (21.1)	<0.001
No difference	8 (57.1)	6 (42.9)	

11.3.7 Satisfaction with information about eye drops and glaucoma

Objective G (paragraph 11.2.1): Most participants rated high satisfaction with information received about their eye drops and glaucoma; out of maximum score of 15, 20 (18.5%) participants scored 8 to 11, 88 (81.5%) participants from 12 to 15; improved satisfaction was not correlated with improved adherence in either the masked phase (r=0.078, p=0.438) or the un-masked phase (r=0.050, p=0.725).

11.3.8 IMAB

Objective H (paragraph 11.2.1): The mean IMAB score for the masked group was 34.9 (SD, 7.5) and for the un-masked 32.4 (SD, 7.75) out of a possible score of 100. There was a significant weak positive correlation in the masked phase with adherence measured by the TDA, (r=0.230, p=0.042), and a very weak negative correlation in the un-masked phase but this was not statistically significant, (r= -0.029, p=0.848). Table 11.6 displays the scores for the individual behavioural

domains in the masked phase. Beliefs about capabilities presented the greatest reported barrier but this was not associated with increased non-adherence.

Table 11.6 IMAB scores for individual behavioural domains and correlation with adherence in the masked phase

Behavioural domains:	IMAB score (SD)	Correlation with adherence (p-value)
Knowledge	2.8 (1.0)	0.098 (0.328) n=102
Skills	2.9 (0.9)	0.095 (0.342) n=102
Memory, attention and decision making processes	3.2 (1.3)	0.090 (0.381) n=96
Social Influences	3.4 (1.3)	-0.007 (0.941) n=100
Environmental constraints	3.5 (1.2)	0.082 (0.428) n=96
Emotions	3.5 (1.4)	-0.109 (0.278) n=100
Motivation and goals	2.8 (1.0)	0.089 (0.376) n=101
Goal conflicts	3.0 (1.1)	0.132 (0.187) n=96
Beliefs about capabilities	4.4 (1.5)	0.178 (0.084) n=96
Beliefs about consequences	3.4 (1.3)	0.143 (0.164) n=96

11.4 Discussion

The React study found no difference in measured adherence in individuals who had taken part in the masked and un-masked study phases suggesting that awareness of study participation and observation of adherence did not cause any significant reactivity effects. However, the evidence confirms the presence of a reactivity effect at least to some magnitude and the interim results suggest a 10% difference in adherence between the masked and un-masked group may be possible if the planned sample of 76 participants is reached when the study concludes. Furthermore, participants with lower measured adherence were less likely to participate in the un-masked phase. Thus, non-adherent participants were missing from the un-masked sample group. If a greater number of non-adherent individuals did continue into the masked phase, then the reactivity effect could have been larger; the mean adherence for the group of participants who took part in the un-masked phase was 45% higher than the mean adherence for the group that only took part in the masked phase.

However, TDA measured adherence was generally higher in patients that felt the TDA made using eye drops easier than the bottle alone, easier to remember and/or easier to apply. When patients preferred using the TDA, they might have been more likely to continue administering eye drops with the TDA and consequently good adherence was recorded. In contrast, those who did not feel any benefit from using the TDA and chose to stop daily administration of eye drops using the TDA (either for the duration of the study or just occasionally, as the bottle of eye drops can be removed and re-inserted easily from the TDA), daily administration of eye drops was not recorded by the TDA resulting in a lower overall TDA adherence score. Further, participants not using the TDA on a daily basis may have been disincentivised to participate in the un-masked study phase compared to patients who felt the TDA had been useful and therefore willing to take part in the un-masked study phase. Arguably, the cause of the TDA measured non-adherence between the two groups may, therefore, have been due to preference for use of the TDA rather than any reactivity effects.

Whilst patients had been asked to use the TDA for the purposes of aiding adherence, they had not been given any specific instructions to use it unconditionally for the duration of the 56-day review period in case they were alerted to the presence of the monitoring capacity of the TDA. In an attempt to try

and ascertain if patients were likely to stop using their TDA prematurely, patients were contacted one week after the TDA was issued to discuss any problems with use of the TDA to try and resolve them with the patient or give the option of discontinuing with use. Therefore, those patients remaining in the sample should have been those who had chosen to use the TDA and recorded missed doses would have been due to non-adherence rather than discontinuation of use of the TDA. Extrapolating results from the TDA has always been contentious, since the measure is only an indication of the intention to use eye drops rather than indisputable evidence that an eye drop was or was not applied as discussed in Paragraph 1.2.6.1.

The MMAS self-reported adherence found that majority of patients did not change their opinion of self-reported adherence when they were aware that their adherence was being monitored. MMAS had poor agreement with adherence measured by the TDA in both the masked and un-masked phase which may indicate that patients were adherent but did not use their TDA on a daily basis. However, these results are in keeping with previous findings that patient self-report is unreliable. Furthermore, the MMAS tool may not be sensitive enough to detect the potentially subtle changes in patients own perception of their adherence behaviour. There was greater agreement between the TDA and MMAS adherence scores in the un-masked phase; however, since adherence measured by the TDA was found to be higher in the un-masked phase because there were more adherent individuals than in the masked group the potential bias could have caused the greater measured agreement.

Previous satisfaction with use of eye drops and information received about glaucoma diagnosis did not improve adherence in the sample. The IMAB results found ‘beliefs about capabilities’ was the behavioural domain with the highest reported barrier to use of travoprost, but this, and the overall scores, were not correlated with increased non-adherence. From these preliminary findings there was no evidence to suggest that the IMAB could detect non-adherent patients, but use of the full 30-question IMAB with patients using multiple-doses of eye drops would be necessary to fully establish the usefulness of the tool within a glaucomatous population.

Recruitment of patients, who had already taken part in the masked phase, into the un-masked phase was only 54%, which was surprisingly low given that NAGS

recruited 87% of approached patients. The low recruitment into the un-masked phase taken together with those who declined to take part in the initial masked phase culminated in only 26% of the 232 patients initially approached participating in the un-masked phase. The reason for the low recruitment is difficult to establish; NAGS recruited treatment naïve patients who may have been encouraged to participate because they were offered support to administer their eye drops with the TDA at a time when they may have felt more challenged by the concept of applying eye drops. Thus, comparing the recruitment rate between NAGS and the React study may not be a fair comparison. Whilst the use of travoprost was essential to the design of the study in order that the bottles fitted the TDA, the solution was to amend the inclusion criteria to include patients who were already on established treatment with travoprost. One of the benefits of including individuals on established treatment was the reduction in the number of individuals that withdrew due to lack of efficacy or side effects to treatment, in comparison to NAGS. However, patient behaviour in the React study may have been altered; experienced eye drop users might have been more self-confident with use of medication both in terms of their routine and administration technique and, therefore, not so amenable to accepting support with a dosing aid and/or not willing to change their habitual behaviour of using eye drops from the bottle alone. Once recruited, the majority of patients who participated were all successfully engaged with the study requirements, as was demonstrated by the low data attrition rate.

Age, gender and diagnosis of either POAG, OH, GS were not significantly different between those who declined participation in either the masked or un-masked phases and therefore, the sample group were not biased by these factors. The majority of those who declined participating in the masked phase either did not give a reason for declining or did not wish to use the TDA. Those who did participate may have been more motivated, prepared to have their adherence monitored or willing to engage in research. Further, the patient perceived usefulness of the TDA was found to improve adherence in the sample; together with so few participants continuing into the masked phase, both these factors suggest that the final masked sample were more motivated and adherent individuals caused by a self-selecting sample bias. Use of a crossover design was beneficial because confounding covariates are reduced as each participant acts as their own control and are, therefore, statistically efficient, requiring fewer subjects

than non-crossover designed studies. However, in the React study this could have introduced the self-selecting bias. Arguably an RCT with a masked and un-masked arm may have eliminated these factors. Although a much larger sample size might have been required for an RCT, given that only approximately one quarter of participants agreed to participate in the un-masked phase, to date over 200 patients have been approached to take part in the masked phase which may be equivalent to the amount of participants that might be required for a between group analysis RCT. Order effects of crossover studies can also introduce practice fatigue or learning effects; participants in the un-masked phase may have become familiar with the TDA and found it easier to use over time in comparison to the un-masked phase. Thus, improvement in adherence may be associated with ease of use of the TDA, rather than any other type of reactivity effect. Conversely, participants may have become over familiar or tired of using the TDA thus negatively influencing their level of adherence.

Without implicitly stating that patients must use the TDA for a certain length of time and therefore alerting them to the fact that the TDA was measuring their adherence during the monitoring phase, not all participants used the TDA for the full 56-day monitoring period required to ensure consistency. In the masked phase when the participants were aware that the TDA was monitoring adherence it was possible to expressly ask the participant to use the TDA for at least 56-days. Due to technical problems with the TDA or when individuals changed treatment, some data was still missing. However, this only affected a small number of participants in both groups and their monitoring period was cut short by just under a week which was not felt to significantly bias the results. The decision to leave the tear drop cue panel visible on the TDA rather than covering it with a label as in NAGS was successful and successfully masked the monitoring properties of the TDA to remain concealed from patients. Furthermore, less React study participants tampered with the devices and removed the battery when compared to those in NAGS.

The aim to recruit 76 participants to the React masked was not reached. As described, due to changes in the prescribing of travoprost at NNUH since the conception of the study fewer patients were using travoprost at the time of recruitment, thus hampering our ability to recruit enough participants in the one year recruitment period. Recruiting individuals from Spire hospital in an attempt to

boost recruitment by increasing the pool of potentially available participants certainly helped increase the numbers, but a further source of eligible participants would have been beneficial. The React study continues to recruit participants and when the required sample size is reached the final analysis can be completed.

The major value of using a masked monitoring design was to maintain usual behaviour patterns that might otherwise be interrupted by awareness of being observed. The React study found evidence that such behaviour changes exist, but the reactivity effect and adherence to medication remains notoriously difficult to measure. The problems encountered using the TDA continues to prevent conclusive findings from being extrapolated from the data. Future studies need an objective measure of adherence to eye drops such that all different bottles fit the monitoring device to enable both treatment naïve and established eye drop users on multiple dosing regimens to participate in such observational studies. Remote electronic monitoring devices may also enable a totally new interface for adherence research in the future as information could be fed back instantly to the researcher enabling an early alert when participants stop using their eye drops and assess the behaviour patterns at the point it occurs, rather than retrospectively scrutinising old data; this would overcome the problem of patients underreporting non-adherence and forgetting the true reasons for their non-adherence. If such technology were to become available a new set of challenges would exist to examine the ethical practicalities and how this type of monitoring in itself would affect adherence behaviour.

Since the retrospective consent method did not give rise to any reported concerns from patients/participants and no-one asked for their data to be withheld from the analysis, future studies may consider using a modified consent method to ensure that individuals who are likely to decline participation in research are still included in the sample, and to overcome the known change in behaviour caused by reactivity effects.

Section 5. Closing summary

Chapter 12. Final discussion and future work

12.1 Final discussion

The introduction in Section 1 of this thesis discussed the importance of good adherence to medication in patients with glaucoma and ocular hypertension. The evidence suggested that patients using glaucoma medication were lacking the support and education required to be adherent to their medication regimens. Thus, the Norwich Adherence Glaucoma Study (NAGS) described in Section 2 was designed to address the research gap by providing an intervention intended to both target beliefs about use of medication and provide tailored education in order to elicit adherent behaviour. NAGS hypothesised that additional education and advice about glaucoma using a Behaviour Change Counselling intervention would improve adherence with glaucoma medication when compared to standard care.

However, the NAGS RCT described in Chapter 3 did not establish improvement in adherence to medication. The NAGS study results revealed that the magnitude of non-adherence amongst the population studied was less than expected; the majority of participants in both arms of the study had very good adherence. In addition to the apparent failure of the intervention, the NAGS results also indicated that, adherence to glaucoma medication in the population studied, might not be such a significant problem as previously suggested.

12.2.1 Providing patient information and support

However, from the participants' perspective the NAGS intervention was reported to provide a valuable source of information and support when additional help and reassurance were required. Furthermore, participants in the intervention group ran out of eye drops less than those in the control group indicating the intervention was successful in informing patients to renew their prescription to obtain travoprost on a monthly basis. The emergent testimonies reported in the User study in Chapter 4 unearthed evidence that participants in the NAGS control group required additional information compared to those who took part in the intervention group. The User study findings indicated that standard care needed to be improved to ensure that patients would be adherent to their medication in the long-

term, in addition to feeling informed and supported in their journey of glaucoma care. The NICE medicine adherence guidelines state that non-adherence represents a fundamental limitation in the delivery of healthcare that is not caused by patients own failure alone.[277] Therefore, it was not surprising that participants felt the NAGS intervention should be made available to all patients in the future.

New initiatives have emerged since the design and implementation of NAGS providing useful resources that might complement NHS standard care and future interventions to improve adherence. One such initiative was the Glaucoma Think Tank meeting held in 2011.[278] In the meeting that was chaired by Professors Peter Shah, David (Ted) Garway-Heath and Peng Khaw and supported by the International Glaucoma Association, patients and professionals came together to encourage communication between the two representative groups. By listening to the testimonies that described the journey of care directly from individuals with glaucoma, patients were given the opportunity to be able to influence future glaucoma care, research and education. The discussions from the Think Tank meeting helped develop a 'glaucoma passport'; a personal health record designed to help patients keep track of their glaucoma care and provide support if they experience difficulties, thus encouraging patient self-care.[279]

12.2.2 Future interventions

Hundreds of patients with glaucoma and members of the public have been involved in the research used to bring this thesis to completion. Many individuals have informally given feedback or discussed their needs and ideas with the researchers throughout the period of study. Together with the formal data collected and reported, a great deal of insight has been amassed around the complex topic of medication adherence, ranging from person-specific needs for glaucoma care to the wider methodological implications of adherence measurement, data collection and reporting. The deeper level of detail and breadth of understanding brought to the subject has the potential to underpin and positively influence future intervention development. However, further research is required to better understand:

- the type of information that should be incorporated into interventions

- the method of delivering interventions, considering both patient preferences and cost implications
- which healthcare professionals are best placed to deliver interventions
- how often an intervention needs to be reinforced
- if patients' carers and/or family members need to be included in the intervention provision particularly with patients who need support from a wider network of carers.

The User study results described in Chapter 4 and new advances in research, such as the work from the Think-Tank meeting[278] or the behaviour change taxonomy,[141] might be able to address some of these questions and provide guidance from which the foundations of future interventions can be designed.

Patients in the NAGS intervention group reported in the User study that they did not feel they had received enough information about their own glaucoma diagnosis, prognosis and progression of disease. One solution to ensure adequate provision of information might be to incorporate the glaucoma passport[279] into a future intervention; should provision of standardised information fail to convey specific details tailored to the individual, the research passport could be a useful tool to involve patients in their own clinical reports, thus empowering them to ask questions. On the downside, adherence motivating resources introduce additional costs; the cost of the glaucoma passport alone is £9.95 per booklet, a relatively expensive resource should all patients with glaucoma to be provided with a copy, such that evidence of the benefit to patient care would be required to justify the expenditure.

Considering the feedback from the User study in Chapter 4, some simple changes in information provision could be implemented with relatively little cost which could address some of the concerns raised by users of the NNUH eye clinic. The main issues highlighted were that NNUH eye clinic was felt to be very impersonal and left patients feeling that they were on a conveyer belt during their visits. The issue appeared to be exacerbated when there were long waiting times for tests to be carried out and waiting to see the clinician. Long waiting times, in combination with patients not understanding the significance of completing the assessments, was stated to lead to increased frustration and distress for some patients. Thus, technicians and clinicians need to take greater care to always explain the reasons for requiring visual field tests and imaging of the optic.

Some patients reported that clinicians did not always introduce themselves which was particularly confusing when there were optometrists, specialist nurses, consultants and junior doctors working in the glaucoma service. Some participants felt that a simple introduction would be more courteous and reassuring for them at the start of their consultation. Interestingly, this is an issue that has already been brought to fore with the new NHS initiative "Hello my Name is…".[280] Hospital staff are reminded to go back to basics and remember to introduce themselves; such behavior is thought to help build trust and make a vital human connection with patients.

Better communication is required with patients in the NNUH eye clinic to overcome some of these reported obstacles. Poster provision may also be a method that is relatively simple to implement and when repeatedly seen around the waiting areas, visually appealing posters might reinforce important educational messages and might be a simple way to impart information to improve patient perceptions and encourage better patient engagement both with patients and any carers who accompany patients to the clinic. Further work is required to establish how patients absorb information and if posters would meet this need but issues that could be addressed by posters are:

- Explain the use of visual field test and imaging, how they are used in clinical practice
- Introduce each member of the glaucoma service team, with a picture together with their name and role in the clinic
- Posters providing information about eye drops, administration techniques, their common side effects, and appropriate action should side-effects be experienced and tips on how to incorporate use of eye drops into a daily regimen.

The User study reported that if patients were well informed about glaucoma and the necessity of using eye drops, individuals would be inclined to be more adherent. Information provision, therefore, would have to be an important element of any future intervention.

However, NAGS participants from both control and intervention groups reported accessing information from a variety of many different sources, including leaflets,

talking to friends and/or other patients with glaucoma, the internet and books. Thus, it is clear that information should be provided in many different forms in order to cater for the changing modes in which our society accesses sources of information and support networks; group-based sessions, digital applications and on-line resources and social media are extremely popular resources and are featuring in new behaviour change interventions. Currently, elderly patients may not be confident with the internet, but future generations are likely to prefer such digital information. In NAGS it was found that the majority of participants in the intervention group requested more information from their GSA each time they attended a follow-up appointment. Thus, an intervention placed only at the point of treatment initiation may have provided insufficient support for patients. When and how often information is provided and reinforced to patients with glaucoma is, therefore, also significant. Integrating more information into standard care and giving patients choice in the type and level of engagement they require to support them through their journey of glaucoma care should certainly be a priority for any future intervention designed to improve adherence to glaucoma medication. The Cromer hospital, which has a satellite clinic to NNUH, has started running group sessions to give information and support to patients with glaucoma. An evaluation of these group sessions could provide useful information from which a complex intervention, incorporating a group-based intervention, as one element of a wider intervention-package could be developed.

Since the NAGS intervention was established, the behaviour change taxonomy[141] has been formulated. The new behaviour change taxonomy characterises the active content of behaviour change techniques known to produce effective interventions. As new adherence related research emerges using the behaviour change taxonomy to define the mode of action with the theoretical construct has the potential to improve the design of future interventions making these more focused and effective.

An important aspect of the NAGS intervention was the availability of a telephone helpline. The majority of calls made to the telephone helpline were about the side-effects of eye drops. At present patients at NNUH may be left for days with an unsatisfactory outcome to their problems with eye drops, which may lead to a decrease in faith in eye drop use. In contrast, for NAGS patients experiencing the intervention, the use of the help-line resulted in participants with drop queries

having these dealt with quickly and efficiently by the GSAs. The NAGS results showed that satisfaction with the support service part of the intervention was high. Thus, a dedicated helpline for treatment side-effect enquiries may might reduce the costs of a glaucoma service by reducing the number of unnecessary eye casualty appointments and ensuring that patients receive a better standard of care. The GSAs ran a glaucoma specific support service during NAGS using a mixed team of healthcare professionals. However, the type of healthcare professional ideally suited to provide a glaucoma specific support services remains unknown. Further research respect to support delivery is required. For development of future potential adherence improving interventions, assessment of the individuals that deliver support is an aspect of intervention design that needs further consideration.

A pharmacist-led telephone advice service has been reported to improve medication adherence in patients with long-term conditions on established medication.[281] Furthermore, in the UK, pharmacists already undertake 'Medication Use Reviews' to target patients most likely to stray from their recommended medication regimens. Not only are pharmacists' experts on medicines, but they are considered to be the most accessible and most consulted health professionals with respect to medication use. Thus, pharmacists may be ideally placed to tackle the issue of poor adherence with eye drops. It was beyond the scope of the NICE medication adherence guidelines to make recommendations about which healthcare professionals would be best placed to deliver interventions to improve adherence, but this remains an important aspect for the design of future interventions and assessment of related cost effectiveness. Unfortunately, the cost benefits of any novel intervention will only be evidenced if the intervention can be proven to improve adherence and therefore robust measures of adherence, which are not biased by reactivity effects, are required.

Finally, whilst NAGS was purely focused on delivering support and information to the patient with glaucoma, the NICE medicines adherence guidelines advocate the need for patients to decide who should be involved in their care and for carers to also have access to appropriate levels of information and support.[277] Future interventions need to ensure access to the wider support and care network that some patients desire and perhaps require to remain fully adherent to their medication(s).

12.2.2 Reactivity effects

Although a variety of adherence measures were used in NAGS, the analysis in Chapter 3 highlighted the difficulties in collecting complete data for the full period of the 8-month study.[187] The literature suggested that objective monitoring of adherence with MEMS was superior to subjective self-reporting of adherence. However, unpacking the user experiences of NAGS in the User study and a follow-up study described in Chapter 5 identified that measuring adherence with the TDA might have caused a variety of reactivity effects that changed behaviour introducing an element of uncertainty regarding the conclusions drawn from the study. The React study was designed to establish if awareness of adherence monitoring caused a statistically significant increase in adherence. The React study required the use of a modified consent procedure, since to determine the magnitude of reactivity effects a proportion of 'studied' participants had to partake in the study unaware that they were being studied and hence without consent. Section 3 described the body of work undertaken to establish that patients and members of the public were largely in favour of using a retrospective consent method in a study that would measure changes in behaviour when individuals participated in research when unaware that their adherence behaviour was to be observed.

Section 4 described and reported the results of the React study, which was designed to establish if awareness of adherence monitoring caused a statistically significant increase in adherence. Whilst no final results can be reported yet, work continues in order to complete the React study. However, an interim analysis of the React study data suggested that reactivity effects caused a change in adherence behaviour. However, adding to the problems associated with adherence research and modified consent, patients with poor adherence measured by an electronic monitoring device were less likely to volunteer to participate in the research study, causing a bias in the sample population.

The current overall findings from the thesis have suggested that measuring adherence is problematic and may itself have a significant role in behaviour change making an assessment of the true magnitude of non-adherence difficult to specify accurately. In the future, more emphasis must be placed on controlling potential reactivity effects in research involving outcome variables that influenced by observation of participant behaviour.

12.2.3 Measuring adherence

Self-report tools remain the easiest and, if accurate, the most cost-effective measure of adherence to administer and are likely, therefore, to remain a popular method for future research. Unfortunately, the results presented in this thesis were not able to prove that currently used self-report measures of adherence were sufficiently robust to prove useful as a sole outcome measure of adherence for topical anti-glaucoma therapy. However, refinement of the wording used and/or visual modifications could improve self-report tools to make them more reliable for the future, this requiring further evaluation.[94]

Use of electronic dosing monitors such as MEMS may remain the best objective method of measuring adherence. Unfortunately, since eye drop bottles are manufactured in different sizes, researchers have difficulty in utilising suitable electronic devices in to which all bottle types can fit. Presently, since the TDA is no longer commercially available, the only devices available are MEMS whereby the bottle of eye drops is placed within the MEMS requiring the user to unscrew the MEMS cap to retrieve the bottle of eye drops, subsequently unscrewing the eye drop cap before administering the dose. Thus, a "bottle within a bottle" method requires multiple extra steps that deviates from the usual administration procedure; the extra processes required have the potential to cause a reactivity effect.[58] A device that fits all sized bottles would aid the creation of a system to measure adherence that could be used to monitor the adherence behaviour of patients on varying dosing regimens and different classes of topical medication. NAGS had to be limited to individuals using a once daily prostaglandin (travoprost) since the TDA electronic device was designed specifically for the Travatan® product. Engagement with a wider range of patients including those with more advanced glaucoma requiring more aggressive treatment therapies and regimens would enable an understanding of the magnitude of non-adherence in a different glaucomatous population, one which arguably should require more attention due to the risk of more imminent sight-threatening progression.

As technology advances, remote real-time streaming of patient medical data is becoming more common place. In time, it might be possible to live-stream medication usage thus allowing researchers to collate patterns of adherence behaviour and react to real-time data. Novel digital electronic technology could be integral to the design of future interventions that could tailor help, advice and

education based on medication use in real-time. Remote monitoring could also resolve the issues of missing data found with current monitors that store data internally particularly in studies requiring a long period of follow-up such as was the case in NAGS when devices malfunctioned before data could be recovered. Remote monitoring would also resolve the problem encountered when participants fail to return devices, either mistakenly or deliberately when perhaps feeling too uncomfortable to return their monitoring device when knowing that their adherence had been sub-optimal.

Using masked studies to ensure that patients are not aware that they are participating in research, or that their adherence is being observed, may have an important role to play in future studies that measures patient behaviour or satisfaction with information. Thus, concealing the use of medication monitors would offer yet another advantage for researchers in their attempts to overcome the reactivity bias thought to be caused by monitoring and participation effects. The React study did not find any participants that declined use of their data collected prior to undergoing retrospective consent and no participants made contact with the researcher to discuss any concerns with respect to use of their data; an indication that the method was well received and raised no misgivings amongst those who took part as suggested by the consultation work undertaken and described in Section 3.

12.2 Recommendations for future work

Maintaining a constant low eye pressure in many patients with glaucoma is deemed crucial; therefore 100% adherence is often considered the goal for patients using glaucoma medication. Thus, persevering with the design of an intervention to improve adherence with anti-glaucoma medication remains an important objective. The advancement in current glaucoma treatments such, as slow release medicated pellets inserted into the eye or laser treatments such as SLT, might in time reduce the need for daily administration of eye drops, or at least might provide a more reliable treatment method for those who struggle to be adherent with their daily glaucoma medication regimens. However, recently introduced treatments for glaucoma are still in their infancy, require further long-term assessment and robust health economic analyses.

In the meantime, and considering the evidence presented in this discussion, the design of an intervention using a health economic analysis to establish the cost benefits of improving adherence to glaucoma medication and supporting patients through their journey of glaucoma care is warranted. The study design and methods used to measure adherence also need further development in order to avoid introducing reactivity bias. Thus, future work must first establish the acceptability of using a modified consent method.

The Medical Research Council's Framework for the development and evaluation of RCTs for complex interventions that improve health[282] provides the guidance required to negotiate the challenges that arose from NAGS. Using a stepwise approach, the active components of a complex intervention should first be identified and piloted in small scale studies which can also be used to identify an appropriate control group, outcome measures and estimates of recruitment before being incorporated into a definitive RCT. With a robust RCT and evaluation of the real life effectiveness using observational studies, the relevance of the intervention in health care is likely to be established.[282]

12.2.1 Detailed plan of future work

Using the MRC Framework for the Development and Evaluation of Complex Interventions the following work needs to be undertaken:

Step 1: Theoretical phase

The evidence ascertained through this thesis provides the basis of the theoretical and modelling steps required.

Step 2: Phase 1 or modelling

Key questions for further investigation:

- Does the design of the intervention need further development?
- What are the active components of the intervention?

Proposed work:

1. Review the evidence gathered through NAGS evaluation data and User study.
2. Re-model the intervention as required referring back to theoretical evidence. Diagram the components such as nature, timing, frequency, duration of inputs and organisational arrangements.
3. Carry out qualitative testing with focus groups and/or surveys if required to help define the active components and refine the intervention.

Step 3: Phase II or Exploratory trial

Key priorities for this phase and questions:

- Refine the intervention
- What is the best method for the RCT to avoid bias?
- What is an appropriate control group?
- What is an appropriate and reliable outcome measure?

Proposed work:

1. Pilot the intervention. Vary the different components to see what effect each has on the intervention and acceptability by participants.

2. Establish how to standardise the intervention by all providers determining which factors need to be controlled to ensure consistency whilst defining the acceptable limits to which practitioners can individualise the intervention. Establish how evidence of any learning curve effect and how this can be monitored and fidelity ensured throughout an RCT.

3. Investigate the experiences of those who took part in the React study to establish participant acceptability of a retrospective consent method and define the recommendations for the methodology of future RCTs.

4. Use the REACT study findings to define the expected reactivity effect and make adjustments to the outcome measures accordingly or pilot the use of a control group which does not reveal signs of a reactivity effect.

5. Design and pilot a MEMs device that accurately records adherence data without causing a reactivity effect.

Step 4: Phase III or main trial

Using the information from steps 1 to 3, design and carry out an RCT to evaluate the complex intervention with sufficient power using a robust outcome measure. The study must minimise reactivity effects and incorporate the standard features of a well designed RCT many of which were used in NAGS.

Step 5: Phase IV and long-term observation

Replicate the findings of the intervention in uncontrolled settings and observe outcomes over a long-term period.

Clearly, there is a vast amount of work still required before the exact formula for an intervention which can improve adherence and be cost effective, can be established. Fortunately, the work commenced with NAGS together with the User and React studies has advanced our understanding of patient behaviour and how in the future we might establish robust methods for measuring adherence that does not elicit reactivity effects. Only when adherence can be measured properly, can moves be made to prove the ideal way by which we could improve the adhernce of our patients with glaucoma.

Chapter 13. References

1. Resnikoff S, Pascolini D, Etya'ale D, et al. Global data on visual impairment in the year 2002. *Bull World Health Organ*. 2004; 82: 844-51.
2. Bunce C and Wormald R. Causes of blind certifications in England and Wales: April 1999-March 2000. *Eye (Lond)*. 2008; 22: 905-11.
3. Quigley HA and Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. *Br J Ophthalmol*. 2006; 90: 262-7.
4. Friedman DS, Freeman E, Munoz B, Jampel HD and West SK. Glaucoma and mobility performance: the Salisbury Eye Evaluation Project. *Ophthalmology*. 2007; 114: 2232-7.
5. Haymes SA, Leblanc RP, Nicolela MT, Chiasson LA and Chauhan BC. Risk of falls and motor vehicle collisions in glaucoma. *Invest Ophthalmol Vis Sci*. 2007; 48: 1149-55.
6. Nelson P, Aspinall P and O'Brien C. Patients' perception of visual impairment in glaucoma: a pilot study. *Br J Ophthalmol*. 1999; 83: 546-52.
7. Green J, Siddall H and Murdoch I. Learning to live with glaucoma: a qualitative study of diagnosis and the impact of sight loss. *Soc Sci Med*. 2002; 55: 257-67.
8. Dielemans I, Vingerling JR, Wolfs RC, Hofman A, Grobbee DE and de Jong PT. The prevalence of primary open-angle glaucoma in a population-based study in The Netherlands. The Rotterdam Study. *Ophthalmology*. 1994; 101: 1851-5.
9. Wensor MD, McCarty CA, Stanislavsky YL, Livingston PM and Taylor HR. The prevalence of glaucoma in the Melbourne Visual Impairment Project. *Ophthalmology*. 1998; 105: 733-9.
10. Mitchell P, Smith W, Attebo K and Healey PR. Prevalence of open-angle glaucoma in Australia. The Blue Mountains Eye Study. *Ophthalmology*. 1996; 103: 1661-9.
11. Abrams LS, Scott IU, Spaeth GL, Quigley HA and Varma R. Agreement among optometrists, ophthalmologists, and residents in evaluating the optic disc for glaucoma. *Ophthalmology*. 1994; 101: 1662-7.
12. Ethical Stratergies Ltd. The Costs of Blindness: An analysis of the Costs of Visual Impairment and Blindness in the United Kingdom 2003.
13. Rein DB, Zhang P, Wirth KE, et al. The economic burden of major adult visual disorders in the United States. *Arch Ophthalmol*. 2006; 124: 1754-60.
14. Tsai JC. Medication adherence in glaucoma: approaches for optimizing patient compliance. *Curr Opin Ophthalmol*. 2006; 17: 190-5.
15. Tielsch JM, Sommer A, Katz J, Royall RM, Quigley HA and Javitt J. Racial variations in the prevalence of primary open-angle glaucoma. The Baltimore Eye Survey. *JAMA*. 1991; 266: 369-74.
16. Leske MC, Connell AM, Schachat AP and Hyman L. The Barbados Eye Study. Prevalence of open angle glaucoma. *Arch Ophthalmol*. 1994; 112: 821-9.
17. Foster PJ and Johnson GJ. Glaucoma in China: how big is the problem? *Br J Ophthalmol*. 2001; 85: 1277-82.
18. Chen PP. Risk and risk factors for blindness from glaucoma. *Curr Opin Ophthalmol*. 2004; 15: 107-11.
19. Broadway DC, Nicolela MT and Drance SM. Optic disk appearances in primary open-angle glaucoma. *Surv Ophthalmol*. 1999; 43 Suppl 1: S223-43.
20. Bunce C and Wormald R. Leading causes of certification for blindness and partial sight in England & Wales. *BMC Public Health*. 2006; 6: 58.
21. ADAM. How Stuff Works.
22. Kanski JJ. Clinical Ophthalmology; A Systematic Approach. Butterworth-Heinemann Ltd, 1994, p. 254.
23. Leske MC, Heijl A, Hussein M, Bengtsson B, Hyman L and Komaroff E. Factors for glaucoma progression and the effect of treatment: the early manifest glaucoma trial. *Arch Ophthalmol*. 2003; 121: 48-56.
24. Weinreb RN and Khaw PT. Primary open-angle glaucoma. *Lancet*. 2004; 363: 1711-20.

25. Quigley HA, Enger C, Katz J, Sommer A, Scott R and Gilbert D. Risk factors for the development of glaucomatous visual field loss in ocular hypertension. *Arch Ophthalmol*. 1994; 112: 644-9.
26. Coleman AL and Brigatti L. The glaucomas. *Minerva Med*. 2001; 92: 365-79.
27. NICE. *Glaucoma: Diagnosis and Management of Chronic Open Angle Glaucoma and Ocular Hypertension*. National Collaborating Centre for Acute Care, National Institute for Health and Clinical Excellence: London, UK, 2009.
28. Broadway D, Miglior S and Myers JS. Fluctuating intraocular pressure. *J Glaucoma*. 2005; 14: 249-51.
29. Drance SM. Diurnal Variation of Intraocular Pressure in Treated Glaucoma. Significance in Patients with Chronic Simple Glaucoma. *Arch Ophthalmol*. 1963; 70: 302-11.
30. Wilensky JT. The role of diurnal pressure measurements in the management of open angle glaucoma. *Curr Opin Ophthalmol*. 2004; 15: 90-2.
31. European Glaucoma Society Guidelines. In: EGS ECot, (ed.).
32. Kass MA, Heuer DK, Higginbotham EJ, et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Arch Ophthalmol*. 2002; 120: 701-13; discussion 29-30.
33. The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. Collaborative Normal-Tension Glaucoma Study Group. *Am J Ophthalmol*. 1998; 126: 498-505.
34. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration.The AGIS Investigators. *Am J Ophthalmol*. 2000; 130: 429-40.
35. Kass MA. Timolol treatment prevents or delays glaucomatous visual field loss in individuals with ocular hypertension: a five-year, randomized, double-masked, clinical trial. *Trans Am Ophthalmol Soc*. 1989; 87: 598-618.
36. Garway-Heath DF, Crabb DP, Bunce C, et al. Latanoprost for open-angle glaucoma (UKGTS): a randomised, multicentre, placebo-controlled trial. *Lancet*. 2015; 385: 1295-304.
37. Heijl A, Bengtsson B, Hyman L, Leske MC and Early Manifest Glaucoma Trial G. Natural history of open-angle glaucoma. *Ophthalmology*. 2009; 116: 2271-6.
38. National Institute for Health and Clinical Excellence. Diagnosis and management of chronic open angle glaucoma and ocular hypertension. *Commissioned by the National Institute for Health and Clinical Excellence Published by the National Collaborating Centre for Acute Care at The Royal College of Surgeons of England, 35-43 Lincoln's Inn Fields, London, WC2A 3PE* 2009.
39. Broadway DC and Cate H. Pharmacotherapy and Adherence Issues in Treating Elderly Patients with Glaucoma. *Drugs Aging*. 2015; 32: 569-81.
40. Johnson PB, Katz LJ and Rhee DJ. Selective laser trabeculoplasty: predictive value of early intraocular pressure measurements for success at 3 months. *Br J Ophthalmol*. 2006; 90: 741-3.
41. Kanski JJ. *Clinical Ophthalmology; A Systematic Approach*.: Butterworth-Heinemann Ltd., 1994, p. 259.
42. Lacey J, Cate H and Broadway DC. Barriers to adherence with glaucoma medications: a qualitative research study. *Eye (Lond)*. 2009; 23: 924-32.
43. O'Brien C, Schwartz B, Takamoto T and Wu DC. Intraocular pressure and the rate of visual field loss in chronic open-angle glaucoma. *Am J Ophthalmol*. 1991; 111: 491-500.
44. Vogel R, Crick RP, Newson RB, Shipley M, Blackmore H and Bulpitt CJ. Association between intraocular pressure and loss of visual field in chronic simple glaucoma. *Br J Ophthalmol*. 1990; 74: 3-6.
45. Stewart WC, Chorak RP, Hunt HH and Sethuraman G. Factors associated with visual loss in patients with advanced glaucomatous changes in the optic nerve head. *Am J Ophthalmol*. 1993; 116: 176-81.

46. Caprioli J and Coleman AL. Intraocular pressure fluctuation a risk factor for visual field progression at low intraocular pressures in the advanced glaucoma intervention study. *Ophthalmology*. 2008; 115: 1123-9 e3.
47. Rossi GC, Pasinetti GM, Scudeller L, Radaelli R and Bianchi PE. Do adherence rates and glaucomatous visual field progression correlate? *Eur J Ophthalmol*. 2011; 21: 410-4.
48. Sleath B, Blalock S, Covert D, et al. The relationship between glaucoma medication adherence, eye drop technique, and visual field defect severity. *Ophthalmology*. 2011; 118: 2398-402.
49. Kyngas H, Duffy ME and Kroll T. Conceptual analysis of compliance. *J Clin Nurs*. 2000; 9: 5-12.
50. Schwartz GF. Persistency and tolerability of ocular hypotensive agents: population-based evidence in the management of glaucoma. *Am J Ophthalmol*. 2004; 137: S1-2.
51. Horne R. Compliance, adherence, and concordance: implications for asthma treatment. *Chest*. 2006; 130: 65S-72S.
52. Haynes RB, Ackloo E, Sahota N, McDonald HP and Yao X. Interventions for enhancing medication adherence. *Cochrane Database Syst Rev*. 2008: CD000011.
53. Schwartz GF and Platt R. Measuring persistency and intraocular pressure-controlled days in patients receiving topical glaucoma medications. *Am J Manag Care*. 2002; 8: S278-80.
54. Muir KW and Lee PP. Glaucoma medication adherence: room for improvement in both performance and measurement. *Arch Ophthalmol*. 2011; 129: 243-5.
55. Olthoff CM, Schouten JS, van de Borne BW and Webers CA. Noncompliance with ocular hypotensive treatment in patients with glaucoma or ocular hypertension an evidence-based review. *Ophthalmology*. 2005; 112: 953-61.
56. Haynes RB, Yao X, Degani A, Kripalani S, Garg A and McDonald HP. Interventions to enhance medication adherence. *Cochrane Database Syst Rev*. 2005: CD000011.
57. Gray TA, Orton LC, Henson D, Harper R and Waterman H. Interventions for improving adherence to ocular hypotensive therapy. *Cochrane Database Syst Rev*. 2009: CD006132.
58. Waterman H, Evans JR, Gray TA, Henson D and Harper R. Interventions for improving adherence to ocular hypotensive therapy. *Cochrane Database Syst Rev*. 2013; 4: CD006132.
59. The World Health Organisation. Adherence to Medical Therapies: Evidence for action. 2003.
60. DiMatteo MR. Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research. *Med Care*. 2004; 42: 200-9.
61. Ajit RR, Fenerty CH and Henson DB. Patterns and rate of adherence to glaucoma therapy using an electronic dosing aid. *Eye (Lond)*. 24: 1338-43.
62. Vermeire E, Hearnshaw H, Van Royen P and Denekens J. Patient adherence to treatment: three decades of research. A comprehensive review. *J Clin Pharm Ther*. 2001; 26: 331-42.
63. Tsai JC, McClure CA, Ramos SE, Schlundt DG and Pichert JW. Compliance barriers in glaucoma: a systematic classification. *J Glaucoma*. 2003; 12: 393-8.
64. Newman-Casey PA, Robin AL, Blachley T, et al. The Most Common Barriers to Glaucoma Medication Adherence: A Cross-Sectional Survey. *Ophthalmology*. 2015; 122: 1308-16.
65. Robin AS, JL. Sleath, B. Covert, DW. Cagle, GD. An objective evaluation in glaucoma patients of eye-drop instillation using video observations patient surveys *American Glaucoma Society Annual Meeting*. 2008.
66. Winfield AJ, Jessiman D, Williams A and Esakowitz L. A study of the causes of non-compliance by patients prescribed eyedrops. *Br J Ophthalmol*. 1990; 74: 477-80.
67. Robin A and Grover DS. Compliance and adherence in glaucoma management. *Indian J Ophthalmol*. 2011; 59 Suppl: S93-6.
68. Murray MD, Morrow DG, Weiner M, et al. A conceptual framework to study medication adherence in older adults. *Am J Geriatr Pharmacother*. 2004; 2: 36-43.
69. Gupta RP, B. Kumar, G. Dada, T. Evaluation of Technique for Instillation of Eye Drops in Glaucoma Patients on Chronic Ocular Hypotensive Therapy. 2010.
70. Tsai T, Robin AL and Smith JP, 3rd. An evaluation of how glaucoma patients use topical medications: a pilot study. *Trans Am Ophthalmol Soc*. 2007; 105: 29-33; discussion -5.

71. Sleath B, Robin AL, Covert D, Byrd JE, Tudor G and Svarstad B. Patient-reported behavior and problems in using glaucoma medications. *Ophthalmology*. 2006; 113: 431-6.
72. Robin AL, Novack GD, Covert DW, Crockett RS and Marcic TS. Adherence in glaucoma: objective measurements of once-daily and adjunctive medication use. *Am J Ophthalmol*. 2007; 144: 533-40.
73. Patel SC and Spaeth GL. Compliance in patients prescribed eyedrops for glaucoma. *Ophthalmic Surg*. 1995; 26: 233-6.
74. Robin AL and Covert D. Does adjunctive glaucoma therapy affect adherence to the initial primary therapy? *Ophthalmology*. 2005; 112: 863-8.
75. Patton MQ. *Qualitative research and evaluation methods*. 3rd. ed. London: SAGE, 2002.
76. Schwartz GF. Compliance and persistency in glaucoma follow-up treatment. *Curr Opin Ophthalmol*. 2005; 16: 114-21.
77. Unni EJ and Farris KB. Unintentional non-adherence and belief in medicines in older adults. *Patient Educ Couns*. 2011; 83: 265-8.
78. Hughes CM. Medication non-adherence in the elderly: how big is the problem? *Drugs Aging*. 2004; 21: 793-811.
79. Cate H, Bhattacharya D, Clark A, Holland R and Broadway DC. Patterns of adherence behaviour for patients with glaucoma. *Eye*. 2013.
80. Kosoko O, Quigley HA, Vitale S, Enger C, Kerrigan L and Tielsch JM. Risk factors for noncompliance with glaucoma follow-up visits in a residents' eye clinic. *Ophthalmology*. 1998; 105: 2105-11.
81. Nordstrom BL, Friedman DS, Mozaffari E, Quigley HA and Walker AM. Persistence and adherence with topical glaucoma therapy. *Am J Ophthalmol*. 2005; 140: 598-606.
82. Tsai JC. A comprehensive perspective on patient adherence to topical glaucoma therapy. *Ophthalmology*. 2009; 116: S30-6.
83. Piette JD, Heisler M and Wagner TH. Cost-related medication underuse: do patients with chronic illnesses tell their doctors? *Arch Intern Med*. 2004; 164: 1749-55.
84. Gurwitz JH, Glynn RJ, Monane M, et al. Treatment for glaucoma: adherence by the elderly. *Am J Public Health*. 1993; 83: 711-6.
85. Dreer LE, Girkin C and Mansberger SL. Determinants of medication adherence to topical glaucoma therapy. *J Glaucoma*. 2012; 21: 234-40.
86. Sleath B, Ballinger R, Covert D, Robin AL, Byrd JE and Tudor G. Self-reported prevalence and factors associated with nonadherence with glaucoma medications in veteran outpatients. *Am J Geriatr Pharmacother*. 2009; 7: 67-73.
87. Friedman DS, Okeke CO, Jampel HD, et al. Risk factors for poor adherence to eyedrops in electronically monitored patients with glaucoma. *Ophthalmology*. 2009; 116: 1097-105.
88. Broman AT, Quigley HA, West SK, et al. Estimating the rate of progressive visual field damage in those with open-angle glaucoma, from cross-sectional data. *Invest Ophthalmol Vis Sci*. 2008; 49: 66-76.
89. Denis P, Lafuma A and Berdeaux G. Medical predictive factors of glaucoma treatment costs. *J Glaucoma*. 2004; 13: 283-90.
90. Klein LE, German PS, Levine DM, Feroli ER, Jr. and Ardery J. Medication problems among outpatients. A study with emphasis on the elderly. *Arch Intern Med*. 1984; 144: 1185-8.
91. Sackett D and Snow J. Magnitude and Measurement of Compliance In: Haynes B, Wayne Taylor D and Sacket D, (eds.). *Compliance in Healthcare*. Baltimore and London: The John Hopkins University Press, 1979.
92. Richardson C, Brunton L, Olleveant N, et al. A study to assess the feasibility of undertaking a randomized controlled trial of adherence with eye drops in glaucoma patients. *Patient Prefer Adherence*. 2013; 7: 1025-39.
93. Okeke CO, Quigley HA, Jampel HD, et al. Adherence with topical glaucoma medication monitored electronically the Travatan Dosing Aid study. *Ophthalmology*. 2009; 116: 191-9.
94. Sayner R, Carpenter DM, Blalock SJ, et al. Accuracy of Patient-reported Adherence to Glaucoma Medications on a Visual Analog Scale Compared With Electronic Monitors. *Clin Ther*. 2015; 37: 1975-85.

95. Ajit RR, Fenerty CH and Henson DB. Patterns and rate of adherence to glaucoma therapy using an electronic dosing aid. *Eye (Lond)*. 2010; 24: 1338-43.
96. Blaschke TF, Osterberg L, Vrijens B and Urquhart J. Adherence to medications: insights arising from studies on the unreliable link between prescribed and actual drug dosing histories. *Annu Rev Pharmacol Toxicol*. 2012; 52: 275-301.
97. Norell SE. Improving medication compliance: a randomised clinical trial. *Br Med J*. 1979; 2: 1031-3.
98. Granstrom PA. Glaucoma patients not compliant with their drug therapy: clinical and behavioural aspects. *Br J Ophthalmol*. 1982; 66: 464-70.
99. Cronin TH, Kahook MY, Lathrop KL and Noecker RJ. Accuracy and performance of a commercially available Dosing Aid. *Br J Ophthalmol*. 2007; 91: 497-9.
100. Friedman DS, Jampel HD, Congdon NG, Miller R and Quigley HA. The TRAVATAN Dosing Aid accurately records when drops are taken. *Am J Ophthalmol*. 2007; 143: 699-701.
101. McCarney R, Warner J, Iliffe S, van Haselen R, Griffin M and Fisher P. The Hawthorne Effect: a randomised, controlled trial. *BMC Med Res Methodol*. 2007; 7: 30.
102. Solomon RL. An extension of control group design. *Psychol Bull*. 1949; 46: 137-50.
103. Campbell DT. Factors relevant to the validity of experiments in social settings. *Psychol Bull*. 1957; 54: 297-312.
104. Berg KM and Arnsten JH. Practical and conceptual challenges in measuring antiretroviral adherence. *J Acquir Immune Defic Syndr*. 2006; 43 Suppl 1: S79-87.
105. Cate H. A pilot study to assess the feasibility of using the Travalert dosing aid to measure adherence. *University of East Anglia, School of Pharmacy*. University of East Anglia, 2011, p. 127.
106. Cramer JA, Scheyer RD and Mattson RH. Compliance declines between clinic visits. *Arch Intern Med*. 1990; 150: 1509-10.
107. Konstas AG, Maskaleris G, Gratsonidis S and Sardelli C. Compliance and viewpoint of glaucoma patients in Greece. *Eye (Lond)*. 2000; 14 Pt 5: 752-6.
108. Spaeth GL. Visual loss in a glaucoma clinic. I. Sociological considerations. *Invest Ophthalmol*. 1970; 9: 73-82.
109. Gurwitz JH, Yeomans SM, Glynn RJ, Lewis BE, Levin R and Avorn J. Patient noncompliance in the managed care setting. The case of medical therapy for glaucoma. *Med Care*. 1998; 36: 357-69.
110. Granstrom PA. Progression of visual field defects in glaucoma. Relation to compliance with pilocarpine therapy. *Arch Ophthalmol*. 1985; 103: 529-31.
111. MacKean JM and Elkington AR. Compliance with treatment of patients with chronic open-angle glaucoma. *Br J Ophthalmol*. 1983; 67: 46-9.
112. Chang JS, Jr., Lee DA, Petursson G, et al. The effect of a glaucoma medication reminder cap on patient compliance and intraocular pressure. *J Ocul Pharmacol*. 1991; 7: 117-24.
113. Osterberg L and Blaschke T. Adherence to medication. *N Engl J Med*. 2005; 353: 487-97.
114. Grymonpre RE, Didur CD, Montgomery PR and Sitar DS. Pill count, self-report, and pharmacy claims data to measure medication adherence in the elderly. *Ann Pharmacother*. 1998; 32: 749-54.
115. Friedman DS, Quigley HA, Gelb L, et al. Using pharmacy claims data to study adherence to glaucoma medications: methodology and findings of the Glaucoma Adherence and Persistency Study (GAPS). *Invest Ophthalmol Vis Sci*. 2007; 48: 5052-7.
116. Choo PW, Rand CS, Inui TS, et al. Validation of patient reports, automated pharmacy records, and pill counts with electronic monitoring of adherence to antihypertensive therapy. *Med Care*. 1999; 37: 846-57.
117. Fitz-Simon N, Bennett K and Feely J. A review of studies of adherence with antihypertensive drugs using prescription databases. *Ther Clin Risk Manag*. 2005; 1: 93-106.
118. Budenz DL. A clinician's guide to the assessment and management of nonadherence in glaucoma. *Ophthalmology*. 2009; 116: S43-7.
119. Kass MA, Gordon M and Meltzer DW. Can ophthalmologists correctly identify patients defaulting from pilocarpine therapy? *Am J Ophthalmol*. 1986; 101: 524-30.

120. Kalichman SC, Cain D, Fuhrel A, Eaton L, Di Fonzo K and Ertl T. Assessing medication adherence self-efficacy among low-literacy patients: development of a pictographic visual analogue scale. *Health Educ Res*. 2005; 20: 24-35.
121. Rigby D. Adherence assessment tools: Drugs don't work when they're not taken. *The Australian Journal of pharmacy* 2007; 88: 32-3.
122. Kass MA, Meltzer DW, Gordon M, Cooper D and Goldberg J. Compliance with topical pilocarpine treatment. *Am J Ophthalmol*. 1986; 101: 515-23.
123. Svarstad BL, Chewning BA, Sleath BL and Claesson C. The Brief Medication Questionnaire: a tool for screening patient adherence and barriers to adherence. *Patient Educ Couns*. 1999; 37: 113-24.
124. Morisky DE, Green LW and Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care*. 1986; 24: 67-74.
125. NICE. Behaviour change: individual approaches.
126. Haynes RB. Determinants of compliance: the disease and the mechanics of treatment. In: Haynes R, Taylor D and Sakett D, (eds.). *Compliance in Health Care*. Baltimore, USA: The Johns Hopkins University Press, 1979, p. 49-62.
127. Gadkari AS and McHorney CA. Unintentional non-adherence to chronic prescription medications: how unintentional is it really? *BMC Health Serv Res*. 2012; 12: 98.
128. Rosenstock IM. Why people use health services. *Milbank Mem Fund Q*. 1966; 44: Suppl:94-127.
129. Dunbar JM, G.D. Hovell M.F. Behavioural strategies for improving Compliance In Compliance in Health Care. In: Haynes RT, D. Sakett, D., (ed.). The Johns Hopkins University Press (May 1, 1979) 1979.
130. Fishbein M and Ajzen I. *Belief, attitude, intention and behavior : an introduction to theory and research*. Reading, Mass. ; London: Addison-Wesley, 1975.
131. Horne R and Weinman J. Predicting treatment adherence: An overview of theoretical models. In: Myers LB and Midence K, (eds.). *Adherence to Treatment in Medical Conditions* London: Harwood Academic, 1998, p. 25-50.
132. Ajzen I and Fishbein M. *Understanding attitudes and predicting social behavior*. Englewood Cliffs ; London: Prentice-Hall, 1980.
133. Armitage CJ and Conner M. Efficacy of the Theory of Planned Behaviour: a meta-analytic review. *Br J Soc Psychol*. 2001; 40: 471-99.
134. Ajzen I. *Attitudes, personality and behavior*. Milton Keynes: Open University Press, 1988.
135. Weinman Ha. Predicting treatment adherence:Social cognition models. In: Myers LB, Midence, K, (ed.). *Adherence to treatment in medical conditions*. 1998, p. 2:33-40.
136. Bandura A. *Social foundations of thought and action: a social cognitive theory*. Englewood Cliffs: Prentice-Hall, 1986.
137. Stryker JE, Beck AD, Primo SA, et al. An exploratory study of factors influencing glaucoma treatment adherence. *J Glaucoma*. 2010; 19: 66-72.
138. Kripalani S, Yao X and Haynes RB. Interventions to enhance medication adherence in chronic medical conditions: a systematic review. *Arch Intern Med*. 2007; 167: 540-50.
139. Gray TA, Fenerty C, Harper R, et al. Individualised patient care as an adjunct to standard care for promoting adherence to ocular hypotensive therapy: an exploratory randomised controlled trial. *Eye (Lond)*. 2012; 26: 407-17.
140. Sleath B, Blalock SJ, Robin A, et al. Development of an instrument to measure glaucoma medication self-efficacy and outcome expectations. *Eye (Lond)*. 2010; 24: 624-31.
141. Michie S, Richardson M, Johnston M, et al. The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. *Ann Behav Med*. 2013; 46: 81-95.
142. Michie S, van Stralen MM and West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. *Implement Sci*. 2011; 6: 42.
143. Taylor SA, Galbraith SM and Mills RP. Causes of non-compliance with drug regimens in glaucoma patients: a qualitative study. *J Ocul Pharmacol Ther*. 2002; 18: 401-9.

144. Roter DL, Hall JA, Merisca R, Nordstrom B, Cretin D and Svarstad B. Effectiveness of interventions to improve patient compliance: a meta-analysis. *Med Care*. 1998; 36: 1138-61.
145. Haynes RB, McDonald H, Garg AX and Montague P. Interventions for helping patients to follow prescriptions for medications. *Cochrane Database Syst Rev*. 2002: CD000011.
146. Okeke CO, Quigley HA, Jampel HD, et al. Interventions improve poor adherence with once daily glaucoma medications in electronically monitored patients. *Ophthalmology*. 2009; 116: 2286-93.
147. Gray TA, Fenerty C, Harper R, et al. Preliminary survey of educational support for patients prescribed ocular hypotensive therapy. *Eye (Lond)*. 2010; 24: 1777-86.
148. Domino FJ. Improving Adherence to Treatment for Hypertension. *Am Fam Physician*. 2005; 71: 2089-90.
149. Miller NH, Hill M, Kottke T and Ockene IS. The multilevel compliance challenge: recommendations for a call to action. A statement for healthcare professionals. *Circulation*. 1997; 95: 1085-90.
150. Sheppard J, Waner J and Kelley K. An evaluation of the effectiveness of a nurse-led glaucoma montiroring clinic. *Ophthalmic Nursing: Internation Journal of Ophthalmic Nursing*. 2003; 7: 15-21.
151. Beckers HJ, Webers CA, Busch MJ, et al. Adherence improvement in Dutch glaucoma patients: a randomized controlled trial. *Acta Ophthalmol*. 2013; 91: 610-8.
152. Blondeau P, Esper P and Mazerolle E. An information session for glaucoma patients. *Can J Ophthalmol*. 2007; 42: 816-20.
153. Kothe EJ and Mullan BA. Interaction effects in the theory of planned behaviour: Predicting fruit and vegetable consumption in three prospective cohorts. *Br J Health Psychol*. 2014.
154. Waterman H, Brunton L, Fenerty C, Mottershead J, Richardson C and Spencer F. Adherence to ocular hypotensive therapy: patient health education needs and views on group education. *Patient Prefer Adherence*. 2013; 7: 55-63.
155. Hudon C, Fortin M, Haggerty JL, Lambert M and Poitras ME. Measuring patients' perceptions of patient-centered care: a systematic review of tools for family medicine. *Ann Fam Med*. 2011; 9: 155-64.
156. Stewart M, Brown JB, Donner A, et al. The impact of patient-centered care on outcomes. *J Fam Pract*. 2000; 49: 796-804.
157. Little P, Everitt H, Williamson I, et al. Observational study of effect of patient centredness and positive approach on outcomes of general practice consultations. *BMJ*. 2001; 323: 908-11.
158. Lane C, Huws-Thomas M, Hood K, Rollnick S, Edwards K and Robling M. Measuring adaptations of motivational interviewing: the development and validation of the behavior change counseling index (BECCI). *Patient Educ Couns*. 2005; 56: 166-73.
159. Hahn SR. Patient-centered communication to assess and enhance patient adherence to glaucoma medication. *Ophthalmology*. 2009; 116: S37-42.
160. Miller WR and Rollnick S. Ambivalence: The Dilemma of Change. *Motivational Interviewing: Preparing People for Change*. 2nd ed. New York: Guildford Press, 2002, p. 13-9.
161. Stryker JE, Beck, A.D, Primo, S.A, Echt, K.V, Bundy, L, Pretorius, C.G, Glanz, K. An exploratory study of factors influencing glaucoma treatment adherence. *J Glaucoma*. 2010; 19: 66-72.
162. Schwartz GF, Plake KS and Mychaskiw MA. An assessment of readiness for behaviour change in patients prescribed ocular hypotensive therapy. *Eye (Lond)*. 2009; 23: 1668-74.
163. Resnicow K, DiIorio C, Soet JE, et al. Motivational Interviewing in Medical and Public Health Settings. In: Miller WR and Rollnick S, (eds.). *Motivational Interviewing: Preparing People for Change*. 2nd ed. New York: Guildford Press, 2002, p. 251-69.
164. Resnicow K, DiIorio C, Soet JE, Ernst D, Borrelli B and Hecht J. Motivational interviewing in health promotion: it sounds like something is changing. *Health Psychol*. 2002; 21: 444-51.
165. Britt E, Hudson SM and Blampied NM. Motivational interviewing in health settings: a review. *Patient Educ Couns*. 2004; 53: 147-55.

166. Miller WR and Rollnick S. Facilitating Change. *Motivational Interviewing: Preparing People for Change*. 2nd ed. New York: Guildford Press, 2002, p. 20-9.
167. Rollnick S and Miller WR. What is motivational interviewing? *Behav Cogn Psychother*. 1995; 23: 325-34.
168. Miller WR and Rollnick S. Motivational Interviewing: Preparing People for Change. 2nd ed. New York: Guildford Press, 2002.
169. Rollnick S, Allison J, Ballasiotes S, et al. Variations on a Theme: Motivational Interviewing and Its Adaptations. In: Miller WR and Rollnick S, (eds.). *Motivational Interviewing: Preparing People for Change*. New York: Guildford Press, 2002, p. 270-83.
170. Dunbar JM and Hovell GD. Behavioural strategies for improving Compliance. In: Haynes RT, D. Sakett, D., (ed.). *Compliance in Health Care*. Baltimore, USA: The Johns Hopkins University Press, 1979.
171. Craig P, Dieppe P, Macintyre S, et al. Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ*. 2008; 337: a1655.
172. Lunnela J, Kaariainen M and Kyngas H. The views of compliant glaucoma patients on counselling and social support. *Scand J Caring Sci*. 2010; 24: 490-8.
173. Horne R and Weinman J. Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. *J Psychosom Res*. 1999; 47: 555-67.
174. Horne R, Hankins M and Jenkins R. The Satisfaction with Information about Medicines Scale (SIMS): a new measurement tool for audit and research. *Qual Health Care*. 2001; 10: 135-40.
175. Horne R, Clatworthy J, Polmear A and Weinman J. Do hypertensive patients' beliefs about their illness and treatment influence medication adherence and quality of life? *J Hum Hypertens*. 2001; 15 Suppl 1: S65-8.
176. Gellaitry G, Cooper V, Davis C, Fisher M, Date HL and Horne R. Patients' perception of information about HAART: impact on treatment decisions. *AIDS Care*. 2005; 17: 367-76.
177. Lu VH, Goldberg I and Lu CY. Use of glaucoma medications: state of the science and directions for observational research. *Am J Ophthalmol*. 2010; 150: 569-74 e9.
178. Bellg AJ, Borrelli B, Resnick B, et al. Enhancing treatment fidelity in health behavior change studies: best practices and recommendations from the NIH Behavior Change Consortium. *Health Psychol*. 2004; 23: 443-51.
179. Burke BL, Arkowitz H and Dunn C. The Efficacy of Motivational Interviewing and Its Adaptions: What we know so far In: Miller WR and Rollnick S, (eds.). *Motivational Interviewing: Preparing People for Change*. New York: Guildford Press, 2002, p. 217-50.
180. Miller WR. Motivational Skill Code (MISC), November 2000 version. 2000.
181. Miller WR, Moyers TB, Ernst D and Amrhein P. Manual for the Motivational Interviewing Skill Code version 2.1. 2008.
182. Charlson ME, Pompei P, Ales KL and MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987; 40: 373-83.
183. Hermann MM, Bron AM, Creuzot-Garcher CP and Diestelhorst M. Measurement of adherence to brimonidine therapy for glaucoma using electronic monitoring. *J Glaucoma*. 2011; 20: 502-8.
184. Hamilton GA. Measuring adherence in a hypertension clinical trial. *Eur J Cardiovasc Nurs*. 2003; 2: 219-28.
185. Fiscella RG, Green A, Patuszynski DH and Wilensky J. Medical therapy cost considerations for glaucoma. *Am J Ophthalmol*. 2003; 136: 18-25.
186. McCambridge J, Witton J and Elbourne DR. Systematic review of the Hawthorne effect: new concepts are needed to study research participation effects. *J Clin Epidemiol*. 2014; 67: 267-77.
187. Cate H, Bhattacharya D, Clark A, Holland R and Broadway DC. A comparison of measures used to describe adherence to glaucoma medication in a randomised controlled trial. *Clin Trials*. 2015; 12: 608-17.

188. Glanz K, Beck AD, Bundy L, et al. Impact of a health communication intervention to improve glaucoma treatment adherence. Results of the interactive study to increase glaucoma adherence to treatment trial. *Arch Ophthalmol*. 2012; 130: 1252-8.
189. Cate H and Broadway DC. Association between intraocular pressure and adherence: is there one? *Eye (Lond)*. 2011; 25: 1238; author reply -9.
190. Ajit RR, Fenerty CH and Henson DB. Response to cate and broadway. *Eye (Lond)*. 2011; 25: 1238-9.
191. McCowan C, Wang S, Thompson AM, Makubate B and Petrie DJ. The value of high adherence to tamoxifen in women with breast cancer: a community-based cohort study. *Br J Cancer*. 2013; 109: 1172-80.
192. Flynn RW, MacDonald TM, Murray GD, MacWalter RS and Doney AS. Persistence, adherence and outcomes with antiplatelet regimens following cerebral infarction in the Tayside Stroke Cohort. *Cerebrovasc Dis*. 2012; 33: 190-7.
193. Taylor A, Chen LC and Smith MD. Adherence to inhaled corticosteroids by asthmatic patients: measurement and modelling. *Int J Clin Pharm*. 2014; 36: 112-9.
194. Langley CA and Bush J. The Aston Medication Adherence Study: mapping the adherence patterns of an inner-city population. *Int J Clin Pharm*. 2014; 36: 202-11.
195. McDonald HP, Garg AX and Haynes RB. Interventions to enhance patient adherence to medication prescriptions: scientific review. *JAMA*. 2002; 288: 2868-79.
196. McCambridge J, Butor-Bhavsar K, Witton J and Elbourne D. Can research assessments themselves cause bias in behaviour change trials? A systematic review of evidence from solomon 4-group studies. *PLoS One*. 2011; 6: e25223.
197. Litcher-Kelly L, Kellerman Q, Hanauer SB and Stone AA. Feasibility and utility of an electronic diary to assess self-report symptoms in patients with inflammatory bowel disease. *Ann Behav Med*. 2007; 33: 207-12.
198. Mankarious E and Kothe E. A meta-analysis of the effects of measuring theory of planned behaviour constructs on behaviour within prospective studies. *Health Psychol Rev*: (2014, accessed 08 July 2014).
199. Michie S, Johnston M, Abraham C, et al. Making psychological theory useful for implementing evidence based practice: a consensus approach. *Qual Saf Health Care*. 2005; 14: 26-33.
200. Strauss AL and Corbin JM. *Basics of qualitative research : grounded theory procedures and techniques*. Newbury Park, Calif.: Sage Publications, 1990.
201. Berg BL. *Qualitative research methods for the social sciences*. 3rd ed. ed. Boston ; London: Allyn and Bacon, 1998.
202. Ritchie J and Lewis J. Qualitative Research Practice: A Guide for Social Science Students and Researchers. London: Sage Pulications, 2003.
203. Pope C, Ziebland S and Mays N. Qualitative research in health care. Analysing qualitative data. *BMJ*. 2000; 320: 114-6.
204. Glaser BG. *The discovery of grounded theory : strategies for qualitative research*. New York: Aldine de Gruyter, 1967.
205. Pope C, van Royen P and Baker R. Qualitative methods in research on healthcare quality. *Qual Saf Health Care*. 2002; 11: 148-52.
206. Ritchie Je, Lewis Je, McNaughton Nicholls Ce and Ormston Re. *Qualitative Research Practice : A Guide for Social Science Students and Researchers*. Second Edition ed.
207. Saldan\a J. *The coding manual for qualitative researchers*. London: SAGE, 2009.
208. Murphy E, Dingwall R, Greatbatch D, Parker S and Watson P. Qualitative research methods in health technology assessment: a review of the literature. *Health Technol Assess*. 1998; 2: iii-ix, 1-274.
209. Creswell JW, Creswell JWQi and research d. *Qualitative inquiry & research design: choosing among five approaches*. 2nd ed. ed. London: SAGE, 2007.
210. Barry CA, Bradley CP, Britten N, Stevenson FA and Barber N. Patients' unvoiced agendas in general practice consultations: qualitative study. *BMJ*. 2000; 320: 1246-50.
211. Van Manen M. *Researching lived experience*. Althouse, 1990.

212. Nguyen TD, Attkisson CC and Stegner BL. Assessment of patient satisfaction: development and refinement of a service evaluation questionnaire. *Eval Program Plann*. 1983; 6: 299-313.
213. Wickstrom G and Bendix T. The "Hawthorne effect"--what did the original Hawthorne studies actually show? *Scand J Work Environ Health*. 2000; 26: 363-7.
214. Beckstead Z. Shifting loyalties: reconsidering psychology's subject matter. *Integr Psychol Behav Sci*. 2009; 43: 221-7.
215. Feil PH, Grauer JS, Gadbury-Amyot CC, Kula K and McCunniff MD. Intentional use of the Hawthorne effect to improve oral hygiene compliance in orthodontic patients. *J Dent Educ*. 2002; 66: 1129-35.
216. Beckstead JW. What we write and what we cite: a comment on Mantzoukas (2009). *Int J Nurs Stud*. 2009; 46: 1161-3.
217. Patton MQ, Patton MQQe and research m. *Qualitative research & evaluation methods*. 3rd ed. ed. Thousand Oaks, Calif. ; London: Sage, 2002.
218. Feldman JM and Lynch JG. Self-Generated Validity and Other Effects of Measuremetn on Belief, Attitude, Intention, and Behaviour. *J Appl Psychol*. 1988.
219. Sherman SJ. On the self-erasing nature of errors of prediction. *J Pers Soc Psychol*. 1980; 39: 211-21.
220. McCambridge J. [Commentary] Research assessments: instruments of bias and brief interventions of the future? *Addiction*. 2009; 104: 1311-2.
221. McCambridge J and Kypri K. Can simply answering research questions change behaviour? Systematic review and meta analyses of brief alcohol intervention trials. *PLoS One*. 2011; 6: e23748.
222. French DP and Sutton S. Reactivity of measurement in health psychology: how much of a problem is it? What can be done about it? *Br J Health Psychol*. 2010; 15: 453-68.
223. Godin G, Sheeran P, Conner M and Germain M. Asking questions changes behavior: mere measurement effects on frequency of blood donation. *Health Psychol*. 2008; 27: 179-84.
224. O'Connor DW, Pollitt PA, Brook CP, Reiss BB and Roth M. Does early intervention reduce the number of elderly people with dementia admitted to institutions for long term care? *BMJ*. 1991; 302: 871-5.
225. Kass MA, Gordon M, Morley RE, Jr., Meltzer DW and Goldberg JJ. Compliance with topical timolol treatment. *Am J Ophthalmol*. 1987; 103: 188-93.
226. Hermann MM, Papaconstantinou D, Muether PS, Georgopoulos G and Diestelhorst M. Adherence with brimonidine in patients with glaucoma aware and not aware of electronic monitoring. *Acta Ophthalmol*. 2011; 89: e300-5.
227. Cate H, Bhattacharya D, Clark A, Fordham R, Notley C and Broadway DC. Protocol for a randomised controlled trial to estimate the effects and costs of a patient centred educational intervention in glaucoma management. *BMC Ophthalmol*. 2012; 12: 57.
228. Sanders MJ and Van Oss T. Using daily routines to promote medication adherence in older adults. *Am J Occup Ther*. 2013; 67: 91-9.
229. Dennis M, O'Rourke S, Slattery J, Staniforth T and Warlow C. Evaluation of a stroke family care worker: results of a randomised controlled trial. *BMJ*. 1997; 314: 1071-6; discussion 6-7.
230. Bhagwanjee S, Muckart DJ, Jeena PM and Moodley P. Does HIV status influence the outcome of patients admitted to a surgical intensive care unit? A prospective double blind study. *BMJ*. 1997; 314: 1077-81; discussion 81-4.
231. Code of Human Research Ethics. In: Society TBP, (ed.). Leicester: The British Psychological Society, 2010.
232. International Ethical Guidelines for Biomedical Research Involving Human Subjects. 2002.
233. NHS National Patient Safety Agency NRES. Issues, Guidance and Evidence - Deception in Medical Research. 2009.
234. Doyal L. Informed consent in medical research. Journals should not publish research to which patients have not given fully informed consent--with three exceptions. *BMJ*. 1997; 314: 1107-11.

235. Boter H, van Delden JJ, de Haan RJ and Rinkel GJ. Patients' evaluation of informed consent to postponed information: cohort study. *BMJ*. 2004; 329: 86.
236. Little P, Williamson I, Warner G, Gould C, Gantley M and Kinmonth AL. Open randomised trial of prescribing strategies in managing sore throat. *BMJ*. 1997; 314: 722-7.
237. Sokol. Can deceiving patients be morally acceptable? *BMJ*. 2007; 334: 984-6.
238. Bosley CM, Fosbury JA and Cochrane GM. The psychological factors associated with poor compliance with treatment in asthma. *Eur Respir J*. 1995; 8: 899-904.
239. Carr A, Thompson P and Cooper C. Factors associated with adherence and persistence to bisphosphonate therapy in osteoporosis: a cross-sectional survey. *Osteoporos Int*. 2006; 17: 1638-44.
240. Krueger RA. *Focus groups : a practical guide for applied research*. 2nd ed. ed. Thousand Oaks ; London: Sage, 1994.
241. Willis GB. *Cognitive interviewing : a tool for improving questionnaire design*. Thousand Oaks, Calif.: Sage Publications, 2005, p.xii, 335 p.
242. Hill M. Participatory research with children. *Child & Family Social Work*. 1997; 2: 171-83.
243. Wilkinson S. Focus groups in health research: exploring the meanings of health and illness. *J Health Psychol*. 1998; 3: 329-48.
244. Hughes R. Considering the Vignette Technique and its Application to a Study of Drug Injecting and HIV Risk and Safer Behaviour. *Sociol Health Illn*. 1998; 20: 381-400.
245. Neff JA. Interactional Versus Hypothetical Others - the Use of Vignettes in Attitude Research. *Sociology and Social Research*. 1979; 64: 105-25.
246. Weckstein DJ, Thomas CA, Emery IF, et al. Assessment of perceived cost to the patient and other barriers to clinical trial participation. *J Oncol Pract*. 2011; 7: 330-3.
247. Melisko ME, Hassin F, Metzroth L, et al. Patient and physician attitudes toward breast cancer clinical trials: developing interventions based on understanding barriers. *Clin Breast Cancer*. 2005; 6: 45-54.
248. Mills EJ, Seely D, Rachlis B, et al. Barriers to participation in clinical trials of cancer: a meta-analysis and systematic review of patient-reported factors. *Lancet Oncol*. 2006; 7: 141-8.
249. Oppenheim AN. *Questionnaire Design, Interviewing and Attitude Measurement*. 2Rev.ed. ed.: Pinter Publrs., 1992.
250. Collins D. Pretesting survey instruments: An overview of cognitive methods. *Qual Life Res*. 2003; 12: 229-38.
251. Sudman S and Bradburn NM. *Asking questions*. San Francisco ; London: Jossey-Bass, 1982.
252. Dillman DA. *Mail and telephone surveys : the total design method*. New York ; Chichester: Wiley, 1978.
253. Sudman S, Bradburn NM and Schwarz N. *Thinking about answers : the application of cognitive processes to survey methodology*. San Francisco: Jossey-Bass Publishers, 1996.
254. McColl E, Jacoby A and Thomas L. *Design and use of questionnaires : a review of best practice applicable to surveys of health service staff and patients*. National Co-ordinating Centre for HTA.Great Britain, 2001.
255. The Royal National Institute for the Blind - Accessible Information
256. Readability: How to produce clear written materials for a range of readers. Niace.
257. Schwarz N, Strack F, Muller G and Chassein B. The Range of Response Alternatives May Determine the Meaning of the Question - Further Evidence on Informative Functions of Response Alternatives. *Social Cognition*. 1988; 6: 107-17.
258. Perreault WD. Controlling Order-Effect Bias. *Public Opin Q*. 1976; 39: 544-51.
259. Moser CAS and Kalton G. *Survey methods in social investigation*. 2nd ed. / (with supplementary bibliography, 1979) by Sir Claus Moser and Graham Kalton. ed. Aldershot: Gower, 1985, 1971.
260. Rosenthal R and Rosnow RL. *Essentials of behavioral research : methods and data analysis*. 3rd ed. ed. Boston: McGraw-Hill, 2008.
261. Deese J and Kaufman RA. Serial effects in recall of unorganized and sequentially organized verbal material. *J Exp Psychol*. 1957; 54: 180-7.

262. Sartori R. Face validity in personality tests: psychometric instruments and projective techniques in comparison. *Qual Quant*. 2010; 44: 749-59.
263. Ericsson KA and Simon HA. *Protocol analysis : verbal reports as data*. Rev.ed. ed. Cambridge, Mass. ; London: MIT Press, 1993.
264. Bulmer M, De Vaus DA and Fielding N. *Questionnaires*. London ; Thousand Oaks: Sage Publications, 2004.
265. Clark HH and Shober MF. Asking questions and influencing answers. In: Tanur JM, (ed.). *Questions about Questions*. New York: Russell Sage Foundation, 1992, p. 15-48.
266. van Someren M. *The Think Aloud Method; A practical guide to modelling cognitive processes*. London: Acadmeic Press, 1994.
267. Schwarz N and Sudman S. *Context effects in social and psychological research : Conference on cognition and survey research : Papers*. Springer, 1992.
268. Murtagh FE, Addington-Hall JM and Higginson IJ. The value of cognitive interviewing techniques in palliative care research. *Palliat Med*. 2007; 21: 87-93.
269. Lewis JR. Sample sizes for usability studies: additional considerations. *Hum Factors*. 1994; 36: 368-78.
270. Van Den Haak MJ, De Jong MDT and Schellens PJ. Retrospective vs. concurrent think-aloud protocols: testing the usability of an online library catalogue. *Behav Inf Technol*. 2003; 22: 339.
271. Parahoo K. *Nursing research : principles, process and issues*. 2nd ed. ed. London: Macmillan, 2006.
272. Cannell CF, Fowler FJ, Jr. and Marquis KH. The influence of interviewer and respondent psychological and behavioral variables on the reporting in household interviews. *Vital Health Stat 2*. 1968: 1-65.
273. Reips UD and Funke F. Interval-level measurement with visual analogue scales in Internet-based research: VAS Generator. *Behav Res Methods*. 2008; 40: 699-704.
274. Issues, Guidance and Evidence - Deception in Medical Research. NHS National Patient Safety Agency, Nation Research Ethics Service, 2009.
275. Easthall C, Wright D, Taylor N and Bhattacharya D. Developing the 'Identification of Medication Adherence Barriers' (IMAB) Instrument: a novel application of behaviour change theoretical frameworks. *UK Society of Behavioural Medicine*. Manchester 2012.
276. C. E, Wright D, N. T and D. B. IMAB-Q Study.
277. NICE. *Medicines Adherence: Involving patients in decisions about prescribed medications and support adherence*. National Collaborating Centre for Acute Care, National Institute for Health and Clinical Excellence: London, UK, 2009.
278. Glaucoma Think Tank.
279. Glaucoma Passport.
280. NHS England: Hello My Name Is Campaign.
281. Lyons I, Barber N, Raynor DK and Wei L. The Medicines Advice Service Evaluation (MASE): a randomised controlled trial of a pharmacist-led telephone based intervention designed to improve medication adherence. *BMJ Quality & Safety*. 2016.
282. Medical Research Council: A framework for development and evaluation of RCTS for complex interventions to improve health. Medical Research Council, 2000.

Appendices

Appendix 1 NAGS ethics approval

National Research Ethics Service
Norfolk Research Ethics Committee
c/o The Norfolk & Norwich University Hospital NHS Trust
First Floor
Aldwych House
57 Bethel Street
NORWICH
NR2 1NR

Telephone: 01603 286 397
Facsimile: 01603 286 573

02 April 2008

Mr David Charles Broadway
Consultant Ophthalmologist
Norfolk & Norwich University Hospital NHS Trust
Colney Lane
NORWICH
Norfolk
NR4 7UY

Dear Mr Broadway

Full title of study: **Helping Adherence with Glaucoma Treatment Through Education: A Randomised, Clinical Trial**
REC reference number: **08/H0310/11**

Thank you for your letter of 12 March 2008, responding to the Committee's request for further information on the above research.

The Vice-Chair, Dr Robert Stone, has considered the further information on behalf of the Committee.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation .

Ethical review of research sites

The favourable opinion applies to the research sites listed on the attached form.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Application: Parts A&B: Sections 1 & 8	5.5	23 January 2008
Application: SSA: NNUH	5.5	23 January 2008
Investigator CV	David C Broadway	23 January 2008
[1]Protocol	5	23 January 2008
Covering Letter	David Broadway	21 January 2008
Summary/Synopsis	1 [appendix 10]	23 January 2008
Study Schedule	5 [appendix 11]	
Peer Review: RfPB Programme - National Institute for Health Research	Ref: PB-PG-0706-10453	15 December 2007
Questionnaire: Education	1 [appendix 8]	23 January 2008
Questionnaire: Final participant	1 [appendix 7]	23 January 2008
Questionnaire: Month 1 participant	1[appendix 6]	23 January 2008
Questionnaire: Initial participant	1 [appendix 3]	23 January 2008
Questionnaire: Social demographic and medical history	1[appendix 2]	23 January 2008
GP/Consultant Information Sheets	1	23 January 2008
Participant Information Sheet	1	23 January 2008
Participant Information Sheet: Options for Glaucoma Treatment?	[appendix 1]	
Participant Information Sheet: What is Glaucoma?	Number 1 [appendix 1]	
Participant Consent Form	1	23 January 2008
Response to Request for Further Information		12 March 2008
Checklist		
Adverse event form	1[appendix 9]	23 January 2008
Resource log	1 [appendix 5]	23 January 2008

R&D approval

All researchers and research collaborators who will be participating in the research at NHS sites should apply for R&D approval from the relevant care organisation, if they have not yet done so. R&D approval is required, whether or not the study is exempt from SSA. You should advise researchers and local collaborators accordingly.

Guidance on applying for R&D approval is available from http://www.rdforum.nhs.uk/rdform.htm.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

[1] Noted – no appendix 4

After ethical review

Now that you have completed the application process please visit the National Research Ethics Website > After Review

Here you will find links to the following

a) Providing feedback. You are invited to give your view of the service that you have received from the National Research Ethics Service on the application procedure. If you wish to make your views known please use the feedback form available on the website.
b) Progress Reports. Please refer to the attached Standard conditions of approval by Research Ethics Committees.
c) Safety Reports. Please refer to the attached Standard conditions of approval by Research Ethics Committees.
d) Amendments. Please refer to the attached Standard conditions of approval by Research Ethics Committees.
e) End of Study/Project. Please refer to the attached Standard conditions of approval by Research Ethics Committees.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nationalres.org.uk .

08/H0310/11	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

Katherine Norton
Acting Committee Coordinator.

Dr Robert Stone MB ChB MA
Vice Chair

Email: katheriner.norton@nnuh.nhs.uk

Enclosures: *Standard approval conditions SL-AC2*
Site approval form [Issue 1]

Copy to: Sponsor: Ms. Kathryn Andrews, R&D manager, NNUH
R&D office for NNUH

Appendix 2 NAGS R&D approval

East Norfolk and Waveney Research Governance Committee

Please reply to: Research Governance Committee Office
Research and Development Department
Level 3, East Block, Room 032
Norfolk & Norwich University Hospitals NHS Foundation Trust
Colney Lane
Norwich
NR4 7UY
Direct Dial: 01603 287408
Internal: 3408
Direct Fax: 01603 289800

e-mail: rdoffice@nnuh.nhs.uk
Website: www.norfolkhealthresearch.nhs.uk

Mr David Broadway
Ophthalmology Department
Norfolk & Norwich University Hospitals NHS Foundation Trust
Colney Lane
Norwich
NR4 7UY

12/08/2009

Dear Mr Broadway

Re: 2009OPTH02 (44-03-09) Helping Adherence with Glaucoma Treatment Through Education: A Randomised, Clinical Trial

Following confirmation of a favourable Ethical opinion I am pleased to confirm that your project has been given full approval from the East Norfolk and Waveney Research Governance Committee and Research Management Team and you may start your research.

Please note that this approval applies to the following sites:

- Norfolk and Norwich University Hospitals NHS Foundation Trust

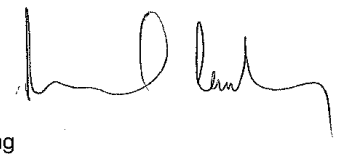
I have enclosed two copies of the Standard Terms and Conditions of Approval. Please sign and return one copy to the Research Governance Committee office. Failure to return the standard terms and conditions may affect the conditions of approval.

Please note, under the agreed standard terms and conditions of approval you must inform this Committee of any proposed changes to this study and to keep the Committee updated on progress.

If you have any queries regarding this or any other study please contact Julie Dawson, Research Governance Administrator, at the above address. Please note, your reference number is **2009OPTH02 (44-03-09)** and this should be quoted on all correspondence.

The Committee would like to take this opportunity to wish you every success with this project.

Yours sincerely



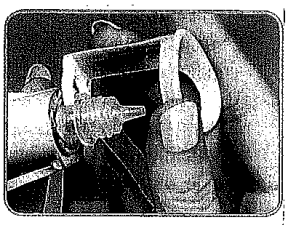
Dr Richard Reading
Chair
Consultant Paediatrician – NHS Norfolk

Encs – Standard terms and conditions
Guidance for screening of patient notes

Appendix 3 TDA operating instructions

Travalert Dosing Aid Instructions

To load the bottle of eye drops into the Travalert:
Firmly push the bottle of eye drops all the way down into the hole at the top, so that only the cap is exposed. Attach the drop guider, found in your kit, by snapping it onto the eye drop bottleneck.
To remove the eye drops from the Travalert:
Pull the drop guider off the neck of the bottle sideways. Pull the old bottle straight up to remove it from the unit. Insert your new bottle as above.



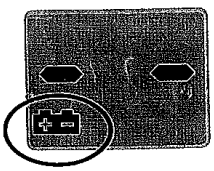
To apply the drops:

1. Wash your hands thoroughly.
2. Remove the cap from the bottle of eye drops.
3. Tip your head backwards or lie down.
4. Hold the Travalert over your eye, placing oval plastic around the eye and look at the nozzle of the bottle ahead.
5. Do not let the tip of the bottle touch your eye or the surrounding area because this could contaminate the solution.
6. **Fully depress the lever until one drop is dispensed, and release.**
   If you keep the lever depressed for too long, the dosing aid will continue to dispense eye drops. If more than one drop gets administered, have a tissue nearby to wipe away the excess.
7. Immediately after administering the eye drops, press on the corner of your eye closest to your nose for about one minute. This is to minimise the amount of medicine that may be absorbed into the bloodstream.
8. Repeat for the other eye if instructed by your doctor.
9. Replace the cap but you can leave the bottle of eye drops installed in the Travalert.

If the device does not dispense a drop when pressing the lever, check that you are pressing the lever down fully and holding long enough for a drop to be dispensed.

You can use the device without the drop guider attached if you prefer. Insert the bottle of eye drops into the Travalert as described but do not attach the oval drop guider. Follow the instructions provided in your box of eye drops dispensed from the pharmacy, but instead of squeezing the bottle, depress the lever on the Travalert to dispense one drop. **Fully depress the lever until one drop is dispensed and release.**

Your Travalert can be cleaned with a cloth lightly moistened with water and a non-abrasive cleaner on the outer casing. Never immerse the unit in liquid.



A battery symbol will be visible on the screen beside the sticker if the battery needs to be replaced. Should this occur, please telephone the Glaucoma Research Office who will send out a new battery and instructions to you in the post.

If you have any concerns or if you are experiencing any problems with the Travalert do not hesitate to contact the Glaucoma Research Office on Tel. No. 01603 288051

Adherence Study
Social Demographic Questionnaire

Study number ☐☐☐☐

Date of Birth: ☐☐ / ☐☐ / ☐☐

Gender: Male ☐ Female ☐

To which of these ethnic groups do you consider you belong? (Please tick one box)

☐ White (includes British, Irish, and any other White background)

☐ Mixed (includes White and Black Caribbean, White and Black African, White and Asian, any other Mixed background)

☐ Asian or Asian British (includes Indian, Pakistani, Bangladeshi, any other Asian background)

☐ Black or Black British (includes Caribbean, African, any other Black background)

☐ Other ethnic group (includes Chinese, and any other ethnic group)
- Please describe: .....

Current Postcode: ☐☐☐☐ ☐☐☐

Housing Tenure: Rented council..... ☐
Rented private ..... ☐
Home owner..... ☐

Marital status: Single..... ☐
Married/Partner..... ☐
Widowed..... ☐
Divorced/separated..... ☐

1. Please describe your current main employment (or previous main employment if retired):-

   .....
   (Please be as specific as possible)

2. Please describe your spouse's current main employment (or previous main employment if retired):-

   .....
   (Please be as specific as possible)

   Tick this box if question 2 is not applicable ☐

Highest Qualification Achieved:

- O-Levels or GCSEs..... ☐
- A-Levels..... ☐
- Degree..... ☐
- Post-graduate ..... ☐
- Apprenticeship/certificate/diploma ☐
- Other..... ☐

Family members affected by glaucoma: (Number affected in each box)

Parent ☐ Brother/Sister ☐ Children ☐

OR

Not known ☐ (please tick)

Study number | | | | |

The Norwich Adherence Glaucoma Study

Initial Participant Questionnaire

Thank you for taking part in this study examining the role and use of education in patient care.

This is the first questionnaire to be completed as part of this study.

Please feel free to add any extra information relating to your answers if you think that it may help us to understand your experience, as a patient.

All of your answers will be treated confidentially and will not in any way affect your normal care.

1. Please **tick one box** for each statement.

Have you received enough information about:	**Too Much**	**About Right**	**Too Little**	**None Received**	**None Needed**
What your eye drops are called	☐	☐	☐	☐	☐
What your eye drops are for	☐	☐	☐	☐	☐
What it does	☐	☐	☐	☐	☐
How it works	☐	☐	☐	☐	☐
How long it will take to act	☐	☐	☐	☐	☐
How you can tell if it is working	☐	☐	☐	☐	☐
How long you will need to use the eye drops	☐	☐	☐	☐	☐
How to apply your eye drops	☐	☐	☐	☐	☐
How to get a further supply	☐	☐	☐	☐	☐
Whether the eye drops have any unwanted effects (side-effects)	☐	☐	☐	☐	☐
What are the risks of you getting side-effects	☐	☐	☐	☐	☐
What you should do if you experience unwanted effects (side-effects)	☐	☐	☐	☐	☐
Whether you can drink alcohol whilst taking these eye drops	☐	☐	☐	☐	☐
Whether the eye drops will interfere with other medicines	☐	☐	☐	☐	☐
Whether the eye drops will make you feel drowsy	☐	☐	☐	☐	☐
Whether the eye drops will affect your sex life	☐	☐	☐	☐	☐
What you should do if you forget to take a dose	☐	☐	☐	☐	☐

2. **Do you currently take any other medication on a regular basis?**

   Yes ☐ No ☐

   If yes, will you use your glaucoma medication at the same time as you take your other medication.

   Yes ☐ No ☐

3. **Do you think you will apply your eye drops yourself or will somebody help you?**

   Apply by self ☐ Need help ☐

4. **Please tick which box best describes your use of any eye drops over the last 3 years or so:**

   Never ☐
   Occasional ☐
   Frequent ☐

5. **Please rate tick one box for each statement.**

Have you received enough information about:	**Too Much**	**About Right**	**Too Little**	**None Received**	**None Needed**
What glaucoma is	☐	☐	☐	☐	☐
How it might affect your vision	☐	☐	☐	☐	☐
How it might affect you if you are a driver	☐	☐	☐	☐	☐

6. **Is there anything that you would like more information about that we have not mentioned?**

   Yes ☐ No ☐

   If yes, please describe: .....
   .....
   .....
   .....

Many thanks for taking the time to fill out this questionnaire.

Study number ☐☐☐☐

The Norwich Adherence Glaucoma Study

Final Participant Questionnaire

Thank you for taking part in this examining the role and use of education in patient care.

This is the final questionnaire to be completed as part of this study.

Please feel free to add any extra information relating to your answers if you think that it may help us to understand your experience, as a patient.

All of your answers will be treated confidentially and will not in any way affect your normal care.

1. Have you experienced any problems with using the eye drops?

Yes ☐ No ☐

If yes, please describe: .....

.....

.....

2. On average, how many times do you miss using your drops?

☐ None

☐ Less than 1 day a month

☐ Less than 1 day a week

☐ Less than 2 days a week

☐ Less than 3 days a week

☐ More than 3 days a week

3. **Are you casual at times about using your eye drops?**

Yes ☐ No ☐

4. **When your vision feels better do you sometimes stop using your eye drops?**

Yes ☐ No ☐

5. **If your vision feels worse when you use the eye drops, do you sometimes stop using it?**

Yes ☐ No ☐

6. **If you have missed using your eye drops, what has been the reason or reasons (if any) for missing them?**
(Please tick **all** that apply)

☐ Forgot

☐ Ran out of medication

☐ Experienced side effects

☐ Experienced difficulty in using the eye drops

☐ Other.....

7. Please **tick one box** for each statement.

Have you received enough information about:	**Too Much**	**About Right**	**Too Little**	**None Received**	**None Needed**
What your eye drops are called	☐	☐	☐	☐	☐
What your eye drops are for	☐	☐	☐	☐	☐
What it does	☐	☐	☐	☐	☐
How it works	☐	☐	☐	☐	☐
How long it will take to act	☐	☐	☐	☐	☐
How you can tell if it is working	☐	☐	☐	☐	☐
How long you will need to use the eye drops	☐	☐	☐	☐	☐
How to apply your eye drops	☐	☐	☐	☐	☐
How to get a further supply	☐	☐	☐	☐	☐
Whether the eye drops have any unwanted effects (side-effects)	☐	☐	☐	☐	☐
What are the risks of you getting side-effects	☐	☐	☐	☐	☐
What you should do if you experience unwanted effects (side-effects)	☐	☐	☐	☐	☐
Whether you can drink alcohol whilst taking these eye drops	☐	☐	☐	☐	☐
Whether the eye drops will interfere with other medicines	☐	☐	☐	☐	☐
Whether the eye drops will make you feel drowsy	☐	☐	☐	☐	☐
Whether the eye drops will affect your sex life	☐	☐	☐	☐	☐
What you should do if you forget to take a dose	☐	☐	☐	☐	☐

8. **Have you looked for any additional advice or information about glaucoma from other independent sources such as leaflets or the internet?**
Yes ☐ No ☐

If yes, please describe: .....

.....

9. **Do you currently take any other medication on a regular basis?**
Yes ☐ No ☐

If yes, do you use your glaucoma medication at the same time as you take your other medication.
Yes ☐ No ☐

10. **Do you apply your glaucoma eye drops yourself or does somebody help you?**
Apply by self ☐ Need help ☐

11. **Please tick one box for each statement.**

Have you received enough information about:	**Too Much**	**About Right**	**Too Little**	**None Received**	**None Needed**
What glaucoma is	☐	☐	☐	☐	☐
How it might affect your vision	☐	☐	☐	☐	☐
How it might affect you if you are a driver	☐	☐	☐	☐	☐

12. **Is there anything that you would like more information about that we have not mentioned?**
Yes ☐ No ☐

If yes, please describe:.....

.....

Many thanks for taking the time to fill out this questionnaire.

Study number ☐☐☐☐

Norwich Adherence Glaucoma Study

Glaucoma Education and Support Services

Thank you for taking part in this study examining the role and effect of education and support in patient care.

This questionnaire is designed to allow us to gain some idea of your opinions about the experience that you have received from the Glaucoma Education and Support Service.

The questionnaire should take no longer than 10 minutes to complete and has two sections:

Section 1 asks you about how helpful you found the service
Section 2 asks you about any effect the service has had on how you use your glaucoma medication

Please feel free to add any extra information relating to your answers if you think that it may help us to understand your experience, as a patient.

All of your answers will be treated confidentially and will not in any way affect your normal care. **Please use the attached envelope to seal your questionnaire if you prefer that your Education Advisor does not see its contents.**

Section 1 relates to your discussion with the Glaucoma Support Assistant and the telephone helpline.

For each of the statements, please tick the box that best applies to you.

Statement	Strongly agree	Agree	Neutral	Disagree	Strongly disagree	Not provided/ not used
I found the information provided about glaucoma helpful	☐	☐	☐	☐	☐	☐
I found the information provided about how to apply eye drops helpful	☐	☐	☐	☐	☐	☐
I found the discussion about the best way to fit my eye drop use into my daily routine helpful	☐	☐	☐	☐	☐	☐
I found the telephone helpline provided by Glaucoma Support Assistants helpful	☐	☐	☐	☐	☐	☐

Section 2 relates to your overall thoughts about the glaucoma education and support service.

For each of the statements, please tick the box that best applies to you.

Statement	Strongly agree	Agree	Neutral	Disagree	Strongly disagree	Not provided/ not used
I feel that the glaucoma education and support service has given me a better understanding of my glaucoma	☐	☐	☐	☐	☐	☐
I feel that the glaucoma education and support service has made me better able to use my eye drops correctly	☐	☐	☐	☐	☐	☐
I feel that the glaucoma education and support service has made me more confident about using my eye drops regularly	☐	☐	☐	☐	☐	☐
I would recommend the glaucoma education and support service to other patients with glaucoma	☐	☐	☐	☐	☐	☐

9. We would very much appreciate any additional comments or suggestions about your experience of the Glaucoma Education and Support Service?

.....

.....

Many thanks for taking time to complete this questionnaire.

Appendix 8 MMAS and FMD questions

Morisky Medication Adherence Scale (MMAS):

Do you ever forget to take your medicine?

Are you careless about taking your medicine?

Sometimes if you feel worse when you take the medicine, do you stop taking it?

When you feel better do you sometimes stop taking the medicine?

Frequency of missed dose (FMD):

On average how many times do you miss using your drops?

- None
- Less than 1 day a month
- Less than 1 day a week
- Less than 2 days a week
- Less than 3 days a week
- More than 3 days a week

Appendix 9 User study ethics approval

NHS

National Research Ethics Service

Norfolk Research Ethics Committee

Victoria House
Capital Park
Fulbourn
Cambridge
CB21 5XB

Tel: 01223 597733
Fax: 01223 597645

04 October 2010

Mr David Charles Broadway
Consultant Ophthalmologist
Norfolk & Norwich University Hospital NHS Foundation Trust
Colney Lane
Norwich
Norfolk
NR4 7UY

Dear Mr Broadway

Study title:	**Helping Adherence with Glaucoma Treatment Through Education: A Randomised, Clinical Trial**
REC reference:	**08/H0310/11**
Amendment number:	**Amendment #6**
Amendment date:	**12 August 2010**
Amendment summary:	Researcher wishes to explore user and provider experience. Change to PIS and CF made to ensure final 50-60 participants are informed of follow-up study and have opportunity to express interest. 16 participants will be invited to take part in focus group as well as all Glaucoma Support Assistants. Protocol, PIS and CF revised. Two new Information Sheets. Increase in sample size from 200 to 250.

The above amendment was reviewed on 27 September 2010 by the Sub-Committee in correspondence.

Ethical opinion: Favourable Opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Covering Letter	from Heidi Cate	24 August 2010
Notice of Substantial Amendment (non-CTIMPs)	Amendment #6	12 August 2010
Participant Information Sheet	6	20 July 2010
Participant Information Sheet: Focus Group	1	12 August 2010
Participant Information Sheet: Focus Group - Glaucoma Support	1	12 August 2010

Assistants		
Participant Consent Form	6	20 July 2010
Participant Consent Form: Focus Group	1	12 August 2010
Participant Consent Form: Focus Group - Glaucoma Support Assistants	1	12 August 2010
Protocol	6.3	22 July 2010

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

08/H0310/11: Please quote this number on all correspondence

Yours sincerely

Miss Anna Bradnam
Committee Co-ordinator

E-mail: Anna.Bradnam@eoe.nhs.uk

Enclosures: *List of names and professions of members who took part in the review*

Cc: Mrs Kathryn Andrews (NHS R&D Contact)
R&D Office
Norfolk & Norwich NHS Trust
Colney Lane, Norwich
NR4 7UY

Norfolk Research Ethics Committee

Attendance at Sub-Committee of the REC meeting on 23 September 2010

Name	*Profession*	*Capacity*
Dr Michael Sheldon (Chair)	Retired Clinical Psychologist	Lay
Dr Robert Stone	General Practitioner	Expert

Also in attendance:

Name	*Position (or reason for attending)*
Miss Anna Bradnam	Committee Co-ordinator

Appendix 10 User study R&D approval

Our Vision
To provide every patient with the care we want for those we love the most

Norfolk and Norwich University Hospitals NHS
NHS Foundation Trust

Research & Development Office
Level 3 East
Norfolk & Norwich University Hospitals NHS Foundation Trust
Colney Lane
Norwich
NR4 7UY

direct dial: 01603 287806
direct fax: 01603 289800
e-mail: rdoffice@nnuh.nhs.uk
website: www.nnuh.nhs.uk

Mr David Broadway
Ophthalmology Department
Norfolk & Norwich University Hospitals NHS Foundation Trust
Colney Lane
Norwich
NR4 7UY

20th December 2010

Dear Mr Broadway

Re: **R&D Reference Number:** 2009OPTH02 (44-03-09)
Project Title: Helping Adherence with Glaucoma Treatment Through Education: A Randomised, Clinical Trial

Further to correspondence regarding amendment 6 for the above study. It was noted that the amendment has already received a favourable opinion from the Norfolk Research Ethics Committee.

Following review of the documentation I am pleased to inform you that Trust approval has been given for these changes.

The documents reviewed and approved are as follows;

- Participant Information Sheet, Version 6, dated 20 July 2010
- Participant Information Sheet: Focus Group, Version 1, dated 12 August 2010
- Participant Information Sheet: Focus Group – Glaucoma Support Assistants, Version 1, dated 12 August 2010
- Participant Consent Form, Version 6, dated 20 July 2010
- Participant Consent Form: Focus Group, Version 1, dated 12 August 2010
- Participant Consent Form: Focus Group – Glaucoma Support Assistants, Version 1, dated 12 August 2010
- Protocol, Version 6.3, dated 22 July 2010

If you have any queries regarding this or any other project please contact Claire Dawdry, Research Governance Administrator, at the above address. Please note, the reference number for this study is **2009OPTH02 (44-03-09)** and this should be quoted on all correspondence.

Yours sincerely

Professor Garry John
Director of Research & Development
Consultant Clinical Biochemist, NNUH

Cc. Heidi Cate, NNUH

Appendix 11 Observing effect of TDA ethics approval

NHS
Health Research Authority

NRES Committee East of England - Norfolk
Nottingham REC Centre
The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

05 March 2013

Mrs Heidi Cate
Ophthalmology Department
Colney Lane
Norwich
NR4 7UY

Dear Mrs Cate

Study title:	**A qualitative observational study of the effect of the Travalert® Dosing Aid and study participation on patient adherence to travoprost.**
REC reference:	**13/EE/0045**
IRAS project ID:	**120089**

Thank you for your letter of 20 February 2013, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Vice-Chair.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the Co-ordinator Tracy Leavesley, NRESCommittee.EastofEngland-Norfolk@nhs.net

Confirmation of ethical opinion
On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites
NHS sites
The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion
The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents
The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
Covering Letter	Letter from Heidi Cate	20 February 2013
Evidence of insurance or indemnity	Zurich Municipal - via UEA	15 May 2012
Interview Schedules/Topic Guides		21 February 2013
Investigator CV	Heidi Cate	03 January 2013
Other: Travalert Dosing Aid Leaflet	1	05 November 2012
Other: Demographic Information Collection Form	1	05 November 2012
Other: CV	Allan Brian Clark	18 December 2012
Other: CV	Mr David Broadway	20 February 2012
Other: CV	Debi Bhattacharya	05 November 2012
Other: Travalert Dosing Aid	2	14 February 2013
Participant Consent Form: Participant Consent Form	2	14 February 2013
Participant Information Sheet: Participant Information sheet - Tracked changes	2	14 February 2013
Participant Information Sheet: Participant Information Sheet - Clean	2	14 February 2013
Protocol	1.1	06 November

Appendix 12 Observing effect of TDA R&D approval

Our Vision:
To provide every patient with the care we want for those we love the most

Norfolk and Norwich University Hospitals NHS
NHS Foundation Trust

Mrs Heidi Cate
Ophthalmology Department
Norfolk and Norwich University Hospital NHS
Foundation Trust
Colney Lane
Norwich
NR4 7UY

Research & Development Office
Level 3 East
Norfolk & Norwich University Hospitals NHS Foundation Trust
Colney Lane
Norwich
NR4 7UY

direct dial: 01603 287806
direct fax: 01603 289800
e-mail: rdoffice@nnuh.nhs.uk
website: www.nnuh.nhs.uk

25 March 2013

Dear Mrs Cate

Re: **IRAS Reference Number:** 120089
R&D Reference Number: 2012OPTH08S (196-12-12)
Project Title: A qualitative observational study of the effect of the TravalertÂ® Dosing Aid and study participation on patient adherenceto travoprost.

I am pleased to inform you that the above project has been given full NHS permission for research at Norfolk & Norwich University Hospitals NHS Foundation Trust.

This NHS permission for research has been granted on the basis described in the application form, protocol and supporting documentation as listed below:

Document	Version No	Date
Protocol	1.1	06/11/2012
Consent Form	2	14/02/2013
PIS	2	14/02/2013
Travelert dosing aid instruction leaflet	2	14/02/2013
Demographic Information collection form	1	05/11/2012
Interview schedule		21/02/2013
NHS SSI form	120089/422202/6/973/183018/267047	
NHS REC form	120089/403688/1/480	

The agreed total local recruitment target for your study is 20 participants.

To support requirements of the National Institute of Health Research (NIHR) we will be monitoring and publishing outcomes of recruitment into your study. This includes benchmarking against a 70 day period from the time of receipt of a valid research application to this time of recruitment of the first patient for your study.

The date of receipt of a valid application for this study is 07 March 2013 and the benchmark of 70 days to recruit the first patient is 16 May 2013.

The R&D Office will contact you in due course to monitor progress against this benchmark.

I have enclosed two copies of the Standard Terms and Conditions of Approval. Please sign both copies and return one copy to the Research & Development Department at the above address and keep the other in your study file. Failure to return the standard terms and conditions may affect the conditions of approval.

Please note, under the agreed Standard Terms and Conditions of Approval you must inform the R&D department of any proposed changes to this study and submit annual progress reports to the R&D department.

If you have any queries regarding this or any other project please contact Seema Gopinath, Research Facilitator, at the above address. Please note, the reference number for this study is **2012OPTH08S (196-12-12)** and this should be quoted on all correspondence.

Yours sincerely

K M Andrews

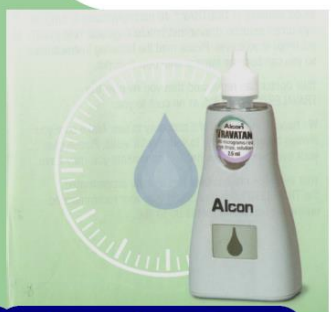
Professor Marcus Flather
R&D Director

Appendix 13 TDA Operating instructions

Travalert Dosing Aid

Glaucoma Services
Norfolk & Norwich University Hospital
Colney Lane
Norwich, NR4 7UY

Tel. 01603 288051



Instructions for use

Version 1, 25/03/2013

To load the bottle of eye drops into the Travalert:

Firmly push the bottle of eye drops all the way down into the hole at the top, so that only the cap is exposed. To remove the eye drops from the Travalert, pull the old bottle straight up to remove it from the unit. Insert your new bottle as above.

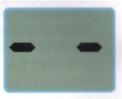
Optional drop guider:

Attach the drop guider, found in your kit, by snapping it onto the eye drop bottleneck. It can be removed by just gently easing it off the bottleneck.

To apply the drops:

1. Wash your hands thoroughly.
2. Remove the cap from the bottle of eye drops.
3. Tip your head backwards or lie down.
4. Hold the Travalert over your eye, placing the oval plastic around the eye and look at the nozzle of the bottle ahead.
5. Do not let the tip of the bottle touch your eye or the surrounding area because this could contaminate the solution.
6. Fully depress the lever until one drop is dispensed, and release. If you keep the lever depressed for too long, the travalert will continue to dispense eye drops.
7. Check the LCD screen to ensure that the drop symbol has been replaced by sleep mode (- -). If not, but you have administered an eye drop, just press the lever again.

- **Sleep mode**

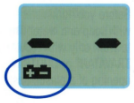


This symbol on the LCD screen means that your travalert dosing aid is 'resting'. There is no need to dose at this time.

- **Dosing mode**

When it is time for you to take your medicine, an eye drops symbol (shown here) will flash on the LCD screen. Once you take your medication, the symbol with disappear until the next day.

- **Low battery indicator**



A low battery symbol will be visible on the LCD screen when your battery needs to be replaced. Contact the number on the back of this leaflet should this occur. We will send you a new Travalert in the post.

Appendix 14 Modified consent ethics approval

NHS
Health Research Authority

NRES Committee South Central - Southampton B
Bristol REC Centre
Level 3 Block B
Whitefriars
Lewins Mead
Bristol
BS1 2NT
Telephone: 01173 421384
Facsimile: 01173 420445

17 May 2012

Mrs Heidi Cate
Glaucoma Research Unit Manager/PhD Student
Norfolk & Norwich University Hospital NHS Trust
Ophthalmology Department
Colney Lane
Norwich
NR4 7UY

Dear Mrs Cate

Study title: **A study to establish patient opinion of modified informed consent methods used in research.**
REC reference: **12/SC/0290**

Thank you for your letter of 14 May 2012, responding to the Proportionate Review Sub-Committee's request for changes to the documentation for the above study and for providing further information on the study.

The revised documentation has been reviewed and approved by the sub-committee.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. Confirmation should also be provided to host organisations together with relevant documentation.

Approved documents

The documents reviewed and approved by the Committee are:

Document	*Version*	*Date*
Covering Letter		27 April 2012
REC application		26 April 2012
Protocol	1.2	01 April 2012
Evidence of insurance or indemnity		26 April 2012
Investigator CV	Heidi Cate	10 February 2012
Other: CV - Debi Bhattacharya		27 March 2011
Other: CV - David Broadway		20 February 2012
Other: CV - Allan Clark		
Advertisement	1	04 April 2012
Interview Schedules/Topic Guides	Focus Group Discussion Guide v1.1	03 April 2012
Response to Request for Further Information		14 May 2012
Participant Information Sheet: Patient Information Sheet	2	14 May 2012
Participant Consent Form: Participant Consent Form	2	14 May 2012
Other: Patient Demographic Information Sheet	2	14 May 2012

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators

- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review.

12/SC/0290	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project,

Yours sincerely

pp. C. Hood

Professor Ron King
Chair

Email: scsha.swhrecb@nhs.net

Enclosures: *"After ethical review – guidance for researchers" [SL-AR2]*

Copy to: *Ms Susan Steel*
Ms Kathryn Andrews, Norfolk & Norwich Univeristy Hospital NHS Trust

Appendix 15 Modified consent approval

Our Vision
To provide every patient with the care we want for those we love the most

Norfolk and Norwich University Hospitals NHS
NHS Foundation Trust

Mrs Heidi Cate
Ophthalmology Department
Norfolk and Norwich University Hospital
Colney Lane
Norwich
NR4 7UY

Research & Development Office
Level 3 East
Norfolk & Norwich University Hospitals NHS Foundation Trust
Colney Lane
Norwich
NR4 7UY

direct dial: 01603 287806
direct fax: 01603 289800
e-mail: rdoffice@nnuh.nhs.uk
website: www.nnuh.nhs.uk

31 May 2012

Dear Mrs Cate

Re: **R&D Reference Number:** 2012OPTH04S (72-05-12)
Project Title: A study to establish patient opinion of modified informed consent methods used in research

I am pleased to inform you that the above project has been given full NHS permission for research at Norfolk & Norwich University Hospitals NHS Foundation Trust.

This NHS permission for research has been granted on the basis described in the application form, protocol and supporting documentation. The agreed total local recruitment target for your study is 16 participants.

The documents reviewed were:

Document	Version No	Date
Patient Information Sheet	2	14/05/2012
Consent Form	2	14/05/2012
Patient Demographic Information Form	2	14/05/2012
Advertisement	1	04/04/2012
Protocol	1.2	01/04/2012
Topic Guide for Focus Groups	1.1	03/04/2012

I have enclosed two copies of the Standard Terms and Conditions of Approval. Please sign both copies returning one copy to the Research Governance office at the above address and keeping the other in your study file. Failure to return the standard terms and conditions may affect the conditions of approval.

Please note, under the agreed Standard Terms and Conditions of Approval you must inform the R&D department of any proposed changes to this study and submit annual progress reports to the R&D department.

If you have any queries regarding this or any other project please contact Seema Gopinath, Research Facilitator, at the above address. Please note, the reference number for this study is **2012OPTH04S (72-05-12)** and this should be quoted on all correspondence.

Yours sincerely

Professor Krishna Sethia
Medical Director

Professor Marcus Flather
R&D Director

Appendix 16 Can you help poster

"Our desire is to carry out research that will make a difference for our patients with glaucoma, both now and in the future"

Mr David Broadway

Glaucoma Specialist Consultant

Can you help us?

Are you a patient at this glaucoma clinic?

Do you use eye drops?

If the answer is yes, please read on…

Discussion groups:

Thursday xxth April
10.30 – 11.30
or
Thursday xxth May
18.00 – 19.00

(Held at the Norfolk & Norwich University Hospital)

The Glaucoma Research Team at the Norfolk and Norwich University Hospital is committed to undertaking research for patient benefit. We would like to know your opinion on the following:

- How should we ask patients to take part in research?
- What information should we give to patients before they take part in research?
- How should patients consent to research?

Do you have an opinion, or just have an interest in this topic? Would you be willing to attend a small discussion group of 8 -10 people to help us understand the issues that are important to you as a patient?

Version 1.
4/4/2012

If you would like to join the group or would like more information please contact:

Heidi Cate, Glaucoma Researcher
Tel. 01603 288870
Email: heidi.cate@nnuh.nhs.uk
Norfolk & Norwich University Hospital

OR

Leave your name and telephone number at the reception desk and Heidi will contact you directly.

Appendix 17 Patient information sheet

University of East Anglia

Norfolk and Norwich University Hospital NHS
NHS Trust

Tel: 01603 288870
Email:heidi.cate@nnuh.nhs.uk

Colney Lane
Norwich
NR4 7UY

An invitation to take part in a research project

What is the purpose of the research?
The aim of this research is to gain a better understanding of what is important to patients when they consider taking part in a research study. In particular, we are interested to know what information patients expect to receive when they are involved in research. Sometimes, researchers feel it is not in the best interests of the study, to fully explain to patients the exact reason for the study, as this information may change patient behaviour. In these situations, is it ever acceptable for researchers to withhold information from participants or expect patients to participate in research without giving their consent? How might researchers proceed with careful respect for patients and minimise the possible negative effects patients may feel from this approach?

The attached information called "How do we carry out research that is right and good (ethical)" has been provided to give you more information about the current practices in research.

What will happen to me if I agree to take part?
If you decide to take part in the study, you will be asked to sign the attached consent form, and complete some questions to describe yourself. The following information will be obtained via a short questionnaire: age, gender, employment status, marital status and your contact details. We would like the opinions of a wide range of people and may not need the help of everyone who decides to take part. Heidi Cate, the researcher, will contact you to confirm if you have (or have not) been selected to join the discussion group and will arrange the time and date of the meeting with you. You will only be required to attend one discussion group.

There will be two discussion groups, held at the Norfolk & Norwich University Hospital, with approximately eight people in each. Heidi will ask the group questions to generate discussion and lead the group to ensure that everyone has the opportunity to share their own opinions. The discussion will be recorded using audio equipment so that Heidi or her assistant can make a written account of the discussion. Any details that may reveal your identity will be changed so that the information is anonymous.

If you incur any travel expenses in order to attend the focus group, this can be reimbursed to you. Please retain all your receipts (bus/parking) and complete the form made available to you at the focus group meeting.

What do I have to do?
Before the discussion you may like to read through the attached information which gives you some more background information about this topic. We will begin the focus group by reviewing this information, so any questions arising from it can be discussed.

What happens when the research ends?
This research is part of an educational project (a PhD) undertaken by Heidi. It is her intention to publish the results; therefore quotations from the discussion group may be used to provide evidence of her findings.

10. Will my participation remain confidential?
Yes. Any involvement in the study will remain strictly confidential. Your participation will not be noted in your medical records and your specific responses will not be discussed with anyone.

All discussions will also remain strictly confidential. The recorded conversation will be securely locked away at the Norfolk & Norwich University Hospital, under the control of the researcher. All the procedures for handling, processing, storage and destruction of your data will be compliant with the Data Protection Act 1998.

Who is organising and funding the research?
This study is being organised and conducted by the Glaucoma Research Unit in the Eye Department at the Norfolk & Norwich University Hospital NHS Trust and the University of East Anglia. The researchers (or their departments) will not be paid for including you in this study.

Where do I find further information?
For further information or any concerns about the study, please contact Heidi Cate on 01603 288870 or heidi.cate@nnuh.nhs.uk.
For independent advice, please contact the Patient Advice and Liaison Service (PALS) at the Norfolk & Norwich NHS Hospital Trust on 01603 289035/36/45 or PALS@nnuh.nhs.uk.

How do we carry out research that is right and good (ethical)?

- Researcher develops the study idea and how this will be carried out.
- Researcher writes a proposal which includes all the details of how the study will be carried out.
- Researcher secures the funding for the study (paying for all salaries, NHS costs etc.)
- Researcher prepares patient information and consent forms for ethical review.
- Researcher must obtain ethical approval by a Research Ethics Committee.
- Researcher can start the study.

Why is Research Ethics so Important?

Research is core to the NHS and other care services to improve care and services for all. Therefore, the public who use these services have a right to expect the highest scientific, ethical and financial standards for research.

Sometimes research carries a degree of risk to those who participate because it involves an additional burden or intrusion, exceeding those involved in normal care. Researchers must show that their research will be worthwhile and the risks and burdens will be minimised for the people taking part in research.

What is a Research Ethics Committee?

The Department of Health reviews all research proposals involving NHS patients. They do this by appointing a Research Ethics Committee who work to specific guidelines and standards. They promote public confidence in research because they maintain the dignity, rights, safety and well-being of those who participate in research.

These committees are served by members of the public and people with specific knowledge that can help the committee understand particular aspects of research proposals. They are always independent of the researchers, organisations of funding and the place where the research will take place.

What is Informed Consent ?

1. Potential participants need information upon which to base their choice.
2. An Ethics Committee will review this information before approving the study.
3. Researchers provide this information to patients before obtaining their consent.

What are the challenges of informed consent?

Some studies need to limit the information provided to patients.

Some studies cannot obtain consent from patients.

How does an Ethics Committee protect patients?

"In this situation, they need to carefully consider if the proposed study, which does not seek consent and withholds information from patients, is justified"

"What do you think about this? Would you join our focus group to discuss this?"

Norfolk and Norwich University Hospitals NHS
NHS Foundation Trust

University of East Anglia

Taking Part in Research:

A survey of people attending an eye clinic

Version 3 08/10/12

1

This questionnaire is to find out what is important to you when thinking about taking part in research. Although we use an example of a research project about an eye condition called *glaucoma* in this questionnaire, we are interested in the opinions of the general public. Whether you have glaucoma or not, your views are important to us.

The questionnaire takes about 10 minutes to complete. Completing the questionnaire is entirely voluntary. Your participation will be anonymous and confidential.

Thank you for your time.

An example of a research project

Whilst reading the example below, try to imagine you are a patient using eye drops for glaucoma and attending an Eye Clinic.

The Example:

Your doctor is carrying out a research project to see if patients use their eye drops as prescribed. The doctor knows how difficult it is for some patients to apply eye drops from a bottle and to remember to use them every day. The doctor would like to find out how much of a problem this is.

The doctor is going to use a bottle holder designed to help patients apply eye drops. This bottle holder is also able to record electronically every time the eye drops have been used. The recording device fits within the bottle holder so patients are unlikely to know that the bottle holder can record the use of eye drops unless it is explained to them.

The doctor has decided to give the bottle holders to patients to help them apply their eye drops, but not tell them anything about the research project or that the device will record their use of eye drops.

Is this research example acceptable?

1. After the research has finished, if the doctor explained the reasons for the research and asked your permission to use the information collected from the bottle holder, would you think this research is acceptable?

Please tick **one** box to indicate your opinion.

☐ I think this research is acceptable.

☐ I do **not** think this research is acceptable.

If you do not think this research is acceptable, please give a reason:

☐ The doctor should ask me for my permission to participate in research and tell me that my use of eye drops will be monitored before I start using the bottle holder.

☐ Other, please describe:

What do you feel about this research?

Researchers are aware that a patient's natural behaviour may change when they are participating in research. Participants might concentrate more on using their eye drops regularly if they know they are taking part in research and that their doctor is going to review their use of eye drops.

To avoid patients changing their behaviour whilst taking part in the research example on page 3, patients will not know that they are taking part in research and will not be told about the bottle holder.

2. Do you think it is acceptable to carry out this research if it would benefit patients in the future?

Tick **one** answer that describes your opinion.

☐ A) Yes, researchers can decide what is appropriate.

☐ B) Yes, but only if participants are told the real reason for the study at the end.

☐ C) Yes, as long as it does not cause a risk to participants.

☐ D) Yes, but only if researchers had already discussed the research with a number of patient representatives, and they had agreed what information will be withheld.

☐ E) No, this should not be allowed.

☐ F) I don't know.

Would you take part in this research?

3. If you had taken part in the research example described on page 3, please consider how you would feel once you were told about the research.

Tick **all** statements which might apply from the list below.

☐ A) It would not concern me at all.

☐ B) I would feel that I had not been treated with respect by my doctor or the researcher who had kept the information from me.

☐ C) It would break the rapport I have with my doctor or researcher who had kept the information from me.

☐ D) I would not trust any doctors or researchers in the future.

☐ E) It would make me consider whether I would take part in research again.

☐ F) Other, please describe:

Experiences of research

4. Have you ever taken part in any health research e.g. at a GP surgery or hospital?

☐ Yes ☐ No ☐ Don't know

If yes, how would you describe your overall experience?

Tick **all** that apply to you.

☐ I have taken part in more than one research project (please describe only the most recent research you took part in).

☐ I found the research very interesting	or	☐ I found the research very dull
☐ I was given enough information about the research	or	☐ I was not given enough information about the research
☐ I valued the experience	or	☐ I did not value the experience

If you ticked 'I valued the experience' or 'I did not value the experience', please describe why. For example, it was inconvenient or, it gave me an opportunity to discuss treatment.

Please describe what sort of research it was?

Taking part in research

5. Would you consider taking part in research in a GP surgery or hospital?

☐ Yes ☐ No ☐ Would depend on the type of research ☐ Don't know

Do you feel any of the statements below describe the concerns you might have about taking part in research?

Tick **all** that might apply.

- ☐ My personal details may be shared with other people (lack of confidentiality).
- ☐ My doctor/the researcher might keep information from me that is important to me and my health.
- ☐ There could be risks to my health and wellbeing.
- ☐ Other reasons, please explain:

Are there any other issues or concerns that you have about taking part in research?

Would you expect to receive information about the possible risks of taking part in research if there were any?

☐ Yes ☐ No ☐ Don't know

What do you feel about the research example?

Please think about the example on page 3 again.

"The doctor feels the research is acceptable because..."

- The care the patients will receive and the use of eye drops will continue just the same whilst taking part in the research.
- The bottle holder does not cause harm and is known to help patients apply eye drops.
- The information collected will help doctors understand the problems that patients may have when using eye drops.
- It might help to design further research which can help patients take their eye drops.

6. After the research has finished, if the doctor explained the reasons for the research and asked your permission to use the information collected from the bottle holder, would you think this research is acceptable?

Please tick **one** box.

☐ Yes, this research is acceptable.

☐ No, this research is not acceptable.

If you would not think it is acceptable, please explain why:

Information about yourself

It would be very helpful if you could provide some information about yourself. These details can help us to understand why people choose to take part in research. All your answers are anonymous and confidential.

7. How would you describe yourself? Tick **all** that apply.

☐ Male ☐ Female

Age:

☐ 39 years or under ☐ 40 – 64 years ☐ 65 years or over

☐ A patient visiting the hospital (but not the Glaucoma Clinic)

☐ A carer / friend / relative of a patient attending the Hospital today

☐ Other (please state)

Please complete this section if you are a patient attending the Glaucoma Clinic:

☐ A patient with glaucoma

☐ A patient attending for a review of suspected glaucoma

☐ A patient with an unknown diagnosis of an eye condition

☐ This is my first visit to the Glaucoma Clinic

If you have attended the Glaucoma Clinic more than once, how often do you attend?

☐ I attend the Glaucoma Clinic about once a year

☐ I attend the Glaucoma more than once a year

Do you currently use or have you ever used eye drops for treatment of your glaucoma or to reduce eye pressure?

☐ Yes ☐ No ☐ Don't know

Do you generally feel that attending appointments at the Glaucoma Clinic are:

☐ Satisfactory ☐ Not satisfactory ☐ I have no opinion

Is there a particular reason for your answer?
Tick **all** that apply.

☐ Travelling to the clinic is a problem for me

☐ The waiting times are too long

☐ I don't like undergoing tests

☐ I don't like seeing a different doctor every visit

☐ I am not able to ask questions

☐ I find seeing the glaucoma nurse reassuring

☐ I find seeing a doctor is reassuring

☐ I find the tests and examinations reassuring

☐ I am able to ask questions

Please give other reasons if you would like to:

Do you think that taking part in a research study in the Glaucoma Clinic would change the experiences you have described above?

☐ They might improve ☐ They might stay the same ☐ They might worsen ☐ Don't know

Principal investigator:	Mrs Heidi Cate, BSc, MSc PhD student and Glaucoma Research Unit Manager
Supervisors:	Mr David Broadway Consultant Ophthalmologist
	Dr Debi Bhattacharya Lecturer in Pharmacy Practice
	Dr Allan Clark Senior Lecturer in Medical Statistics
Contact point:	Glaucoma Research Unit Norfolk & Norwich University Hospital Colney Lane, NR9 5SD
Email:	heidi.cate@nnuh.nhs.uk
Telephone:	01603 288870

If whilst completing this questionnaire you have any concerns or questions about the conduct of research, you are very welcome to discuss these with Heidi Cate, the researcher working on this study.

Thank you for completing this questionnaire.

Norfolk and Norwich University Hospitals NHS
NHS Foundation Trust

University of East Anglia

Taking Part in Research:

A survey of patients and members of the public

Version 7 29/01/13

1

This questionnaire is to find out what is important to you when thinking about taking part in research. We will use an example of a research project about an eye condition called *glaucoma* in this questionnaire. We are interested in the opinions of the general public so whether you have glaucoma or not, your views are important to us.

The questionnaire takes about 10 minutes to complete. Completing the questionnaire is entirely voluntary. Your participation will be anonymous and confidential.

Thank you for your time.

An example of a research project

Whilst reading the example below, try to imagine you are a patient using eye drops for glaucoma and attending an Eye Clinic. The following questionnaire is based upon this example.

The Example:

It is difficult to apply eye drops from a bottle and to remember to use them every day. To find out how much of a problem this is your doctor is carrying out a research project to see if patients, regardless of their age or ability, use their eye drops as prescribed.

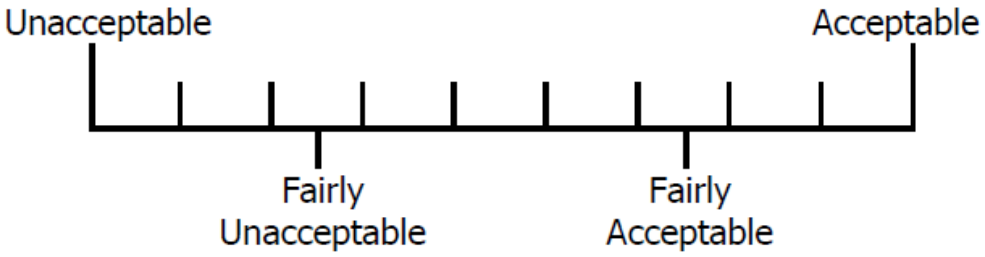
Your doctor is going to give you a bottle holder designed to help you apply the eye drops. This bottle holder also electronically records when you use your eye drops.

The recording device fits within the bottle holder so you are unlikely to know that it is recording the use of your eye drops unless this was explained to you. But your doctor can collect this information from the bottle holder for use in his research project.

Is this research example acceptable?

1. The doctor decides not to tell patients anything about the research project or that the device will record their use of eye drops. Do you think this is acceptable?

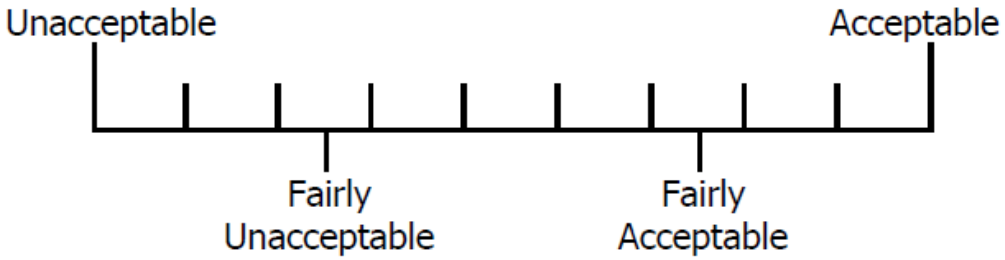
Please place a mark on the line below (e.g. —X—) to indicate your opinion. The far left indicates it is not acceptable at all, and the far right indicates it is totally acceptable, with varying degrees in between as shown.



Patient's natural behaviour changes when they are participating in research. Evidence has shown that participants concentrate more on using their eye drops regularly if they know their doctor is measuring their use of eye drops. This will cause doctors to gather incorrect information from research which will not be of benefit to their patients using eye drops in the future.

This is why, in the research example you read on page 3, the doctor decided not to tell patients anything about the research project or that the device will record their use of eye drops.

2. Does this change your opinion of the research example? Please indicate your opinion on the line below, whether it is the same as your answer to question 1, or different now.



If the doctor did carry out this research in his clinic, which of the following would be important to you:

Read the statements from the list below then tick **all** which might apply.

☐ A) That the research project will not cause a risk to participants.

☐ B) That participants are told the real reason for the research project at the end.

OR

☐ C) I do not agree with statements, A or B as the doctor should not carry out this research project.

Would you take part in this research?

3. If you had taken part in the research example described on page 3 without your knowledge, please consider how you would feel once you had been fully informed about the research.

Read the statements from the list below then tick **all** which might apply.

☐ A) It would not concern me at all.

☐ B) I would feel initially concerned, but not after the reason for the research had been fully explained to me at the end of the study.

☐ C) I would feel that I had not been treated with respect by my doctor or the researcher who had kept the information from me.

☐ D) It would break the rapport I have with my doctor or researcher who had kept the information from me.

☐ E) I would not trust any doctors or researchers in the future.

☐ F) It would make me consider whether I would take part in research again.

☐ G) Other, please describe:

Experiences of research

4. Have you ever taken part in any health research e.g. at a GP surgery or hospital? Tick one box

☐ Yes ☐ No ☐ Don't remember

If yes, how would you describe your overall experience?

Tick **all** that apply to you.

☐ I have taken part in more than one research project (please describe only the most recent research you took part in).

☐ I found the research very interesting	or	☐ I found the research very dull
☐ I was given enough information about the research	or	☐ I was not given enough information about the research
☐ I valued the experience	or	☐ I did not value the experience

If you ticked 'I valued the experience' or 'I did not value the experience', please describe why. For example, it was inconvenient or, it gave me an opportunity to discuss treatment.

Please describe what sort of research it was?

Taking part in research

5. Would you take part in research in a GP surgery or hospital? Tick one box.

☐ Yes ☐ No ☐ Would depend on the type of research ☐ Don't know

Do you feel any of the statements below describe the concerns you might have about taking part in research?

Tick **all** that might apply.

- ☐ My personal details may be shared with other people (lack of confidentiality).
- ☐ My doctor/the researcher might keep information from me that is important to me and my health.
- ☐ There could be risks to my health and wellbeing.

Or if you have no concerns please tick:

- ☐ I have no concerns.

Are there any other issues or concerns that you have about taking part in research?

Would you expect to receive information about the possible risks of taking part in research if there were any?

☐ Yes ☐ No ☐ Don't know

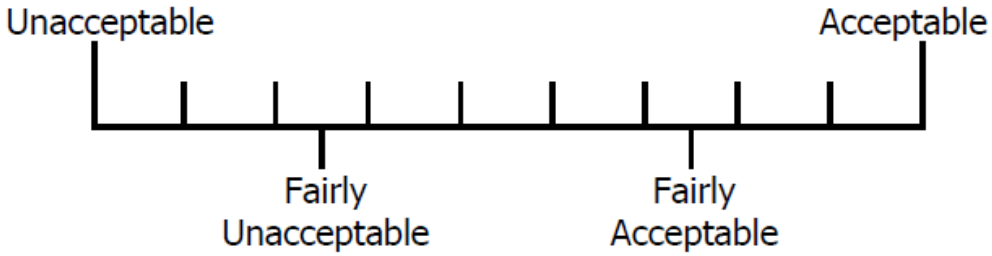
What do you feel about the research example?

The doctor feels the research example you read on page 3 is acceptable for the reasons listed below.

- The care the patients will receive and the use of eye drops will continue just the same whilst taking part in the research.
- The bottle holder does not cause harm and is known to help patients apply eye drops.
- The information collected will help doctors understand the problems that patients may have when using eye drops.
- It might help to design further research which can help patients take their eye drops.
- The doctor will explain the reason for the research and ask your permission to use the information collected from the bottle holder at the end.

6. Considering your opinion of the above statements, would you think this research example is therefore acceptable?

Please place a mark on the line below to indicate your opinion.



Information about yourself

It would be very helpful if you could provide some information about yourself. These details can help us to understand why people choose to take part in research. All of your answers are anonymous and confidential.

7. How would you describe yourself? Tick **all** that apply.

☐ Male ☐ Female

Age:

☐ 39 years or under ☐ 40 – 64 years ☐ 65 years or over

☐ A patient attending the hospital today

☐ A carer / friend / relative of a patient attending the hospital today

☐ Other (please state)

Please complete this section if you are a current patient attending a glaucoma clinic:

☐ A patient with glaucoma

☐ A patient attending for a review of suspected glaucoma

☐ A patient with an unknown diagnosis of an eye condition

☐ This is my first visit to a glaucoma clinic

If you have attended a glaucoma clinic more than once, how often do you attend?

☐ I attend a glaucoma clinic every one–two years

☐ I attend a glaucoma clinic more than once a year

Do you currently use or have you ever used eye drops for treatment of your glaucoma or to reduce eye pressure?

☐ Yes ☐ No ☐ Don't know

Do you generally feel that attending appointments at a glaucoma clinic are:

☐ Satisfactory ☐ Not satisfactory ☐ I have no opinion

Is there a particular reason for your answer?
Tick **all** that apply.

☐ Travelling to the clinic is a problem for me	☐ Travelling to the clinic is **not** a problem for me
☐ The waiting times are too long	☐ I don't mind having to wait
☐ I don't like undergoing tests and examinations	☐ I find the tests and examinations are tolerable
☐ I don't like seeing a different doctor every visit	☐ I don't mind which doctor or nurse I see each visit
☐ I am **not** able to ask questions	☐ I am able to ask questions
☐ I find the doctor or nurse is **not** approachable	☐ I find the doctor or nurse is approachable.

Please give other reasons if you would like to:

Principal investigator:	Mrs Heidi Cate, BSc, MSc PhD student and Glaucoma Research Unit Manager
Supervisors:	Mr David Broadway Consultant Ophthalmologist
	Dr Debi Bhattacharya Lecturer in Pharmacy Practice
	Dr Allan Clark Senior Lecturer in Medical Statistics
Contact point:	Glaucoma Research Unit Norfolk & Norwich University Hospital Colney Lane, NR9 5SD
Email:	heidi.cate@nnuh.nhs.uk
Telephone:	01603 288870

If whilst completing this questionnaire you have any concerns or questions about the conduct of research, you are very welcome to discuss these with Heidi Cate, the researcher working on this study.

Thank you for completing this questionnaire.

Appendix 20 React study ethics approval

NHS
Health Research Authority
NRES Committee East of England - Norfolk
Nottingham REC Centre
The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

Telephone: 0115 8839309

25 September 2013

Mrs Heidi Cate
Ophthalmology Department
Colney Lane
Norwich
NR4 7UY

Dear Mrs Cate,

Study title:	**An observational study of the effect of the Travalert® Dosing Aid and study participation on adherence to travoprost.**
REC reference:	**13/EE/0256**
IRAS project ID:	**135088**

Thank you for your letter of 23 August 2013, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Alternate Vice-Chair.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the REC Manager Tracy Leavesley, NRESCommittee.EastofEngland-Norfolk@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

1. It should state that the East of England - Norfolk Ethics Committee has reviewed the study in the Participant Information Sheet.

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which can be made available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable)

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering Letter	Letter from Heidi Cate	23 July 2013
Evidence of insurance or indemnity	UEA / Zurich Municipal	22 May 2013
Investigator CV	Heidi Cate	03 January 2013
Investigator CV	Allan Brian Clark	18 December 2012
Letter of invitation to participant	Patient Cover Letter - Version 1	25 March 2013
Letter of invitation to participant	Patient Letter - Version 1	25 March 2013
Other: CV	Debi Bhattacharya	05 November 2012
Other: CV	Mr David Broadway	20 February 2012
Other: Patient Letter - Completion of Study	1	25 March 2013
Other: Patient Letter 2	1	25 March 2013
Other: Patient Letter 3	1	25 March 2013
Other: Travealert Dosing Aid	1	25 March 2013
Other: TDA Review Contact Details	1	25 March 2013
Other: Patient flow chart	1	21 August 2013
Other: Patient Letter 2	2	21 August 2013
Other: Patient letter 3	2	21 August 2013
Other: Patient Letter	1	25 March 2013
Other: Patient Cover Letter	1	25 March 2013
Participant Consent Form	1	25 March 2013
Participant Information Sheet	1	25 March 2013
Protocol	1.1	23 July 2013
Questionnaire: Review of the Travalert Dosing Aid and use of eye drops	1	25 March 2013
Questionnaire: Measuring Patient use of Travoprost	1	25 March 2013
REC application	135088/481294/1/11	24 July 2013
Response to Request for Further Information	From Heidi Cate	23 August 2013

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

13/EE/0256 **Please quote this number on all correspondence**

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

With the Committee's best wishes for the success of this project.

Yours sincerely

J. Parliament

pp
Dr Michael Sheldon
Chair

Email:NRESCommittee.EastofEngland-Norfolk@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Sponsor - Ms Yvonne Kirkham*
R&D Contact - Ms Kathryn Andrews

Appendix 21 React study R&D approval

Our Vision
To provide every patient with the care we want for those we love the most

Norfolk and Norwich University Hospitals NHS
NHS Foundation Trust

Research & Development Office
Level 3 East
Norfolk & Norwich University Hospitals NHS Foundation Trust
Colney Lane
Norwich
NR4 7UY

direct dial: 01603 287806
direct fax: 01603 289800
e-mail: rdoffice@nnuh.nhs.uk
website: www.nnuh.nhs.uk

Mrs Heidi Cate
Ophthalmology Department
Norfolk and Norwich University Hospitals
NHS Foundation Trust
Colney Lane
Norwich
NR4 7UY

02 October 2013

Dear Mrs Cate

Re: **IRAS Reference Number:** 135088
R&D Reference Number: 2013OPTH01S (120-08-13)
Project Title: An observational study of the effect of the TravalertÂ® Dosing Aid and study participation on adherence to travoprost.

I am pleased to inform you that the above project has been given full NHS permission for research at Norfolk & Norwich University Hospitals NHS Foundation Trust.

This NHS permission for research has been granted on the basis described in the application form, protocol and supporting documentation as listed below:

Document	Comments	Version No	Date
Patient Letter 3		2	21/08/2013
Patient Flow Chart		1	21/08/2013
Protocol		1.1	23/07/2013
Travelert Dosing Aid - Instructions for Use	Appendix 1	1	25/03/2013
TDA Review Contact Details	Appendix 2	1	25/03/2013
Questionnaire - Patient Review of TDA and use of eye drops	Appendix 3	1	25/03/2013
Patient Letter 1 - Completion of Review Phase	Appendix 4	1	25/03/2013
Patient Letter 2 - Thank you for review phase	Appendix 5	2	21/08/2013
Patient Information Sheet		1	25/03/2013
Participant consent Form	Appendix 6	1	25/03/2013
Patient Cover Letter	Appendix 7	1	25/03/2013
Questionnaire - Measuring patient use of travoprost	Appendix 8	1	25/03/2013
Patient Letter - Completion of Study	Appendix 9	1	25/03/2013

The agreed total local recruitment target for your study is 76 participants.

To support requirements of the National Institute of Health Research (NIHR) we will be monitoring and publishing outcomes of recruitment into your study. This includes benchmarking against a 70 day period from the time of receipt of a valid research application to this time of recruitment of the first patient for your study.

The date of receipt of a valid application for this study is 25/09/2013 and the benchmark of 70 days to recruit the first patient is 04/12/2013.

The R&D Office will contact you in due course to monitor progress against this benchmark.

I have enclosed two copies of the Standard Terms and Conditions of Approval. Please sign both copies and return one copy to the Research & Development Department at the above address and keep the other in your study file. Failure to return the standard terms and conditions may affect the conditions of approval.

Please note, under the agreed Standard Terms and Conditions of Approval you must inform the R&D department of any proposed changes to this study and submit annual progress reports to the R&D department.

If you have any queries regarding this or any other project please contact Seema Gopinath, Research Facilitator, at the above address. Please note, the reference number for this study is **2013OPTH01S (120-08-13)** and this should be quoted on all correspondence.

Yours sincerely

pp Rachael Mold.

Professor Marcus Flather
R&D Director

Appendix 22 React study recruitment script

React Study - The six steps to follow to recruit

Introduction of role (not associated with research)

My name is….. and I am the Specialist Glaucoma Nurse.

Introduction of the review:

We are interested in finding ways of helping apply their eye drops. We have the Travalert dosing aid which helps people apply their eye drops.

Reasons it might be helpful:

- The Travalert is easier to hold and has a big lever on the back to press to help you squeeze the eye drop out of the bottle.
- There is also a guide that can be attached to the bottle to help you position the bottle in the correct place above your eye to avoid you actually touching the dropper onto the surface of your eye or eye lids.
- The screen also displays a tear drop when it is time to take your daily dose and will disappear when you have used it that day, so you know that you have used it and not forgotten to take it.

Informing patients what is involved for them:

We are keen to know if patients find the Travalert helpful and therefore would like you to use the Travalert for 2 months, then we will send you a questionnaire to fill in to send us your feedback.

Confirm patient happy to help:

Would you be happy to take part in this review of the Travalert Dosing Aid?

Next steps

If so – patient will receive the dosing aid in the post and then a member of the glaucoma team will phone them in one weeks' time to check they are happy using the device. They can decide to stop using it the Travalert if they don't get on well using it.

Important: DO NOT discuss that this part of a bigger research project.

Appendix 23 React study data collection sheet

Norfolk and Norwich University Hospital NHS
NHS Trust

A Review of the Travalert® Dosing Aid

Part A: **ID No.** ☐☐☐

Patient Name: .....

Hospital No. .....

Contact Telephone No. .....

Address: .....

.....

Date TDA dispensed: .....

Date to call patient to ensure TDA is being used (1 week):.....

Date of follow-up in two months:.....

Detach Part A before giving to research team if patient has not signed consent form.

Part B:

Data collection **ID No.** ☐☐☐

Please complete this section for every patient you offer the TDA to, even if they decline:

Gender:
- ❑ Male
- ❑ Female

Year of birth: .....

Type of glaucoma:
- ❑ POAG/NTG,
- ❑ Glaucoma suspect,
- ❑ Ocular hypertension

❑ Patient stopped using device at one week follow-up check

❑ Patient declined and reason if given.....

.....

TDA review contact details: Version 1, 25/03/2013

A review of the Travalert® Dosing Aid and use of eye drops

Patient questionnaire

- This questionnaire is designed to give us your feedback about the Travalert Dosing Aid and how you feel about using eye drops. This will help us to understand the difficulties people may face when using eye drops.
- There are no right or wrong answers to the questions asked, we are simply interested in your honest views.
- The questionnaire takes approximately 10-15 minutes to complete.

Enquiries to Glaucoma Specialist Nurse:
Tel. 01603 288051

Version 1. 25.03.2013

Part A: The Travalert® Dosing Aid

For each question below, please place a tick in the box that best describes your opinion.

Do you think the Travalert® Dosing Aid:	Yes	No	No difference
...was easier to use than the bottle of eye drops alone?			
... helped you to remember to use your eye drops?			
... helped you to apply your eye drops?			

Any comments you wish to add?.....

.....

.....

.....

Part B: Using travoprost eye drops

For each question below, please place a tick in the box to answer either yes or no.	Yes	No
Do you ever forget to use your travoprost?		
Are you careless at times about using your travoprost?		
When your eyes feel better do you sometimes stop using your travoprost?		
When your eye feel worse, do you sometimes stop using your travoprost?		

Part C: Your opinion of how you manage and feel about your eye condition

For each statement below, please place a tick in the box that best describes your opinion.	Strongly Agree	Agree	Neither agree nor disagree	Disagree	Strongly Disagree
I know how to order, collect and use my travoprost as prescribed					
I am able to use my travoprost as prescribed					
I can easily be distracted at the time I usually take my travoprost					
I trust my eye doctor(s) with decisions about my glaucoma care					
Using my travoprost as prescribed is too expensive for me					
Using my travoprost as prescribed is an unwelcome reminder of my condition					
Using my travoprost as prescribed is high on my list of priorities					
I have enough time to order, collect and use my travoprost prescription					
If I experienced difficulties when using my travoprost I would know how to overcome these					
Using travoprost as prescribed could be harmful to me					
I have the information I need to be able to order, collect and use my travoprost with ease					
I have a system in place to help me order, collect and use my travoprost					
I have my own reasons for not taking my travoprost as prescribed					
I have the support that I need from others to help me use my travoprost as prescribed					
Statements continue over leaf					

	Strongly Agree	Agree	Neither agree nor disagree	Disagree	Strongly Disagree
I struggle to use my travoprost as prescribed when there are changes to my daily routine					
Using my travoprost as prescribed is a burden to me					
I intend to use my travoprost as prescribed					
Life gets in the way of me using my travoprost as prescribed					
I could easily overcome any difficulties that arise from side effects of using my travoprost					
If I don't use my travoprost as prescribed my condition will get worse					
I have experienced problems using eye drops in the past					
I am satisfied with the information I have received about my diagnosis					
I am satisfied with information I have received about my travoprost					

Part D: How to receive a replacement dosing aid and information about a research study

Please send me a replacement dosing aid (tick box if required) ☐

	Yes*	No
Would you be interested in taking part in a research study where you will use the Travalert® for two months? No extra appointments are necessary as the questionnaire is sent by post and a follow-up telephone call is made.		

*If you answer yes, we will send you some more information so you can decide if you would like to take part.

Thank you for taking the time to complete this questionnaire.

Appendix 25 End of review phase – letter 1

Norfolk and Norwich University Hospital NHS
NHS Trust
Colney Lane
Norwich
NR4 7UY

Tel: 01603 288051
Email: corinne.haynes@nnuh.nhs.uk

Date:

Patient Address

Dear….

I am writing to you since you have been using the Travalert® Dosing Aid for the past two months. I would be grateful if you could now return the Travalert® in the original box, in the freepost envelope provided with this letter. We are keen to learn from your experiences and would therefore appreciate a few moments of your time to complete the enclosed questionnaire about the Travalert® Dosing Aid and using eye drops.

If the Travalert Dosing Aid has been helpful to you and you would like a replacement dosing aid, please indicate this on the questionnaire and I will organise this for you.

My research team are currently working on a number of projects to try and establish how we can best support patients using eye drops for glaucoma. I would therefore be grateful if you would consider helping with a new research study which involves using the Travalert® for two months. No additional appointments are required and all correspondence is carried out by post and telephone. If you are interested in taking part, please indicate this on the questionnaire enclosed and I will send you some further information about it.

If you have any further queries, please do not hesitate to contact me via my secretary on the telephone number or email address above.

My sincere thanks for your help with this project.

Yours sincerely

David Broadway
Specialist Glaucoma Consultant

Patient letter. Version 1, 25.03.13

Appendix 26 End of review phase - letter 2

University of East Anglia

Norfolk and Norwich University Hospital NHS
NHS Trust

Tel: 01603 288051

Colney Lane
Norwich
NR4 7UY

Date:

Patient Address

Dear....

Thank you for returning the Travalert® Dosing Aid and questionnaire to the Glaucoma Clinic. We would like to use the information collected from your questionnaire and from your Travalert® Dosing Aid to help us understand how often patients use their medication, how they feel about using their medication and using the Travalert® Dosing Aid. We are able to do this as the Travalert® Dosing Aid in addition to helping patients apply their eye drops, has recorded when the eye drops were applied because it contains an electronic monitoring device. When the Travalert® is plugged into a computer, the information stored in the device can be reviewed to find out when the eye drops have been used.

My PhD student, Heidi Cate, would like to use this information collected as part of her educational qualification and it may be published in a medical or research journal in the future. By sharing research findings in this way, we can inform clinicians and researchers to help improve treatment and services to patients with glaucoma in the future. I can assure you that all of your data will be kept completely confidential and anonymous. **I will not be given any of your personal information and it will not be shared with any member of the hospital care team or your GP.**

Before we started this project, we asked over 200 patients and members of the public what they thought about this research project and almost all agreed that the study was acceptable, or had no opinion either way. The project has also been reviewed and approved by a NHS research ethics committee. However, if you have any concerns about your data being used for the purposes described above, please do not hesitate to contact me to discuss this.

If you are willing for us to use the information that we have collected from you as described above, you do not need to take any further action. If

you do not want us to use this information for the project, please complete the attached form and return it in the freepost envelope provided.

Yours sincerely

David Broadway
Specialist Glaucoma Consultant

A review of the Travalert® Dosing Aid

If you are happy for your information collected from your questionnaire and Travalert Dosing Aid to be used in this project,
you do not need to take any further action.

Thank you

Please only complete the boxes below if you **do not** want the following data to be used:

Please tick those applicable.

☐ Information from my completed questionnaire.

☐ Information collected from my Travalert® Dosing Aid.

Name……

Date of Birth (for identification purposes only)……

Please return this page in the freepost envelope provided.

Patient letter 2 Appendix 5. Version 2, 21.08.13

University of East Anglia

Norfolk and Norwich University Hospital NHS
NHS Trust

Tel: 01603 288870
Fax: 01603 288261
Email: heidi.cate@nnuh.nhs.uk

Colney Lane
Norwich
NR4 7UY

Researcher: Mrs Heidi Cate, BSc, MSc

A study to measure patient use of Travoprost

Patient Information Sheet

1. **Invitation to take part**

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. You are under no obligation to take part and your decision to join the study or not will not compromise your care in anyway. Please ask if there is anything that is not clear or if you would like more information.

2. **What is the purpose of the study?**

Glaucoma is often associated with raised pressure within the eyeball which can cause damage to the optic nerve. People cannot feel this raised pressure and may not notice any damage to the optic nerve until the later stages. If glaucoma is left untreated a slow reduction in vision can occur and this may result in blindness. Lowering eye pressure is therefore essential and is usually treated with eye drops.

It can be difficult, when treating a condition that causes no symptoms in its early stages, to remember to take eye drops on a daily basis. We are undertaking this research to find out if using eye drops regularly is a problem for people with glaucoma. We believe that some people may find it difficult to stick to the regular routine of using eye drops for a variety of reasons.

3. **Why do we choose some people and not others?**

We are choosing people with glaucoma who are already using Travoprost eye drops to treat this condition and have previously used the Travalert® Dosing Aid.

4. Do I have to take part?

It is up to you to decide whether or not to take part. This study is run on a voluntary basis. If you do decide to take part you will complete a consent form but you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive thereafter.

5. What will happen to me if I take part?

We will ask you to use a Travalert® Dosing Aid which is designed to help people apply their eye drops and records when eye drops are applied as it contains an electronic monitoring device. When the Travalert® is plugged into a computer, the information stored in the device can be reviewed by the researcher to find out when eye drops have been used.

You will start the study by using the Travalert® Dosing Aid you received in the post with this information sheet to administer your eye drops as instructed by your doctor or pharmacist and continue this for two months. During the first week of using the Travalert® Dosing Aid, you will receive a phone call from the research team so that you can ask any questions.

After two months you will be contacted by letter to ask you to complete a questionnaire. The questionnaire will help us to understand how you feel about using your eye drops and how often you use them. Once completed, you return your Travalert® Dosing Aid and questionnaire in the freepost envelope provided. When the research team receive the Travalert® we can download the information about your use of eye drops recorded on it.

You should note that if you agree to take part in the study, you would not be expected to attend any extra appointments. The only additional procedures you will be asked to do, over and above those of standard care, will be to use the Travalert® Dosing Aid and complete a questionnaire.

6. What happens when the research study stops?

You will continue to receive the standard care and management of your glaucoma as felt necessary by your eye doctor. There is no change to your standard care during the study.

7. **What are the possible disadvantages and risks of taking part?**
There are no risks in taking part in this study, although the time taken to fill in questionnaire could be considered a disadvantage.

8. **What are the possible benefits of taking part?**
There is no guaranteed personal benefit to you by taking part in this study. However, the Travalert® device has been designed to assist you in applying your eye drops more easily.

9. **Will my participation remain confidential?**
Yes. Any involvement in the study will remain strictly confidential. All the procedures for handling, processing, storage and destruction of your data will be compliant with the Data Protection Act 1998. Any details that may reveal your identity will be removed so that your information is anonymous.

10. **What will happen if I don't want to carry on with the study?**
You are free to withdraw from the study at any time. If you withdraw from the study, we will use the data collected up to the time of your withdrawal. Withdrawal from the study will not affect the ordinary course of your medical care or treatment.

11. **What will happen to the results of the research study?**
This research is part of an educational project (a PhD) undertaken by Heidi Cate. We plan to publish the results; but no information that could identify you will be reported. We will also inform all participants of the study our findings.

12. **Who is organising and funding the research?**
This study is being organised and conducted by the Glaucoma Research Unit in the Eye Department at the Norfolk & Norwich University Hospital NHS Trust in collaboration with the University of East Anglia. The Norwich Glaucoma Research Fund will fund the study.

13. **Who has reviewed the study?**
This study has been reviewed and approved by the East of England – Norfolk Ethics Committee.

14. **What if there is a problem?**

We do not expect you to experience any problems by taking part in this study. If you have any concerns about this study, please contact Heidi Cate, the project co-ordinator in the Glaucoma Research Unit or her supervisor, Mr David Broadway. Alternatively, you may wish to contact the Research and Development Office at the Norfolk and Norwich University Hospital. For independent advice, or if you have a complaint please contact the Patient Advice and Liaison Service or the Norfolk & Norwich University Hospital Complaints Department. Contact details can be found below.

What should you do if you would like to take part in this study?

If you would like to take part in this study, please initial each box on the consent form provided to confirm you agree with each statement and then print your name, date and sign where indicated. Return the consent form in the freepost envelope supplied. You may start using the Travalert® Dosing Aid you received in the post with this information sheet to administer your eye drops as instructed. When the research team receive your consent form they will contact you to ensure you have no further questions and that you have started using the Travalert® Dosing Aid.

You should continue to use the Travalert® Dosing Aid until you receive a letter in the post from the research team, which will be in approximately two months time. The letter will ask you to complete a questionnaire which you then post back with your Travalert® Dosing Aid to the research team using a freepost envelope which will be provided.

Thank you

Glaucoma Research Unit: 01603 288870 (Heidi Cate)

Project Supervisor: 01603 288373 (Mr David Broadway)

Patient Advice and Liaison Service (PALS): 01603 289035

Research and Development Department: 01603 287408

Complaints Department: 01603 289686

University of East Anglia

Norfolk and Norwich University Hospital NHS
NHS Trust

Tel: 01603 288870
Email:heidi.cate@nnuh.nhs.uk

Colney Lane
Norwich
NR4 7UY

Researcher: Heidi Cate, PhD Researcher

A study to measure patient use of Travoprost

CONSENT FORM

If you wish to be involved in this study, please **initial** each box, then print your name, date and sign where indicated.
Once completed, please return the form in the envelope provided.

1. I confirm that I have read and understand the PATIENT INFORMATION LEAFLET (Version 1, dated 25th March 2013) about the above study and have been given a copy to keep. I have had the opportunity to ask questions and understand why the research is being done. ☐

2. I understand that my participation in this study is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected. ☐

3. I understand that the data collected during the study may be looked at by individuals from regulatory authorities or from the NHS Trust where it is relevant to my taking part in this research. I give permission for these individuals to have access to these records. ☐

4. I understand that I will be contacted by the research team using information stored in my hospital records. All my information will be kept anonymous and confidential. ☐

I agree to take part in the above study

Full name (BLOCK CAPITALS)	Date	Signature

Appendix 28 Cover letter for participation in study

University of East Anglia

Norfolk and Norwich University Hospital NHS
NHS Trust

Tel: 01603 288870
Email:heidi.cate@nnuh.nhs.uk

Colney Lane
Norwich
NR4 7UY

Date:

Patient Address

Dear….

Thank you for requesting further information about our research project called "A study to measure patient use of Travoprost".

Please find the attached information sheet for your further consideration and a new Travalert® Dosing Aid to use if you decide to take part.

If you decide you would like to take part, please complete the attached consent form and return it in the freepost envelope provided. You may then start using your new Travalert® Dosing Aid. I will telephone you to confirm when I receive your completed consent form and to ensure you have no further questions.

However, if you would like to discuss the study with me before deciding whether or not to take part, please do not hesitate to telephone me on the above number.

I am very grateful to you for taking the time to consider participating in this study. If I do not hear from you within about a week, I will give you a courtesy call in case you have any further questions for us.

With kind regards,

Yours sincerely

David Broadway
Specialist Glaucoma Consultant
&
Heidi Cate
Glaucoma Research Co-ordinator and PhD Student

Version 1, 25.03.13

Measuring patient use of travoprost

Patient questionnaire

- This questionnaire is designed to give us your feedback about the Travalert Dosing Aid and how you feel about using eye drops. This will help us to understand the difficulties people may face when using eye drops.
- There are no right or wrong answers to the questions asked, we are simply interested in your honest views.
- The questionnaire takes approximately 10-15 minutes to complete.

Enquiries to Study Co-ordinator: Heidi Cate
Tel. 01603 288870

Version 1. 25.03.2013

Part A: The Travalert® Dosing Aid

For each question below, please place a tick in the box that best describes your opinion.

Do you think the Travalert® Dosing Aid:	Yes	No	No difference
...was easier to use than the bottle of eye drops alone?			
... helped you to remember to use your eye drops?			
... helped you to apply your eye drops?			

Any comments you wish to add?.....

.....

.....

.....

Part B: Using travoprost eye drops

For each question below, please place a tick in the box to answer either yes or no.	Yes	No
Do you ever forget to use your travoprost?		
Are you careless at times about using your travoprost?		
When your eyes feel better do you sometimes stop using your travoprost?		
When your eye feel worse, do you sometimes stop using your travoprost?		

Part C: Your opinion of how you manage and feel about your eye condition

For each statement below, please place a tick in the box that best describes your opinion.	Strongly Agree	Agree	Neither agree nor disagree	Disagree	Strongly Disagree
I know how to order, collect and use my travoprost as prescribed					
I am able to use my travoprost as prescribed					
I can easily be distracted at the time I usually take my travoprost					
I trust my eye doctor(s) with decisions about my glaucoma care					
Using my travoprost as prescribed is too expensive for me					
Using my travoprost as prescribed is an unwelcome reminder of my condition					
Using my travoprost as prescribed is high on my list of priorities					
I have enough time to order, collect and use my travoprost prescription					
If I experienced difficulties when using my travoprost I would know how to overcome these					
Using travoprost as prescribed could be harmful to me					
I have the information I need to be able to order, collect and use my travoprost with ease					
I have a system in place to help me order, collect and use my travoprost					
I have my own reasons for not taking my travoprost as prescribed					
I have the support that I need from others to help me use my travoprost as prescribed					
Statements continue over leaf					

	Strongly Agree	Agree	Neither agree nor disagree	Disagree	Strongly Disagree
I struggle to use my travoprost as prescribed when there are changes to my daily routine					
Using my travoprost as prescribed is a burden to me					
I intend to use my travoprost as prescribed					
Life gets in the way of me using my travoprost as prescribed					
I could easily overcome any difficulties that arise from side effects of using my travoprost					
If I don't use my travoprost as prescribed my condition will get worse					
I have experienced problems using eye drops in the past					
I am satisfied with the information I have received about my diagnosis					
I am satisfied with information I have received about my travoprost					

Thank you for taking the time to complete this questionnaire.

Please return this questionnaire with your Travalert® Dosing Aid in the return envelope supplied.

Appendix 30 Completion of study – letter 3

University of East Anglia

Norfolk and Norwich University Hospital NHS
NHS Trust

Tel: 01603 288870
Email:heidi.cate@nnuh.nhs.uk

Colney Lane
Norwich
NR4 7UY

Date:

Patient Address

Dear....

Thank you for taking part in the study to measure patient use of Travoprost. I would be very grateful if you could complete the enclosed questionnaire as the final part of this study.

Please replace the Travalert® in the box and return it in the freepost envelope provided along with your completed questionnaire. If you would like a replacement dosing aid to help you apply your eye drops, please let me know and I will be very happy to provide you with one.

If you have any further queries, please do not hesitate to let me know. My sincere thanks for your help with this study.

With kind regards,

Yours sincerely

Heidi Cate
Glaucoma Research Co-ordinator and PhD Student

Version 1, 25.03.13

Appendix 31 Request for data from review phase – letter 4

University of East Anglia

Norfolk and Norwich University Hospital NHS
NHS Trust

Tel: 01603 288051

Colney Lane
Norwich
NR4 7UY

Date:

Patient Address

Dear….

Thank you for returning the Travalert® and your questionnaire for the study you took part in 'Measuring patient use of Travoprost'.

You may remember that before you took part in this study, you used the Travalert® for two months and completed a questionnaire similar to the one used in this study. If you agree, then I would also like to include this information as part of my study.

I am interested to learn if taking part in a study and being aware that your use of eye drops was being monitored by the Travalert Dosing Aid altered the way in which you used your drops or how you felt about using them. The information we collected from you before you took part in this study is therefore very useful in helping us to understand if responses to the questionnaires and frequency of eye drops use changed when taking part in research. **Your personal information will not be shared with any member of the hospital care team or your GP.**

Before we started this project, we asked over 200 patients and members of the public what they thought about this research project and almost all agreed that the study was acceptable, or had no opinion either way. The project has also been reviewed and approved by a NHS research ethics committee. However, if you have any concerns about your data being used for the purposes described above, please do not hesitate to contact me to discuss this.

If you are willing for us to use the information that we have collected from you as described above, you do not need to take any further action. If you do not want us to use this information for my study, please complete the attached form and return it in the freepost envelope provided.

With kind regards,

Version 2, 21/08/2013

Yours sincerely

Heidi Cate
Glaucoma Research Co-ordinator and PhD Student

Version 2, 21/08/2013

A review of the Travalert® Dosing Aid

If you are happy for your information collected from your questionnaire and Travalert Dosing Aid to be used in this project,
you do not need to take any further action.

Thank you

Please only complete the boxes below if you **do not** want the following data to be used:

Please tick those applicable.

☐ Information from my completed questionnaire.

☐ Information collected from my Travalert® Dosing Aid.

Insert comments box

Name……

Date of Birth (for identification purposes only)……

Please return this page in the freepost envelope provided.

Version 2, 21/08/2013