A PILOT STUDY TO ASSESS THE FEASIBILITY OF USING THE TRAVALERT® DOSING AID TO MEASURE ADHERENCE

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Abstract

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Glaucoma is a chronic condition, leading to progressive visual field loss and eventual blindness if left untreated. With adequate medical therapy, progression of the disease can be reduced. Non-adherence to glaucoma medication is a significant issue requiring further research. However, rigorous evidence for novel adherence interventions requires a valid and reliable measure of adherence. A gold standard for measuring adherence to glaucoma therapy has yet to be established. This study evaluated the Travalert® dosing aid (TDA) as an effective measure of adherence to travoprost.

One hundred patients prescribed travoprost for glaucoma or ocular hypertension, were approached and stratified by phase of travoprost use: newly prescribed or follow-up. At baseline, self-reported adherence to travoprost was obtained from follow-up participants using questionnaires (Morisky Medication Adherence Scale and Frequency of Missed Dose). All participants were given a TDA and daily adherence data were collected for 2 months. Self-reported adherence was obtained from both newly prescribed and follow-up participants. Satisfaction with information received about travoprost was assessed using the Satisfaction with Information about Medications Scale questionnaire.

The results suggested that future adherence studies should monitor adherence in excess of 100 days to overcome initial monitoring effects. Furthermore, the use of intraocular pressure as a short-term clinical outcome measure to assess adherence to glaucoma medication was found to be unreliable and thus requires further investigation.

This study has provided preliminary evidence that the TDA does not significantly alter patient eye drop use behaviour. It has been demonstrated as a feasible, objective adherence measure revealing that 40.9% of participants deviated from their prescribed treatment regimen. A further application of the TDA could be investigation of patient medication usage patterns to advance understanding of the complex area of non-adherence to glaucoma medication and aid the design of future adherence interventions.

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Chapter 1

Introduction

1 Introduction

Glaucoma is a significant contributor to vision loss throughout the world with more than 70 million people affected worldwide (1). Studies have shown that about half of all glaucoma cases remain undiagnosed in the Western developed countries (2), the prevalence of this disease appears set to rise. Furthermore, sight loss resulting from glaucoma causes problems with everyday activities and lifestyle; such problems can also have prominent psychological effects for those who suffer from the disease (3, 4). Glaucoma has thus been described as 'an important global public health concern…ever increasing due to the rapidly aging population' (5).

Glaucoma is a disease of the optic nerve, which can be 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 increased aqueous in turn increases the intraocular pressure (IOP), potentially causing permanent damage to the optic nerve. Without medical intervention this can lead to a chronic and slowly progressive disease. However, in some cases the drainage angle can become completely closed, in an acute manner, which causes a sudden elevation of IOP resulting in associated pain and 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 it is due to compromised drainage of the aqueous within the eye that causes elevation of IOP, or changes in IOP, which causes damage to the optic nerve. Currently available treatment for glaucoma is aimed at reducing IOP by inhibiting the production and/or increasing drainage of the aqueous.

There are fundamental risk factors that link race with both the prevalence and type of glaucoma, and associated severity. For example, the rate of blindness

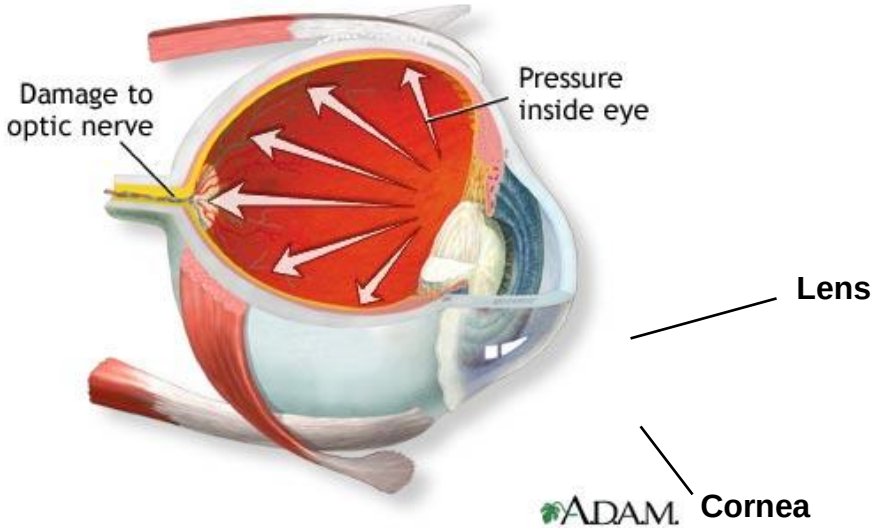
is higher in those of black race than white, and generally believed to be unrelated to socio-economic factors (6) (which are thought to exist when comparing black and white populations). Ethnic origin can play a role with respect to glaucoma risk and PACG, for example, is relatively less common compared with POAG in European regions but is more prevalent in Asia where it is almost equal to that of POAG (7). 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% of POAG and 25% of PACG) (8).

The most significant risk factor for glaucoma blindness is advanced loss of vision when the condition is first detected (9). 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, with no patient symptoms until significant damage has occurred, and as such, for all the types of glaucoma, POAG holds a particular challenge for clinicians in terms of diagnosis, treatment and patient education.

1.1 Primary open angle glaucoma

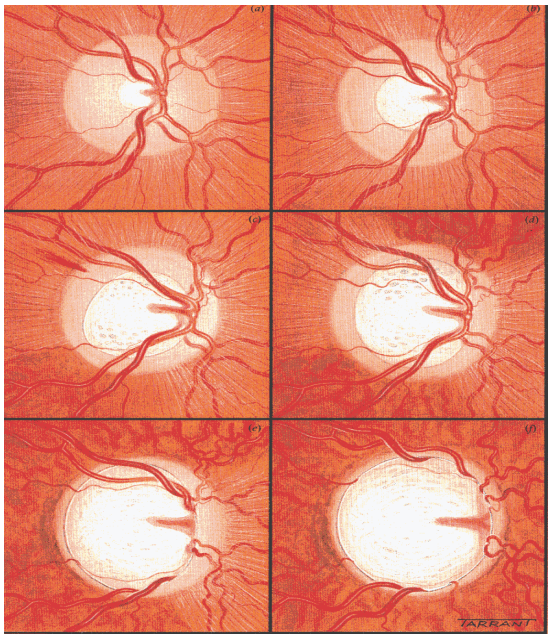
Primary open angle glaucoma is characterised by progressive loss of retinal ganglion cells, reduction of retinal nerve fibre layer thickness and characteristic thinning of the neuroretinal rim at the optic nerve head (figure 1.1a and 1.1b) (10). No single factor has been identified to cause POAG. The 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 later in the disease, this can even affect central vision. 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 (11).



Adapted from A.D.A.M (12)

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



Artwork by Tarrant T.R. (13)

Figure 1.1b Front view of optic nerve head showing progressive glaucomatous optic nerve damage

1.2 Diagnosis

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 1.2a. Figure 1.2b 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.

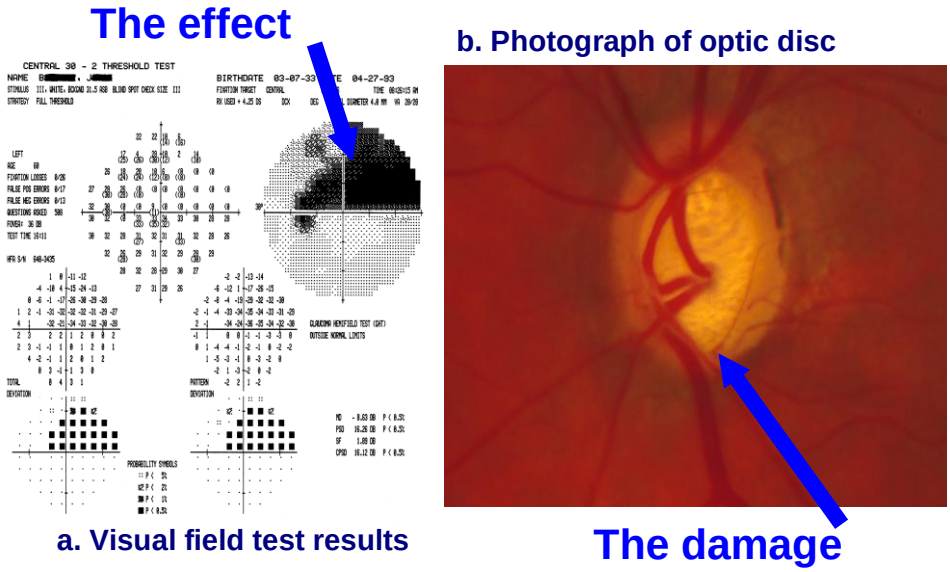


Figure 1.2 An illustration of nerve damage and corresponding visual field loss for the left eye of a POAG patient. a. Visual field test results showing the visual field loss 'arc' and b. photograph of the optic nerve head showing the point of nerve damage

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 (14). 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 (15.5mmHg) 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 (15). The main risk factors for POAG are age, level of IOP, African descent and family history (6, 16). It has also been suggested that diabetes, hypertension and migraine are associated risk factors(17).

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) (18), thus making elevated IOP a significant risk factor, but not the only causal factor of glaucoma. Evidence suggests that fluctuation of IOP plays an important role in the progression of optic neuropathy (19). Drance (20) 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 (21). 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. Thus, the available evidence for the role of fluctuation in IOP in the progression of glaucoma is controversial (19).

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 can expect to retain vision for the duration of their lives.

1.3 Ocular hypertension

Patients with an elevated IOP without detectable glaucomatous damage on standard clinical tests have ocular hypertension (OH). The treatment of 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 (16). 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 (16). The current recommendation from the National Institute for Clinical Excellence (NICE) is to ensure that patients with significant risk of developing POAG should have treatment initiated before visual loss occurs. However, patients with low risk of developing POAG should not be given unnecessary long-term therapy (18). Much research and debate continues in unravelling the complexity of detecting and treating glaucoma and its risk factors appropriately.

1.4 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 iron out the fluctuations in IOP over a 24-hour period. The general therapeutic goal is a reduction in intraocular pressure by 20% - 30% from the initial pressure at which damage occurs and below 21 mmHg for cases of OH (15, 18). Studies have shown that adherence to treatment regimens that achieve this IOP reduction may play a role in halting the progression for visual field loss in glaucoma (22) (14). 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 (14).

In addition to this, consideration to the reduction of IOP fluctuation must be given particularly in the case of NTG patients. Case studies have shown where a 30% reduction in IOP has been achieved but the magnitude of fluctuation remains unchanged, glaucomatous progression has been detected (19).

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, adherence to treatment, the likelihood of surgical success and patient preferences regarding treatment options (18). Many patients with early glaucomatous visual field loss and/or disc damage may not require treatment until progressive disease has been identified, although at present it remains impossible to accurately predict which patients will have significant progressive disease and which will have relative stability at any one time point.

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 and past/present medical history (18). Frequent follow-up is required to ensure that target eye pressure is maintained and the risk of progressive field loss minimised. At follow-up visits patients need assessment of IOP, visual fields and optic nerves. If target IOP is achieved but progression continues, further pressure lowering intervention is warranted and a new target IOP should be set (19).

1.5 Treatment options

Topical ocular hypotensive medications are a common choice for initial therapy and there are various types, which can be used alone or in combination. Other

options include laser and filtration surgery techniques that can be employed to lower IOP by increasing aqueous outflow. 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 optic nerve function) (17).

1.5.1 Medical therapy

There are many factors to consider when prescribing eye drops. There are several medical contraindications to the use of certain medications such 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, whether the patient has the manual dexterity required to administer the drops to one or both eyes (glaucoma manifestation and progression is not always symmetrical between eyes).

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 not effective 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 controlling progression with review of the treatment regimen at each follow-up visit (18).

Medical therapy is the main form of treatment for glaucoma and thus adherence with glaucoma medication is an important factor in the control of glaucoma. The level of adherence required should be expressed in relation to the clinical outcome to determine its clinical relevance (23). An 80% adherence rate is widely quoted as acceptable for many systemic medications (24). However, the

desired adherence rate for topical glaucoma medication has yet to be quantified. The reasons for failure to establish a desired adherence rate for ocular hypotensive therapy include 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, ophthalmologists at the Norfolk & Norwich University Hospital aim for 100% adherence for their patients. Knowing that ocular hypotensive agents not only lower mean IOP, but also iron out IOP fluctuations, only strengthens the perceived requirement for 100% adherence. 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 with be higher, causing peaks and troughs in IOP. The non-adherent patient may thus inadvertently increase the risk of developing progressive glaucomatous visual loss. However, the complexity and ethical implications associated with such a theory prevents the collection of empirical evidence.

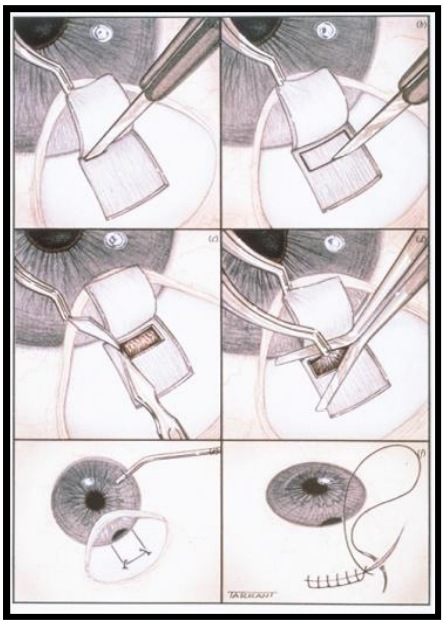
1.5.2 Laser therapy

When there is a failure of medical therapy (effect or adherence related) 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 (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. 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 (25). Cyclodiode laser reduces the production of the aqueous fluid by partial destruction of the ciliary processes (part of the ciliary body that produces 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 is often used when an eye has become blind but because of elevated pressure remains painful.

1.5.3 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 1.3 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 1.1. 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, 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. (26)

Figure 1.3 Diagram of trabeculectomy procedure

1.6 Measuring rate of progression

Glaucoma is usually a slowly progressive disease with the finality of blindness typically taking decades. In spite of treatment, most glaucoma will continue to progress (18), 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 the 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 (18). 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 looking at 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 observation or treatment (topical ocular hypertensive medication). The primary outcome 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). Therefore, 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 (27).

Other studies have found that patients with normal tension glaucoma, a reduction in IOP from 16 mmHg to 11 mmHg resulted in a reduction risk of progression from 60% to 20% (Collaborative Normal Tension Glaucoma Study)(28). In the Advanced Glaucoma Intervention Study, patients with POAG and moderate to severe visual field loss with low IOP below 18 mmHg, no net progression of visual field loss was noted during 8 years of follow-up (29). The results of the OHTS, CNTGS and AGIS studies have demonstrated the importnace for 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.

There is a clear association between adequate IOP control and patient health outcome. Given that current medical treatment to achieve IOP control requires daily dosing, adherence to such therapy is paramount. Patients not adherent with their prescribed medical regimen risk the reduction of their remaining eye-sight and eventual blindness.

1.7 Adherence

The language used to describe patient medication-taking behaviour has evolved with time. There are many different terms used to describe adherence, often interchangeably, including compliance, adherence, and concordance. Each has a different connotation and subtleties that need further explanation.

Traditionally practitioners have used the term ‘compliance’ to describe the extent of conformity to treatment regimens with respect to timing, dosage and frequency. Use of the term ‘compliance’ has become strongly criticised since it is thought to imply a negative image relationship between the prescriber as “the instructor” and patient as “follower of doctors orders”. In view of this, the term ‘adherence’ has been favoured as recognising a patient’s right to choose and remove the concept of blame when non-adherence ensues. It accepts that the patient has a freedom to decide whether or not to adhere to the doctor’s recommendations (30).

The term ‘concordance’ is used to describe the interaction between the prescriber and patient at the point of prescribing. However, in recent years ‘concordance’ has been used to describe the consultation process from the doctor and patient agreement on therapeutic decisions, to prescribing communication and patient support in taking medicine. This recognises the need for patients and doctors to work together to reach agreement even when there may be conflicting views (30). Whereas adherence refers to the extent of conforming to the recommendations in terms of timing, dosage and frequency, the term persistence describes the duration of medication use from initiation to discontinuation. Thus, a patient remaining adherent to the dosing regimen in terms of dosing frequency but discontinues use of the treatment earlier than recommended, is adherent but not persistent.

1.7.1 Magnitude

Adherence does not just relate to taking medication but also to lifestyle and exercise regimens and dietary considerations in relation to health. As such, The World Health Organisation (WHO) adherence project group have adopted their own definition of adherence: ‘*the extent to which a person’s behaviour – taking medication, following a diet, and/ or executing lifestyle changes, corresponds with agreed recommendations from a health care provider’* (31). In 2003, the WHO 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 (31).

A meta-analysis of studies from 1948-1998 reporting adherence to medical treatment was published in 2004 by DiMatteo *et al*. The average non-adherence rate was 24.8%; adherence was highest in HIV disease, arthritis, gastrointestinal disorders or cancer and lowest in pulmonary disease, diabetes or sleep. In chronic diseases such as hypertension or diabetes, medication adherence, at best, was thought to be estimated at 75% (32).

Successful management of glaucoma relies on establishing effective IOP lowering medication regimens. However, establishing efficacy is fraught with problems. Winfield *et al*. found that, even if asked, 69% of patients taking glaucoma medication would not tell practitioners they were having problems with adherence and persistence, and approximately 50% of the individuals started on glaucoma medications have been reported to discontinue them within 6 months (33). It can, therefore, be difficult for clinicians to establish true efficacy of prescribed ocular hypotensive eye drops. If a patient fails to respond to therapy, a change in therapy is often tried or additional topical agents added; this only leads to further adherence problems since adherence with therapy appears to decline with increasingly complex regimens (33).

Previous glaucoma adherence studies have demonstrated high rates of non-adherence. Olthoff *et al*., through a systematic review of 34 literary articles, found that percentages of patients who deviated from their prescribed medication regimen ranged from 5 - 80% [20]. More recently, studies using the Travalert Dosing Aid®, an electronic eye drop monitoring device, have reported adherence rates in the order of 75% (34). It is likely that the wide range in reported adherence rates is due to inconsistency in the definition of non-adherence and differences in the methodology for assessing non-adherence (an issue discussed further in section 1.10).

Other factors affecting the studies reviewed by Olthoff *et al*. include a lack of adjustments made for confounding variables. As an example, the study by Konstas *et al*. (35) used a cross-sectional assessment of patients using various eye drops for treatment of their glaucoma. No adjustment was made for patients who were required to use eye drops more frequently or with more complicated dosing regimens, which has been reported to prohibit adherence. Length of adherence 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. Whilst lacking in good quality and quantity of adherence studies, it is not surprising that studies of comprehensive methodological design have been compared under one umbrella. Ideally, only comparisons of studies using the same methodology should be used for this topic area because of the known complexity of adherence; only then will we begin to understand true trends and adherence rates to guide future research.

Research has shown that even when patients do adhere to their medication regimen, drop application technique is poor. Only 60% of patients instilled the correct number of drops in a study observing 140 experienced glaucoma patients (36). The most commonly cited problems have been reported include difficulty or problems 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%) (37). A recent study carried out to evaluate techniques for instillation of eye drops in glaucoma patients found that nine out of ten glaucoma patients were not able to correctly instil eye drops into the eye. 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 (38). In addition it has been determined that 38% of patients reported not always administering their own eye-drops (33). It is important, therefore, that family members, carers and friends of a significant proportion of patients with glaucoma are educated about proper drop administration.

1.7.2 Cost and health implications

Once diagnosed, patients with glaucoma require lifelong control of IOP with careful monitoring of the optic disc and visual field; the costs associated with the management of such a disease are therefore high. The annual economic burden of glaucoma in the UK was estimated at £62 million in direct medical costs in 1994 (39). The Cost of Blindness Report in 2003 estimated that as a chronic illness, requiring life-long treatment and follow-up, an individual lifetime cost for a patient with glaucoma was as high as £40,000 in the UK at that time (40).

Several studies have noted that the rate and extent of visual field loss are worse with higher mean and peak IOP measures (41, 42). 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 (cf 21.3 ±3.2 and 39.2 ±11.0mmHg, mean and peak IOP respectively, for those with decreased vision; $p<0.001$)(43). Stewart *et al.* found that patients who lost visual function were significantly less adherent with medical and surgical recommendations in comparison with patients whose vision remained stable ($p<0.001$). Glaucoma progression was seen in 50% of all patients noted to have poor adherence and remained stable in 90% of adherent patients. However, the methodology for assessing adherence was not described by Stewart *et al*. (43).

The evidence suggests that prevention of glaucoma is essential, having clear health and financial implications both for patient and society. In a study to describe 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 OH and POAG patients (44). Lower costs were positively associated with 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. It is accepted that non-adherence can be mistaken for low medical efficacy leading to

unnecessary additional prescribing or surgery. 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 (44). Non-adherence can be managed as treatment failure necessitating more frequent hospital appointments and/or diagnostic tests, this leading to increased healthcare expenditure. Treatment failure can also result in changes to medication prescribed, wastage of unfinished pharmaceutical supplies or the costs of surgery that may have been unnecessary. If surgical treatment is required, this not only increases the cost of glaucoma care significantly, but adds surgical risk to the patient (44). The presence of glaucoma rather than OH has also been shown to increase healthcare costs (44) suggesting that early interventions in prevention of glaucoma are justified if cost and economic evaluation are to inform therapy decision making.

1.8 The barriers to identifying non-adherence

One of the major methodological problems highlighting the complexity of non-adherence is the use of correct classification systems for the causes of non-adherence. Tsai *et al.* created a four category classification of 71 identified barriers to adherence, naming regimen factors, individual patient factors, medical provider factors and situational (i.e. social/environmental) factors as significant obstacles to adherence (45). In addition, Olthoff *et al*., subdivided determinants of adherence into four groups to summarise the following findings:

(1) Demographic / sociographic variables; age was found to have no relation to adherence, males were positively associated with non-adherence (though in most cases results were not significant) and there was a ‘probable’ relationship between ethnic background and adherence (though this has not been uniformly investigated).

(2) Knowledge, attitude and health-behaviour related variables; a link between knowledge of glaucoma and compliance was concluded to be inconsistent. However, ‘non-adherers’ were considered to be less knowledgeable than

‘adherers’ when assessed on single items of knowledge rather than their general level of knowledge about glaucoma.

(3) Aspects of disease; non-adherence was positively associated with better visual acuity. No association was found between duration of glaucoma and non-adherence.

(4) Aspects of treatment; non-adherence was found to be greater when regimes required more than two eye drops. Complexity of regimen, whilst evident in three studies, was concluded as unlikely to affect adherence (23).

It is unsurprising that complex interventions are most effective given the multifactorial nature of non-adherence. A meta-analysis of psychosocial interventions to improve medication adherence across a range of conditions, demonstrated that adherence-enhancing interventions could improve medication-taking behaviour beyond the level achieved through standard patient education and medical care. An average 35% decrease in non-adherence was reported post intervention, with the best techniques producing a decrease of up to 44%. The most effective interventions were multi-component and ‘personal’ intervention methods (involving personal contact) rather than those that were purely ‘technological’(46). Multi-component adherence interventions however, have frequently lacked grounding in such theory, resulting in ineffective components and thus a less cost effective model. It is therefore proposed that it is necessary to develop and trial an intervention that targets the factors elucidated in theoretical models to determine their impact on adherence.

1.9 Behavioural Models

The Health Belief Model (HBM) was first described in 1966 by Rosenstock (47) and this was summarised by Dunbar *et al*. in 1979 (48). The model states that health practitioner’s directions will be followed providing the patient believes the following elements:

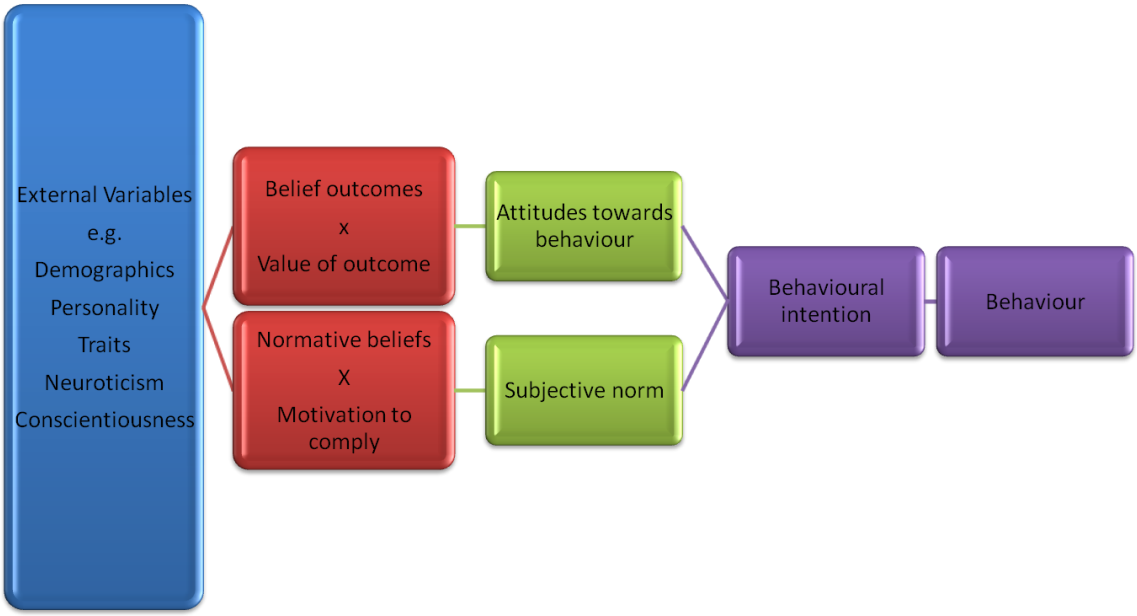
- they have susceptibility to the illness,
- the consequences of such illness are serious,
- the health practitioner's directions will be beneficial in reducing risk or severity of the disease,
- the costs of the action do not exceed the benefits.

The application of health promotion is key in this model for providing the patient with knowledge of their condition to enable them to recognise the importance of these elements.

The HBM focuses on patient behaviour related to illness prevention but provides no explanation of medication use behaviour or to adherence for patients already suffering from a chronic illness. However the theory of Reasoned Action addresses these issues and has been used to predict patient adherence.

1.9.1 Theory of Reasoned Action and Theory of Planned Behaviour

The Theory of Reasoned Action (TRA) is a general model of behaviour, which states that behaviour is determined by a person's intention to perform that behaviour (Figure 1.4). The intention is governed by two factors; attitude toward the behaviour (beliefs about the outcomes of the behaviour and the value of these outcomes) and the influence of the social environment and subjective norm surrounding that person (beliefs about what other people think the person should do and motivation to comply with the opinions of others). The TRA suggests that in a healthcare setting, patients will evaluate the benefits and drawbacks or the barriers of adhering, which then forms their intentions and predicts their behaviour.



Adapted from Horne and Weinman (49)

Figure 1.4 Theory of Reasoned Action (TRA)

The Theory of Planned Behaviour (TPB) adds to TRA the concept of perceived control over the opportunities, resources and skills necessary to perform a particular behaviour and overcome the potential barriers. In a healthcare setting TBP would relate to what a patient feels about the behaviour that is within their control, such as confidence in their own abilities. Potential barriers might include manual dexterity and memory problems. Figure 1.5 shows how these factors interlink with the TRA.

The TBP suggests that the best predictor of medication-taking behaviour is intention; the strength of intention is determined by the attitude towards the behaviour, the subjective norm and perceived control, and can all be influenced by patient demographics. Attitudes towards behaviour are formed from beliefs about the likely outcome of behaviour and value of that outcome. The subjective norm is the standard at which the patient would like to be. The subjective norm is formed by the patient's own beliefs regarding the views of others in relation to their behaviour and motivation to comply with the views of others. Perceived control is formed from beliefs about the existence of barriers or facilitators of adherence and their relative strength.

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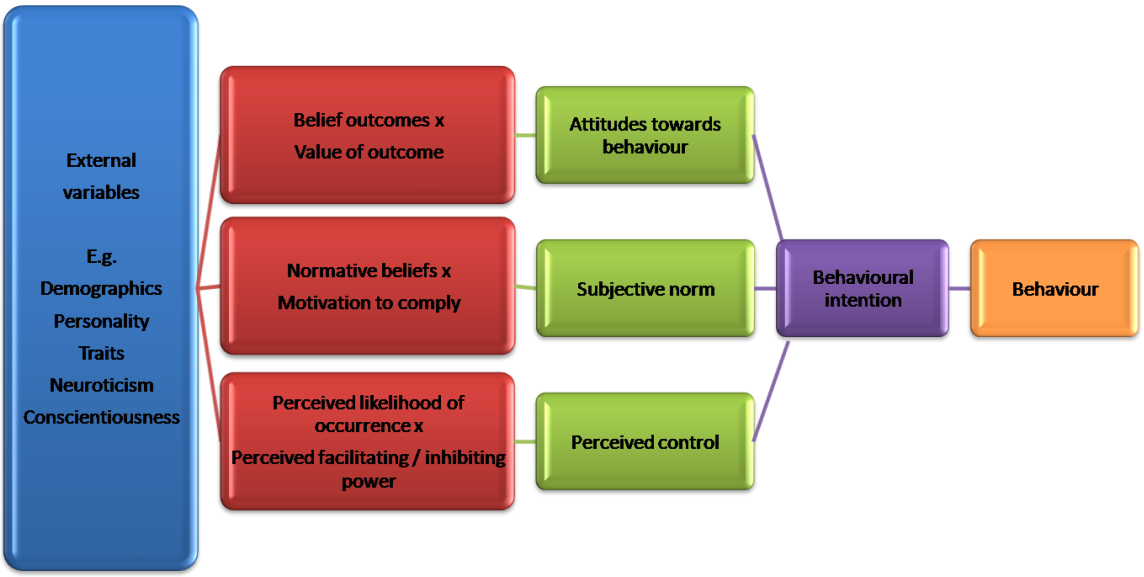


Adapted from Horne and Weinman (49)

Figure 1.5 Theory of Planned Behaviour (TPB)

A meta-analysis of research using TPB was carried out by Armitage *et al.*, who reviewed a database of 185 studies published to the end of 1997 (50). The TPB accounted for 27% and 39% of the variance in behaviour and intention, respectively using an objective measure. When behaviour measures were self-reports (a subjective measure), the TPB accounted for 11% more of the variance in behaviour than when behaviour measures were objective or observed. The meta-analysis suggested that greater adherence could be achieved with TPB. However, further work is needed to look at the methodological aspects of such research since the variance achieved relied upon self-report of medication-taking behaviour (50). Evidence suggests that data from patient self-report could lack validity and reliability due to self-presentational biases thought to be induced by this methodology (51). Despite potential methodological biases, behavioural decision-making models such as the TRA and TPB have tended to rely on the data generated by self-reports; the threat to reliability of the model having, to some extent, been subsequently ignored.

1.9.2 Social cognitive theory

The key constructs from social cognitive theory (SCT) are self-efficacy and outcome expectations. The SCT implies that in order to achieve optimal adherence, the individual must believe in his or her capability to perform the appropriate behaviour. Outcome expectations relate to whether the individual believes that certain behaviour will have a positive impact on a health condition. The person must value the outcomes or consequences that he or she believes will occur as a result of performing a specific behaviour or action. Self-efficacy can be increased in many ways, for example, providing clear instructions and giving an opportunity for training and modelling the desired behaviour. Using the theoretical framework of SCT, the implication is that if an individual believes that taking eye drops will help their glaucoma then that individual is more likely to administer their eye drops than someone who does not believe that they are helpful.

A recent study carried out by Sleath *et al*. (n=191) developed two instruments to measure self-efficacy and outcome expectation in glaucoma patients using eye drops (52). The self-efficacy scale was modelled on the medication self-efficacy scale in hypertensive patients scale because glaucoma was considered similar to hypertension with respect to the asymptomatic and chronic nature of both conditions. The glaucoma outcome expectations instrument was modelled on an outcome expectations scale from asthma. To assess validity, Sleath *et al.* distributed two self-report measures of adherence (the Morisky Medication Adherence Scale (53) and a visual analogue scale measure) to 60 glaucoma patients. The self-efficacy scales used had a significant association with the patient self-report of adherence measures. The six-item self-efficacy scale had a Cronbach α-coefficient of 0.87, with scores ranging from 7.91 to 18 indicating the scales were internally consistent. Sleath *et al.* concluded that patients with higher self-efficacy were significantly more likely to be adherent with their glaucoma medications. However, the outcome expectations scale did not correlate significantly with either adherence measure (52). The self-efficacy and outcome expectations scales identified by Sleath *et al.* 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 providers could educate and attempt to improve self-efficacy and medication adherence for these individuals.

1.10 Measuring adherence

Research that aims to develop new adherence interventions or assess existing interventions for patients with glaucoma is problematic. Olthoff *et al*. reviewed intervention protocols for glaucoma adherence studies and concluded that all studies reported a significant improvement in adherence (23). However, they suggested that more work needed to be done in this area due to the majority of studies having poor research design. Only the studies of Norell and Granstrom (54, 55) 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. It is widely accepted that electronic monitoring is the 'gold standard' measurement for assessing adherence (56).

Review of the literature has revealed that it is the adherence measure itself that remains the obstruction to gathering good empirical evidence for adherence interventions. Designing and implementing measures of adherence is fraught with difficulties and without the correct tools, researchers will never truly understand or be able to evaluate adherence interventions. Furthermore, it is plausible that every health condition and the treatment options available for that condition will also carry their own set of measuring difficulties.

Measures of adherence can be categorised as either objective or subjective and each have their advantages and disadvantages. Whilst objective measures remain the gold standard of clinical trials they have several drawbacks.

1.10.1 Therapeutic outcome

In some diseases, therapeutic outcome can be related to patient adherence such as in the case of epilepsy. Objective observations can be made which are directly attributable to the medication. Hypertension can be assessed by taking blood pressure readings and diabetes by glucose or HbA_1 monitoring.

The ultimate goal in the current management of glaucoma is the avoidance of progressive optic nerve damage and the associated deterioration in visual field. The chronic nature of the condition, however, means that determination of the effectiveness of therapy, or adherence to therapy, would require long term follow-up if such measures as optic nerve damage or visual field loss were to be used. An alternative would be to measure IOP as an assessment of therapeutic efficacy and/or adherence. However, when assessing outcomes for the effectiveness of ocular hypotensive medications used to treat glaucoma or OH, there is no universal standard to measure achieving IOP thresholds, IOP-controlled days and percentage reduction from peak or mean IOP (57).

There are several reasons as to why assessment of IOP control is problematic with respect to determining medication efficacy or adherence. 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 (peak, trough and calculation of a daily average), or integrating

IOP measures collected at several time points during the study period (as in the Ocular Hypertension Treatment Study (27)). However, this methodology is timely and inconvenient and can also increase participant awareness that they are being monitored. Adherence research is by its very nature difficult since simply trying to measure adherence will naturally encourage patients to adhere to their medication regimens. Patient reactivity to improve or modify their behaviour simply in response to the fact that they are being studied is known as the Hawthorne effect, a well-documented effect for a variety of conditions (58). Making a distinction between real changes in adherence levels and experimental effects is difficult to achieve, but inclusion of a control group can help quantify experimental effects.

There have been six studies that have assessed non-adherence in relation to IOP or the progression of visual field loss (35, 59-63). 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.* (35) found non-adherent patients to have a higher mean IOP than adherent patients (n=100) (22.9 vs 18.5 mmHg; $p>0.001$). Adherence in this study was determined by patient self-report of missed doses per month and this correlated with level of IOP. However, this was a study of relatively small sample size and it relied upon patient self-report of adherence, which is known to underestimate adherence.

A failure to consistently demonstrate a relationship between adherence and IOP control (23), could be explained by the lack of a quantified correlation or that the methodological quality of the studies performed so far 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’.

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.

1.10.2 Blood and serum samples

Many reviews have suggested that biologic assays are the most accurate measure of patient non-adherence (64). Any 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 assessed, 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 been used to assess adherence with ocular hypotensive medications.

1.10.3 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 used. However, while collection of a prescription shows intention to use medication, it does not ensure its use.

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 (65). In the patients using antihypertensive's (n=286) it was revealed that refill prescription patterns were moderately correlated with electronic monitoring (refill adherence r=0.32) and it was suggested that pharmacy dispensing records could be used

with predictive validity; gaps in the medication supply suggesting possible non-adherence (65).

Prescription claims databases as described in the Choo *et al.* (65) study 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 (66).

Consideration of inter-country healthcare systems are required as elements of cultural disparity and structural differences between healthcare systems can affect health beliefs and attitudes which may affect adherence. Patients paying for medication may be less likely to adhere when a condition is asymptomatic *(67).*

1.10.4 Electronic monitoring

Electronic drug monitoring is one of the more reliable methods employed to measure adherence, especially when dealing with eye drops, since 'pill counting methods' cannot be employed. There is the potential that the practice will change patient behaviour because the monitoring is so obvious (Hawthorne effect). However, a study carried out by Cramer *et al.* found that reactivity bias to medication monitoring devices was short lived and patients quickly return to their self-medication behaviour patterns (56).

Both studies by Norell and Granstrom used electronic medication monitors to obtain an objective measure of adherence with topical ocular hypotensive medication (54, 55) and reported significantly improved adherence following additional education and tailoring programmes. However, adherence was only

monitored using the devices for a 20-day period following the educational intervention. As suggested by Cramer *et al*. (56), the 20-day period may not have been a long enough period of monitoring to overcome the reactivity bias to 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 improved adherence persists following an intervention, but the use of an electronic device to measure adherence would appear to be satisfactory and little else at present can compete.

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) (manufactured by Alcon® eye drop due to aperture size restricting other and shaped bottles from fitting the aid. Three studies using the TDA have reported that it accurately records drop administration (68-70).

However, electronic bottle monitoring, pill counting or bottle weighing may also suggest to patients that they are not being trusted, resulting in resentment by the patient and a possible reduction in adherence or an undermining of any intervention itself (71). Electronic devices are also expensive to fund, often more difficult to operate than the bottle itself, and thus lead to a predetermined selection of participants who would be able to operate such devices rather than being usable by the greater patient population.

1.10.5 Physician estimated adherence

It has been reported that ophthalmologists do a poor job of detecting non-adherence in their patients (72). In a study published in 1986, eye drop medication monitoring data was compared with ophthalmologist predictions of adherence (73) 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 using the TDA, (n= 196) virtually no correlation between physician predictions and of adherence and electronic monitor recordings (intraclass correlation coefficient, 0.09; 95% confidence interval, 0.00 – 0.19) was identified (70).

Furthermore, a study of non-compliance to eye drops (33) found that 69% of patients 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. This latter finding was echoed in a more recent study by Lacey et al*.,* that examined the barriers to adherence, in which it was found that there was unsatisfactory hospital-led education where "doctors appeared too busy clinically to have time to provide adequate education … and poor communication" *(67)*. Thus, physician estimation of adherence is not a reliable measure of adherence.

1.10.6 Self-report of adherence

Patient self-report is used frequently as a measure of indirect adherence measurement. It includes questionnaires, dairies and/or interviews. The advantages of using self-report tools are that they are well-used, well-validated, generally cheap and simple to carry out and specific to non-adherence. However, it has been suggested that self-report measures can yield higher adherence estimates in comparison with objective measures (70). 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 given time is not necessarily representative of adherence over a period of time.

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 useful in assessing medication adherence in lower-literacy populations (74).

The missed-dose method for assessment of adherence is simple and straightforward 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 (75). 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. The missed-dose technique for assessment of adherence has the advantage of acknowledging that many people have difficulties with taking medication, thus indicating it is acceptable to experience a degree of non-adherence. For example, one could say to a patient “that people often have difficulty taking their medication for one reason or another and I am interested in finding out any problems that occur so that I can understand them better”.

A recent glaucoma adherence study reported by Ajit et al (34) 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.* (70) and Kass *et al.* (76) and it appears therefore, that relying on patient reports of adherence in glaucoma studies is prone to error.

1.10.6.1 Brief Medication Questionnaire (BMQ)

Svarstad et al (77) developed the Brief Medication Questionnaire (BMQ), a self-report instrument for measuring and monitoring adherence from the a 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. 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 a Medication Events Monitoring System (MEMS) and the BMQ achieved a sensitivity level of 80-100% and accuracy of 95% (77).

1.10.6.2 The Morisky Medication Adherence Scale (MMAS)

The Morisky Medication Adherence Scale (MMAS) was reviewed in 1986 to test the validity of the structured four-item self-reported adherence measure 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 ($P<0.001$) (53). The MMAS tool has been used since as a four-item validated measure of self-reported adherence with systemic antihypertensives. Although not validated for use in glaucoma patients, MMAS has been used in hypertension studies with a similar asymptomatic characteristic to that of glaucoma and thus has the potential to be useful for the latter condition.

1.10.6.3 The Medication Adherence Rating Scale (MARS)

The Medication Adherence Rating Scale (MARS) is a ten-item self-report measure of medication adherence developed by Thompson *et al.* (78). The scale was adapted from the MMAS and Drug Attitude Inventory (DAI). The new inventory was administered to 66 patients, the majority of whom were diagnosed with schizophrenia. Lithium levels and carer ratings of adherence were used to check adherence in order to validate the new scale. Using a

continuous scale to grade adherence rather than labelling a person either adherent or non-adherent has been an effective research tool (79).

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.

1.11 Potential predictors of non-adherence

Clear predictors of non-adherence have not yet been established. 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. Other predictors of non-adherence need to be tested for glaucoma patients.

1.11.1 The Satisfaction with Information about Medicines Scale (SIMS)

Research has shown that patient's requirements for information about medicines varies among individuals to ensure that medicines are taken appropriately and that the likely risks and benefits are understood. Thus, the quality of the information given to patients should be measured by the extent to which individuals perceived needs have been met in relation to their medication information (79, 80). The SIMS offers a valid and reliable method of assessing patients satisfaction with medicines information that can be used to quantify information requirements (81). SIMS is a questionnaire comprising of 17 items derived from published recommendations of the Association of the British

Pharmaceutical Industry. SIMS is able to elicit the type of information that is required to enable safe self-management of medication (82).

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 patients satisfaction with information they have received about HAART (Highly Active Anti-Retroviral Therapy) among patients attending Human Immunodeficiency Virus (HIV) clinics in Brighton (82).

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 (82).

The SIMS tool has been evaluated previously in a variety of clinical settings, both for ease of use, internal consistency and test-retest reliability (80). 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 HIV infection. Higher levels of satisfaction with medicines information have been shown to be associated with higher levels of reported adherence (80). With this evidence, it is possible that SIMS will prove able to be used as a potential predictor of non-adherence to ocular hypotensive medication.

Potential predictors of adherence are important as they not only improve patient long-term care but have the potential to reduce healthcare (eg National Health Service) expenditure. The additional costs of non-adherence in the

management of glaucoma could be avoided by being able to predict the areas that cause non-adherence and target them specifically.

1.12 Conclusions

At the 2006 Annual Congress of the Royal College of Ophthalmologists, it was identified that there is an ongoing challenge in the education and counselling of glaucoma patients, particularly in the area of instruction for correct drop administration technique. There was a call for new strategies to improve patient education, disease awareness and communication. Previous research has largely focussed on oral solid dose therapy, whereas glaucoma patients use eye drops that may be more difficult to administer than pills. There is a need to address the issues specific to non-adherence with topical medication.

A review of the literature has revealed how an understanding of health behaviour models could be used to improve adherence. Aiming for improved adherence with antiglaucoma therapy is an important objective in achieving patient adherence to glaucoma medication since evidence suggests that a degree of non-adherence with glaucoma treatment should 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 to achieve an improvement in ocular hypotensive topical medication adherence, our understanding of the methodological principles of measuring adherence needs further development, the literature reviewed above revealing where past research studies have failed. A discreet and effective way of measuring adherence and impact of an intervention is 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 what 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. A study is required to estimate the magnitude of adherence with antiglaucoma therapy and help our understanding of the varying degrees of non-adherence. Once it is possible to measure adherence with an adequate degree of accuracy, reliability and repeatability, then high quality studies can be performed to determine how adherence levels can be improved.

Chapter 2

Methods

2 Methods

2.1 Aims

This pilot study was designed to evaluate the feasibility of using the Travalert® Dosing Aid (TDA) as an adherence measure.

2.2 Objectives

The objectives of this study were to:

- Estimate the agreement between the TDA and patient self-reported adherence.
- Estimate the magnitude of adherence to travoprost for the treatment of glaucoma.
- Identify any predictors of non-adherence to travoprost.
- Estimate the effect of adherence monitoring on self-reported adherence.
- Determine if reduction in IOP could be used as an adherence measure.
- To identify any potential problems with the use of the TDA as an adherence measure.
- To test participant acceptability of data collection tools.

2.3 Method

2.3.1 Overview

A two month cohort study of adherence to glaucoma medication using questionnaires and an electronic adherence measure in individuals with glaucoma, or OH requiring treatment with travoprost eye drops.

2.3.2 Ethical and Research Governance approvals

The study received ethical approval from the Norfolk Research Ethics Committee (appendix 1) and research governance approval from the East Norfolk and Waveney Research Governance Committee (appendix 2).

2.3.3 Sample Size

Because there is no definition in the literature for an acceptable level of adherence, 80 % was chosen as *a priori* to represent what was believed to be an adequate level. A sample size of 100 was selected to allow for the withdrawal of 4 participants with 96 participants giving an absolute deviation from the population of 8%.

2.3.4 Sample population

Patients attending the Norfolk and Norwich University Hospital Out-Patients Glaucoma Clinic were randomly approached and stratified by experience of travoprost use; patients already using travoprost and thus experienced drop users (follow-up group) and patients prescribed travoprost at the time of recruitment and thus drop naïve (newly prescribed group). Stratification was to allow the following:

- Estimation of the TDA impact on the eye drop use of the existing user group
- Determination of whether the TDA presented new problems with administration for the follow-up group
- Determination of whether the TDA presented problems with administration for a newly prescribed travoprost group
- Identify any association between adherence and duration of treatment with travoprost.

2.3.5 Period of data collection

The recruitment period was June 2009 – December 2009 and the duration of the observation was approximately 8 weeks. The duration of data collection was thus 32 weeks.

2.3.6 Participant identification

Inclusion Criteria:

The newly prescribed group:

- Newly diagnosed or previously untreated glaucoma or OH patients (using established standard criteria as documented in the European Glaucoma Society Guidelines) (83)

The follow-up group:

- Treated glaucoma patients using travoprost, which had been shown to be efficacious with no hypersensitivity or other unwanted side effects

Both groups:

- Able to provide signed, informed consent
- Adequate ability to read and understand English
- Aged 18 or above

Exclusion Criteria:

- Patients whose travoprost eye drops would be applied by care home staff / home-helpers
- Additional therapy required for treatment of glaucoma.

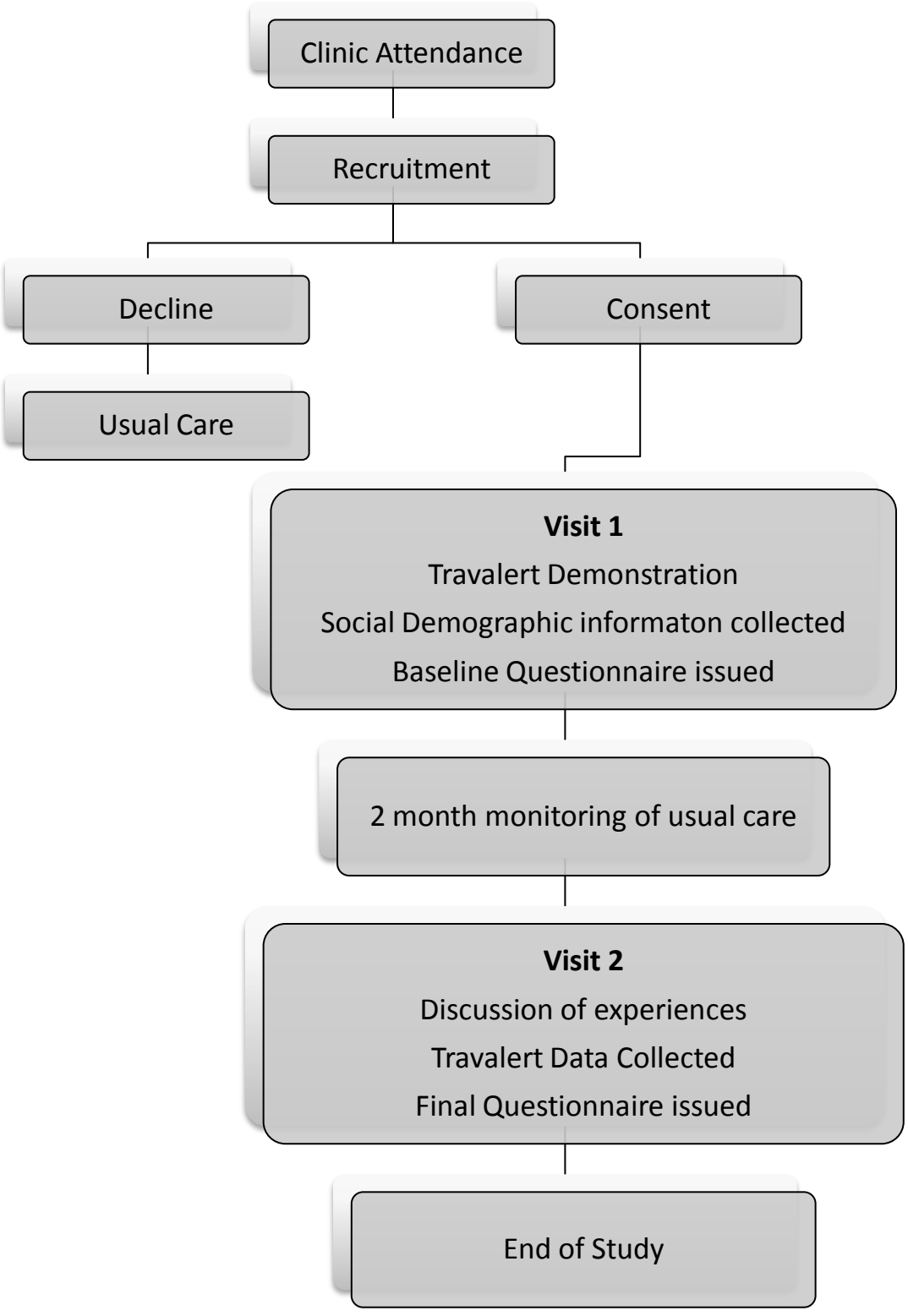
2.3.7 Recruitment

Eligible patients were identified at the time of clinic consultation by their clinician and referred to the research assistant to explain the nature of the research and obtain consent following standard consent procedures. If the research assistant was unavailable, the patient was contacted by telephone and verbal consent obtained followed by written consent in the post.

2.4 Data collection

Participants were given a demonstration of the TDA by one of the research assistants. Socio demographic details were collected using a structured interview (see appendix 3). The initial questionnaire was given to patients to complete at home and return in the pre-paid envelope provided. Participants used the TDA for a period of approximately 8 weeks and either returned to the clinic as part of their routine follow-up care where the final questionnaire was issued and the Travalert device collected or, the questionnaire was sent in the post and a pre-paid envelope provided for collection of the TDA. If the participant failed to return their questionnaire within two weeks of dispensing, the participant was telephoned to remind them. Figure 2.1 shows the data collection points and the patient flow through the study.

Figure 2.1 The patient pathway



2.4.1 Travalert® Dosing Aid

Figure 2.2 illustrates the TDA which is a device designed to assist patients in taking travoprost that also records when drops are administered. When a bottle of travoprost is inserted, the lever is pressed to squeeze out a drop. A built-in memory chip records the time and day when the lever is fully depressed. The TDA is designed not primarily as an electronic adherence monitor, but as an aid to dosing, it is easy to use, ergonomic and non-intrusive. This overcomes the problem of some medication monitors which are difficult to use and can thus bias the participants who can be selected for such studies to those whom would be able to operate a more complex device.

However, as the device is designed as an adherence aid it has two additional functions; an audible and visual dosing reminder; an intermittent beeping sound and a tear drop appears in the window at the time that dosing is required see figure 2.2a. In order to ensure the TDA remained an adherence 'monitor' rather than an adherence 'aid', the audible alarm was switched off using the Travalert software at the time of TDA set-up. The software does not allow the turning off of the visual reminder thus, a sticker was placed over this window to hide the tear drop, see figure 2.2b. Participants were asked not to remove the sticker and shown that the bottom left hand corner of the screen is visible in case the battery symbol appears which would indicate that the battery needs changing. Participants were asked to contact the research unit if a new battery was required.

Participants were shown how to use the TDA including how to replace the bottle themselves after collecting their repeat prescription via their General Practitioner. Participants were also instructed to ensure the lever was fully depressed when apply their drops to ensure the TDA recorded the application of the drop. Participants were asked to use the dosing aid to administer their travoprost eye drops as recommended by their clinician during their clinic consultation. Participants continued using the TDA for an approximate 8 week period then returned their device so the usage data could be retrieved.

Figure 2.2a TDA with visual reminder

Figure 2.2b TDA with visual reminder obscured.

2.5 Questionnaires

A questionnaire was designed to elicit patient medication taking behaviour and potential predictors of adherence. The initial questionnaire requested the newly prescribed participant group to disregard questions relating to medication taking behaviour with travoprost. The initial and final questionnaires are outlined in appendix 4 and 5 respectively.

All questionnaires were provided at the baseline (initial questionnaire) and then post TDA monitoring (final questionnaire) in order to assess the following:

- Patient acceptability of the questionnaire completion
- Any impact of the TDA monitoring on patient questionnaire response

2.5.1 Content

The Questionnaires comprised of four distinct sections:

Section one

- Determination of whether participant had previous experience of eye drop use.
- Description of any problems experienced if eye drops had previously been used.

Section two

- Self reported adherence via two approaches; frequency of missed doses and the Morisky Medication Adherence Scale (MMAS) (53).
- Additionally, any reasons for reported non-adherence were sought via providing the most frequently cited reasons plus an opportunity to report other reasons

1. Self reported adherence via frequency of missed doses during a one month period.

In order to quantify the extent of non-adherence, participants were required to report missed dose frequency. Below is the sample of this question:

On average, how many doses of your drops to you miss each month?

☐ None
☐ 1 dose
☐ 2-3 doses
☐ 4-9 doses
☐ 10-19 doses
☐ 20 or more doses

This scale was chosen in order to help participants quantify their missed dose frequency with ease. The scale was then categorised into 5 adherence % groups for comparative analysis.

None = 100% Adherent

1 dose = 97% Adherent

2-3 doses = 92 % Adherent

4-9 doses =80% Adherent

10-19 doses = 57% Adherent

20 or more = Less than 50%

For both groups, the data were used to compare the TDA missed dose rate to patient self-report of missed doses. Additionally, for the follow-up group, a comparison of adherence between the initial and final visits allowed an estimate of the TDA effect accepting the limitation of a before and after study in terms of identifying causal links.

2. Self reported adherence via MMAS

The MMAS is a commonly used adherence screening tool (53). MMAS is composed of four yes/no questions about past medication use patterns and it is thus quick and simple to use during drug history interviews. Participants answering '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. However, the sensitivity of this test was unknown and thus further analyses used a 0 score to dichotomise the adherent group and 1-4 to dichotomise the non-adherent group. Minor changes to the wording of the validated questionnaire were made in order to make MMAS relevant to eye drops and the final question was modified to read: "Do you ever forget to use your eye drops?" to provide more detailed information about the reasons for non-adherence. Below is the example of the modified question:

If you have missed using your eye drops, what has been the reason or reasons (if any) for missing them?

☐ Forgot

☐ Ran out of medication

☐ Experienced side effects

☐ Experienced difficulty in using the eye drops

☐ Other ……..

Participants who ticked the 'forgot' box were attributed a score of 1 as per the scoring system used for MMAS.

For the newly prescribed group, the data were used as an adherence screening tool. For the follow-up group, this allowed a comparison of adherence between the initial and final visits as an estimate of the TDA effect.

Section three

- Satisfaction with Information about Medicines Scale (SIMS)

An abbreviated 14-item version of SIMS was used to assess participants' perception of the information they had received from their clinician about their eye drops. SIMS has previously been used to report the association of higher levels of adherence with greater satisfaction of medicine information, and lower levels of satisfaction with stronger concerns about the potential adverse effects of medicines (80). Participants were requested to rate the information they had received about their medication using a response scale; 'too much', 'about right', 'too little', 'none received', and 'none needed'. The wording of the questions was adapted in order to relate to eye drops.

Collection of this data at the initial visit and final visit allowed a comparison of any changes in participant attitudes towards the information required for safe eye drop administration during the periods of adherence monitoring. It also allowed the testing of patient acceptability of questionnaire completion.

Section four

- Additional information sought

"Is there anything that you would like more information about that we have not mentioned?"

"Have you looked for any additional advice or information about glaucoma from other independent sources such as leaflets or the internet?"

- Existing medication regimes

"Do you currently take any other medication on a regular basis?

"If yes do you use your glaucoma medication at the same time as you take your other medication?

- Help received to apply eye drops

"Do you apply your glaucoma eye drops yourself or does somebody help you?"

The same questions were given at the start and finish of the study to enable the review of attitudes before and after the adherence monitoring period to provide evidence of any effects adherence monitoring may have and patient acceptability of questionnaire completion.

2.5.2 Assessment of face validity

A test or questionnaire has face validity when it appears valid to those who complete the questionnaire. A test that seems relevant to the lay person is said to have "face validity" (84). Face validity was sought from non-clinical hospital staff. Four colleagues were randomly selected to view three different versions of the same questionnaire and comment on:

1. Overall readability and formatting
2. Ease of use
3. Understanding of the questions
4. Other general comments

There was one questionnaire that was chosen over the others for ease of use due to its clear and bold formatting and ‘tick box’ grid.

2.6 Intraocular pressure measurements

Participant IOP values were measured by Goldmann applanation tonometry. The time points of the IOP assessments used were different for each group:

- Newly prescribed group – IOP recorded during their consultation with the clinician just before recruitment and again at the participant follow-up appointment at the time of their final visit. Thus, only those participants who received IOP measurements after 8-weeks as part of their routine follow-up care had this data collected.
- Follow-up group – the IOP recording documented in their eye note records at the time of starting treatment with travoprost and the last documented IOP measurement in the patient ophthalmic records. Thus the time period between the IOP measurement at baseline and follow-up was greater than the 8-week period used in the new travoprost user group. Participants, who had switched from any other IOP lowering treatment to travoprost without a treatment break, did not have baseline untreated IOP data available.

The mean IOP (in mmHg) from the right and left eye were calculated for both the initial and final visit. For participants using travoprost in only one eye, the IOP measurement from the treated eye was used. The difference in IOP measurements between the initial and final visits was compared to the adherence percentage rate to determine if this revealed a correlation.

2.7 Demographic and clinical information

Demographic and clinical information were obtained by one-to-one structured interview carried out between participant and research assistant. A full copy of the social demographic and medical history questionnaire is provided in Appendix 3. Data collected included date of birth, gender, ethnic origin, employment, level of education, family members affected by glaucoma, marital status, and general medical history.

2.8 Participant trial design issues

On study completion, participants were engaged in a 10 minute semi-structured interview via telephone or face-to-face. Face-to-face was used for the newly prescribed group that were attending their routine two month follow-up visit. Telephone conversation was adopted for any participants, particularly the follow-up group, that were not attending a two month follow-up visit as part of routine care. The interviews were designed to capture participant opinion regarding the following trial aspects:

1. Ease of questionnaire completion and approximate time taken
2. Ease and acceptability of the TDA

The discussion template is shown in appendix 5.

2.9 Data analysis

- The patient population was characterised by using descriptive analysis.
- The magnitude of adherence was reported by using descriptive analysis.
- Cohen's Kappa was used to measure the agreement between the TDA score and patient self-reported adherence.

- A Fisher-exact test was used to measure the association between non-adherence with non-completion of the MMAS and frequency of missed dose questionnaires, and problems encountered with the TDA.
- TDA data were dichotomised into adherent or non-adherent and logistic regression was used to identify possible predictors of adherence.
- Variation in adherence with the TDA monitoring period was identified using ANOVA.
- McNemar tests were used to test for association between satisfaction with information received about travoprost before and after monitoring.
- Spearman's co-efficient tests were used to test the relationship between the number of days using travoprost and satisfaction with information received, and magnitude of difference in IOP and adherence.

2.9.1 Calculation of Travalert® adherence score

The TDA was pre-set with the patient study number and date of birth for identification purposes. The TDA is also set with the patient preferred dosing time +/- 2 hours and whether it was unilateral or bilateral dosing. The electronic data are extracted and adherence calculated by software using the following calculation:

$$Adherence\ score = \left(\frac{No.of\ dosage\ units\ taken\ within\ patient\ specified\ time\ +/-2\ hours}{Expected\ no.dosage\ units\ taken} \right) \times 100$$

However, it is known that the device has the potential to make extra recordings when the lever is depressed erroneously (69). Thus, more than 1 dose taken per eye per day was not counted in the adherence rate calculation, therefore making uni-/bil-ateral dosing irrelevant to the adherence calculation. In addition, the Travalert software relied upon the patient specifying what time they expected to dose +/- two hours, so this could be pre-set at the time of their initial consultation. For the newly prescribed group, they may not have had the opportunity to think about or know how using eye drops would fit into their daily regimen, therefore making discussion about the agreed dosing time particularly difficult and arbitrary. It was felt that if this regimen was not complied with and they actually found that they regularly used their drops earlier or later than this

agreed time, it would suggest that the patient was non-adherent, leading to false reporting of adherence.

Therefore, a mathematical programme that calculated adherence from the TDA data collected from the TDA was designed to calculate the mean time of dosing over the period of monitoring. The use of this programme ensured the TDA could be dispensed to the patient without the need for a pre-specified dosing time, thus allowing the patient to dose at a time to fit in with their own regime, generating a more naturalistic adherence monitor.

However, the TDA data used the 24 hour clock which did not conform to statistical summary measures using means and standard deviations. For example, if a dose was taken at 23:59 the first night and 00:01 the second night, the mean average time would be calculated to 12:00 (noon) when it should be 00:00 (midnight). However, circular data analysis was used to convert time to degrees from which an average degree could be found and then converted back to a time.

The prescribing information for travoprost states that it should be used in the 'evening'. Patients are rarely given any further dosing instructions by their clinicians other than they may be encouraged to use the drops 'before they go to bed'. There is no agreement on the exact time that travoprost should be used and thus an evening dosing time of between 5 pm and 5 am has been assumed. Any dose that falls outside of these time points was classed as non-adherent.

The following calculation was used to calculate adherence % by the adherence calculator:

$$Adherent\ dose = calculated\ mean\ average\ time\ (between\ 17{:}00\ and\ 04{:}59\ hrs) \\ +/-\ 2\ hours$$

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

2.9.2 Identifying predictors of non-adherence

Regression analysis was used to determine the relative importance of any factors identified as being associated with adherence. A linear relationship between measured non-adherence was unlikely to exist given the positively skewed distribution and thus adherence was treated as a dichotomous variable:

- Adherent = if the score is ≥to 80%
- Non-adherent = if the score is < 80%

Logistical regression analysis was used to examine the effect of potential explanatory factor in a univariate model by estimating the odds ratio of adherence along with the corresponding 95% confidence interval and p-value. Forward selection was used to select the independent factors for constructing a multivariate model in a structured fashion.

2.9.3 Examination of poor agreement between participant self-report and TDA adherence measures

A Cohen's Kappa test was used to measure agreement between MMAS and the TDA adherence score. A Fishers-exact test was used to measure agreement between non-completion of the questionnaires and non-adherence. The effects of monitoring adherence on patient self-report was also analysed by comparing the self-reported adherence levels before and after the monitoring period using a McNemar Test.

2.9.4 Satisfaction with information about travoprost

1. SIMS scored from 0 to 14 with a score of 0 indicating complete dissatisfaction and 14, complete satisfaction. A median (IQ) SIMS score was calculated for each participant.

2. A total satisfaction rating was obtained by summing the scores of each item. If participants endorsed the information received by reporting 'about right' or 'none needed', they received a score of 1. If participants were dissatisfied with the information received reporting 'too much' too little' or 'none received', a 0 score was given. Thus scored ranged from 0 to 14 with high scores indicating a high degree of overall satisfaction with the medication information received concerning travoprost.

3. The mean SIMS score for each information profile was compared to reveal if there were any differences in the initial SIMS report and the final SIMS report for each individual.

2.9.5 Association between IOP and adherence

Only those participants who have baseline untreated IOP measurements were used. (In some cases, participants were using a different form of IOP lowering medication before switching to travoprost.) IOP measurements were obtained from the time Travoprost was started through to the last documented IOP measure as recorded in their ophthalmic records. For the newly prescribed group this was at the time of recruitment through to the 8 week follow-up visit where available.

2.9.6 Identify any potential problems with the use of the TDA and questionnaires as reliable measures for use in a full trial

Notes were taken of the participant responses during the semi-structured interview at the end of the study. These transcriptions were analysed using inductive coding and then evaluated for extensiveness. For example, 13 codes emerged for the for the question, how long did it take you to complete the questionnaire; 2 mins, 3 mins, 5 mins, 10 mins, 5-10 mins, 15 mins, 20 mins, 30 mins, "a short time, not long, quickly", and "don't remember completing it".

These codes were then combined to reveal 5 main categories and the number of responses for each category counted. Questions relating to use of the TDA were coded into themes and frequency reported.

Chapter 3

Results

3 Results

3.1 Sample demographics

From the 100 patients invited to participate, 98 consented and completed the necessary documentation. The number of participants stratified to the 'follow-up group' was 49 and a further 49 to the 'newly prescribed group'. Table 3.1 summarises the demographic characteristics of the sample population. It can be seen that the 'follow-up' and 'newly prescribed' groups were well matched in terms of age and gender distribution. The 'newly prescribed' group did however have a greater proportion of employed and those who left school at 16 years of age, whereas the follow-up group had a greater proportion of people with significant previous / current medical conditions.

Table 3.1 Population demographics

		Total cohort (n=98)	**Follow-up group (n=49)**	**Newly prescribed group (n=49)**
Gender	No. (%) Male	51 (50%)	22 (45%)	29 (59%)
Age (n=98)	Years, Median (IQ)	72 (63, 78)	72 (63, 78)	70 (62,78)
Employed (n=92)	No. (%) Yes	72.8 (67%)	25 (51%)	38 (83%)
British (n=97)	No. (%) Yes	96.9 (95%)	49 (100%)	46 (94%)
Married/Partner (n=91)	No. (%) Yes	73.6 (67%)	32 (70%)	35 (78%)
Education (n=90)	No. (%) Left school at 16 yrs	55.6 (50%)	19 (43%)	31 (67%)
Family members with glaucoma (n=79)	No. (%) No	65.8 (52%)	25 (68%)	29 (69%)
Previous / current medical condition (n=91)	No. (%) Yes	58 (63.7%)	33 (73%)	25 (54%)

Further sub-categorisation defined the employment status of the sample population as 25 (27.2%) in paid employment, 66 (71.7%) retired and 1 (1.1%) participant unemployed. The marital status was 68 (74.7%) married, 13 widowed (14.3%), 7 (7.7%) divorced or separated, and 3 (3.3%) single. The education status was 26 (28.9%) had undertaken some form of certification, apprenticeship or diploma, 26 (28.9 %) had left school at age 16, 23 (25.6%) left school before they were age 16, 6 (6.7%) left school at age 18 and 9 (10%) had a degree.

3.2 Data from the TDA

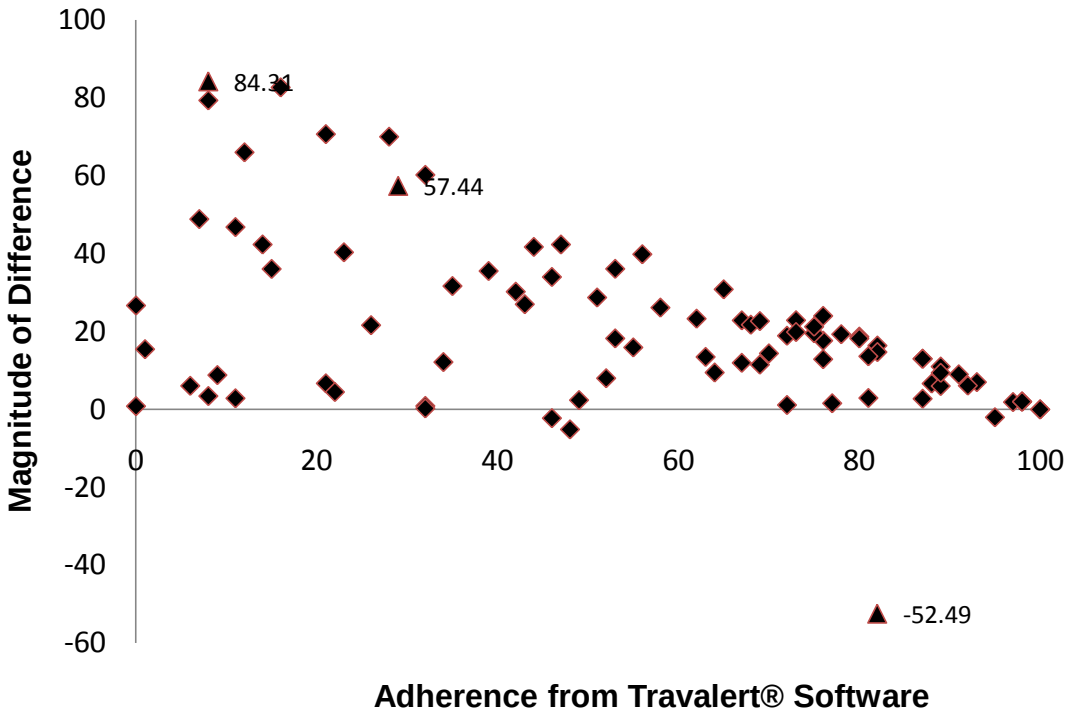
Data from the TDA were collected from 88 participants, TDA data were missing from 10 participants for the following reasons:

- Participant did not return the TDA (2)
- Failure of the TDA (1)
- Participant decided not to use the TDA - preference for manual delivery of drops (4)
- Participant lost to follow-up (2)
- Participant stopped treatment due to illness (1)

3.2.1 Comparison of the Travalert® software adherence calculation and the adjusted adherence calculation

Before accepting the adjusted adherence calculation described in section 2.9.1 as the methodology to report TDA % adherence, a comparison of the magnitude of difference between the % adherence rate calculated by Travalert® software and the adjusted adherence calculator was made (N=88). Figure 3.1 shows the scattergram of these results; the mean difference was 20.33 (SD 21.98); indicating that the calculation of adherence by the adjusted adherence calculator increased the adherence rate.

Figure 3.1 The magnitude of difference between the adherence scores calculated by the Travalert® Software and adjusted adherence calculation



It can be seen that at high levels of adherence, agreement between the two calculation methodologies was good. However, when the Travalert® adherence rate was low, the difference was greater. One notable deviation was a -52.49% difference in adherence as a result of the patient stopping use of the drops after 22 days due to developing a Bell's palsy. The Travalert® registered that 18 of those 22 days were adherent resulting in 82% of doses being adherent. However, the period of travoprost use was actually 61 days thus adherence to the regimen was only 29.51%. At lower adherence levels, however, the most frequent reason for the discrepancies was dosing times being set incorrectly. An example being the 84.31% difference in adherence due to the estimated dosing time discussed at the initial consultation being set too late in the evening. Thus, when the patient actually used their travoprost earlier in the evening, the device only registered 8% of doses being within the 4 hour adherent window. However, the pilot study data calculator averaged the mean

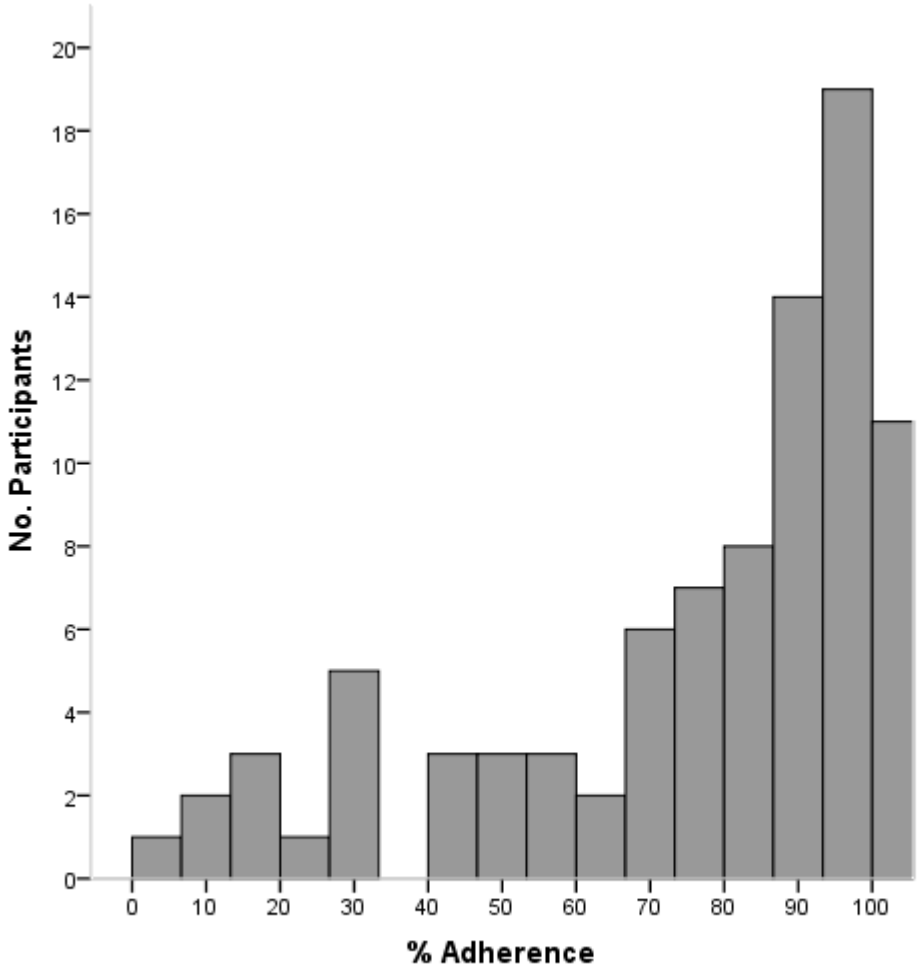
dosing time to be earlier in the evening and thus registered 92.31% of doses as adherent.

Given the deviations between the Travalert® software calculations and adjusted adherence calculations, together with the rationale for these deviations, the adjusted adherence calculator was used for this study to report the percentage adherence score.

3.3 Adherence

Using the TDA adjusted adherence calculation, the median adherence was 86.89% (IQ 60.83, 96.15). Figure 3.2 illustrates the distribution of the Travalert scores for the 88 participants, the positive skew indicating that the majority of participants had high percentage adherence.

Figure 3.2 Distribution of TDA Scores



3.3.2 Comparison of adherence measures

The measure of adherence was collected using three different methods TDA as described in section 2.9.2, MMAS and frequency of missed dose (FMD) as described in section 2.5.1. Table 3.2 compares the results of the three different methodologies. The patient self-report methodologies (MMAS and FMD) found almost 100% adherence. Further examination of the MMAS scores reveals that 72 participants categorised themselves as having perfect adherence, 9 moderate and 1 poor and so using this more sensitive scoring system, greater non-adherence is detected. The FMD questionnaire revealed that 57 participants reported being 100% adherent and 13 being 97% adherent.

Table 3.2 Comparison of adherence using the three different adherence measures

	% non- adherent participants
Travalert Dosing Aid (n=88) ≥ 80% is adherent , < 80% is non-adherent	40.9% (n=36)
MMAS (n=82) = 0/1 is adherent, 2/3/4 is non-adherent	1.2% (n=1)
= 0 is adherent, 1/2/3/4 is non-adherent	12.2% (n=10)
FMD (n=70) ≥ 80% is adherent	0% (n=0)

3.4 Agreement between TDA and self-report

Table 3.3 shows a cross tabulation of both self-report methodologies (FMD and MMAS) compared to the TDA adherence score. A Cohen's Kappa test was used to measure the agreement between MMAS (applying the sensitive scale, only 0 being adherent) and TDA adherence score. The result indicated a slight, but not significant, disagreement. Furthermore, 4 participants have reported non-adherence despite being TDA adherent. This suggests patient over-reporting of non-adherence.

Table 3.3 Comparison between TDA identified non-adherence to self-report measures.

Self Report Measures (n=64)	TDA Adherent (n)	TDA non-adherent (n)	%	Agreement (Kappa)
Morisky adherent	39	20	92.2	-0.056 (p=0.525)
Morisky non-adherent	4	1	7.8	
FMD adherent	43	21	100	N/A
FMD non-adherent	0	0	0	

3.5 Examination of poor agreement between participant self-report and TDA adherence measures

Only 70 participants completed the final FMD questionnaire and 82 participants completed the final MMAS questionnaire. Table 3.4 illustrates the distribution of self report respondents compared with TDA recorded adherence.

Table 3.4 Association of non-completion of the Morisky and FMD questionnaire to adherence.

	TDA (N=88)		Association (Fishers Exact)
	Adherent n (%)	Non-adherent n (%)	
Final MMAS Questionnaire (n= 82)			
Completed (84%)	47 (53)	30 (34)	p = 0.346
Not-completed	5 (6)	6 (7)	
Final FMD Questionnaire (n=65)			
Completed (66%)	43 (49)	22 (25)	p = 0.029*
Not completed	9 (10)	14 (16)	

*Statistically significant

The results revealed that more non-adherent participants did not complete the final FMD than the final MMAS questionnaire. There was a statistically significant relationship between not completing the Final FMD Questionnaire and non-adherence, suggesting that adherence might affect completion of this questionnaire. It is not known why more people completed the final MMAS questionnaire, but as the percentage rate of those completing the questionnaires was lower for FMD Questionnaire any further analysis would be biased.

3.5.2 Effect of the TDA on self reported adherence

The initial and final MMAS questionnaires were fully completed by 37 participants. Using the sensitive MMAS score (0 score = adherent, 1/2/3/4 = non-adherent), the initial MMAS questionnaire identified 13 (13.3%) participants as non-adherent and the final MMAS questionnaire identified 8 (20.5%) participants. A matched pairs test comparing the initial and final MMAS scores found no difference in self-reported non-adherence after 2 months of monitoring ($p = 0.125$, McNemar Test). Of the 24 participants completing the initial and final MMAS there was one participant initially reporting to be adherent who then reported non-adherence after 2 months, and those reporting non-adherence initially were still reporting non-adherence after 2 months. The results suggested that monitoring with the TDA did not affect adherence.

3.6 Demographic characteristics

The following comparisons between demographic characteristics and other possible predictors of adherence were carried out using adherence as a dichotomous variable. Due to ethnicity of the group being predominantly a British population (97%), the effect of ethnicity on adherence was not analysed. The results are summarised in table 3.5.

Table 3.5 Comparison between adherence and demographic characteristics

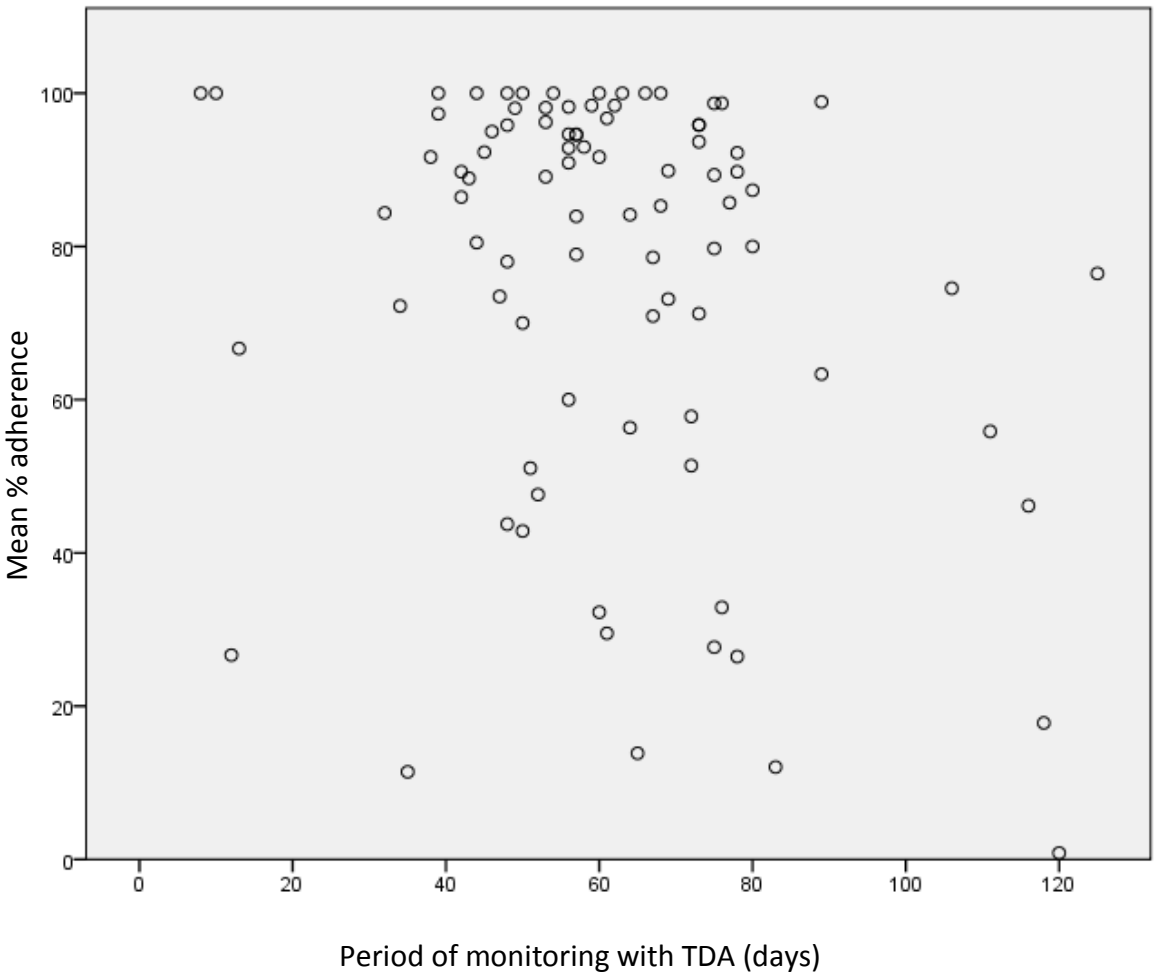
	Adherent		Unadjusted		Selected*	
Variable	**Yes**	**No (%)**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Gender						
Male	26	20 (43.5)	1.25 (0.53,2.93)	0.608	-	-
Female	26	16 (38.1)	1			
Age						
Mean age	71	71	0.995 (0.95, 1.04)	0.836	-	-
Education						
Left school <=16	30	17 (36.2)	0.79 (0.33,1.93)	0.610	-	-
Further Education >16	21	17 (41.7)	1			
Marital status						
Married/partner	33	26 (44.1)	1.688 (0.60, 4.75)	0.321	-	-
Not married / partner, widowed or single	15	7 (31.8)	1			
Employment						
Employed	34	27 (44.3)	0.63 (0.22, 1.78)	0.383	-	-
Not employed/retired	14	7 (33.3)	1			
Administration of travoprost						
Self administered	34	23 (40.4)	1.353 (0.47, 3.87)	0.573	-	-
Administered with help	14	7 (33.3)	1			
Previous / current medical conditions						
Yes	32	23 (41.8)	1.366 (0.54, 3.48)	0.513	-	-
No	19	10 (34.5)	1			
Medication naïve						
Yes	11	4 (26.7)	1.932 (0.55, 6.74)	0.301	-	-
No	37	26 (41.3)	1			
Other medication administered at same time as travoprost						
Yes	10	5 (33.3)	0.643 (0.19, 2.17)	0.476	-	-
No	27	21 (43.8)	1			

	Adherent		Unadjusted		Selected*	
Variables	**Yes n**	**No (%) n**	**OR 95%**	**p-value**	**OR (95%)**	**p-value**
Family member with glaucoma						
Yes	13	11 (45.8)	1.862 (0.68, 5.10)	0.227	-	-
No	33	15 (31.3)	1			
Additional information about glaucoma sought from independent source						
Yes	15	9 (37.5)	0.990 (0.37, 2.68)	0.984	-	-
No	33	20 (37.7)	1			
Problems experienced using eye drops						
Yes	15	13 (46.4)	1.787 (0.69, 4.64)	0.232	-	-
No	33	16 (32.7)	1			
Period of travoprost usage						
Mean period of use in days	339	383	1.000 (1.00, 1.00)	0.682	-	-
Total Satisfaction with SIMS						
Mean score	9	8	0.897 (0.79, 1.02)	0.088	-	-
Difference in level of IOP after 2 months						
Mean IOP in mmHg	6	7	1.030 (0.94, 1.13)	0.517	-	-
Period of monitoring days						
Mean no. of days	57	94	1.026 (1.00, 1.05)	0.024	1.076 (1.01, 1.15)	0.022

***using forward selection**

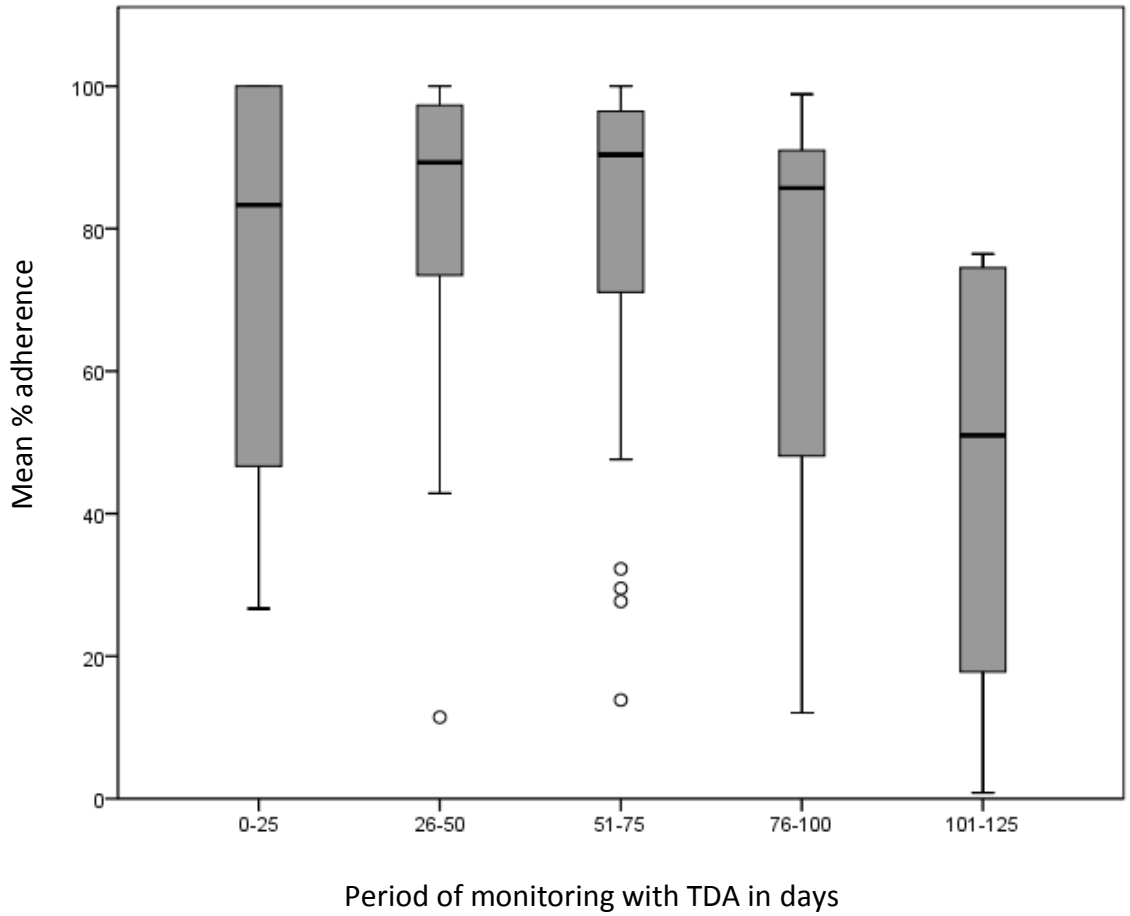
Period of monitoring days was the only independent factor of significance affecting adherence. The scattergram in Figure 3.3 shows that the longer the period of monitoring, the greater the level of non-adherence. A Spearman's rho correlation analysis shows r=-0.236; p=0.028.

Figure 3.3 Comparison of % adherence and period of monitoring with the TDA.



However, adherence appeared to decline after 100 days of monitoring. Thus, rather than looking at the correlation as a linear trend, the period of monitoring was split into quintiles. The mean percentage adherence of each quintile was plotted to look at a non-linear trend. The results are shown in Figure 3.4 and the highest percentage adherence was for participants who were monitored for 51 – 75 days (n=44), which was the target period of monitoring for this study (42-70 days), but greater non-adherence was seen after 100 days of monitoring (ANOVA F=2.970, p=0.024). However there were only 6 participants monitored for 101-125 days.

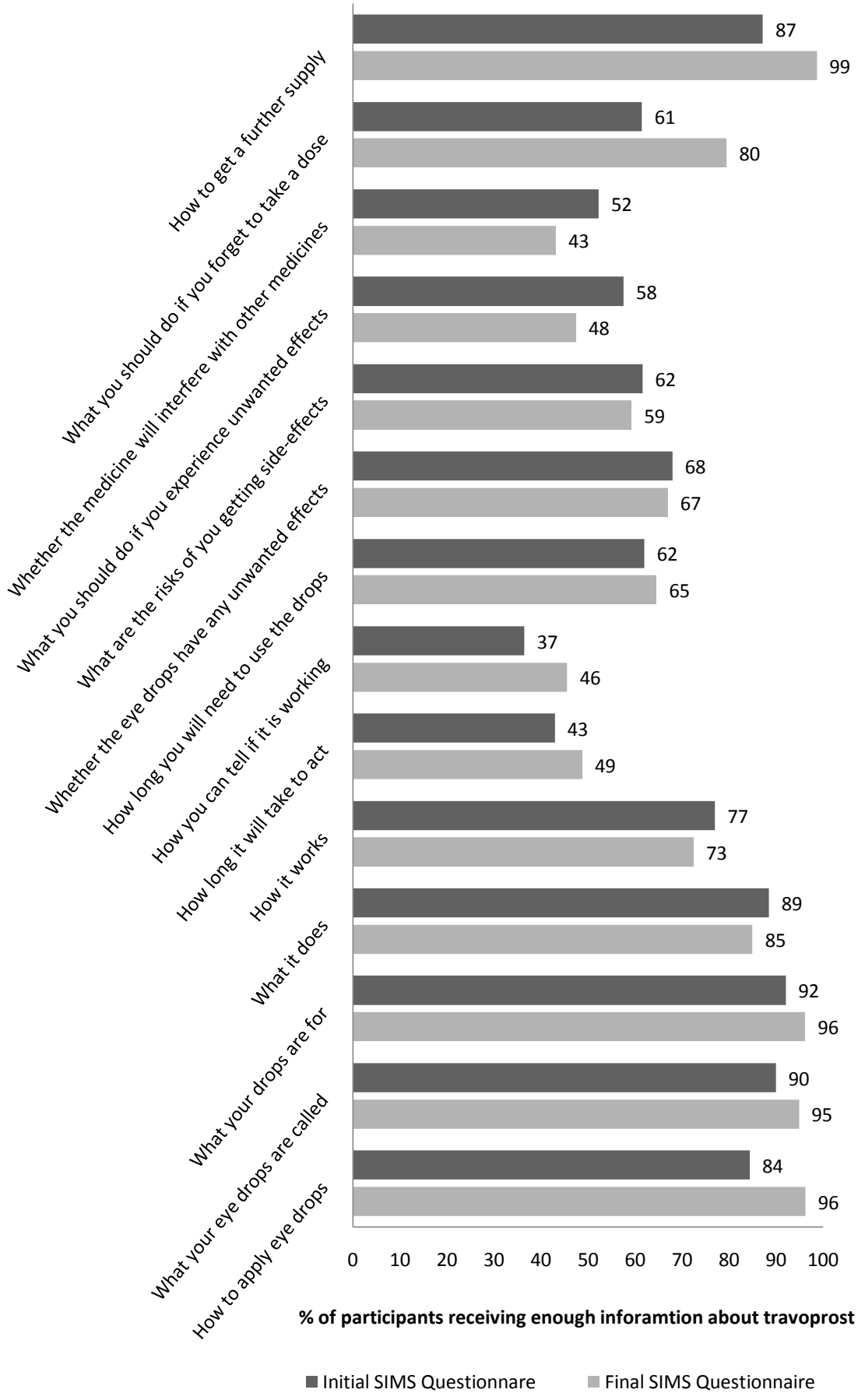
Figure 3.4 Comparison of % adherence and period of monitoring with the TDA using quintiles



3.7 Satisfaction with information about travoprost

The initial satisfaction with information about travoprost questionnaire was completed by 90 participants. Scores can range from 0 to 14 with high scores indicating a high degree of overall satisfaction with the information received about travoprost. The median SIMS score for this group was 8.5 (IQ 5, 12). The final satisfaction with information about travoprost questionnaire was completed by 83 participants, with a median of 9 (6, 11). The results for both questionnaires are shown in Figure 3.5.

Figure 3.5 Comparison of the initial and final SIMS questionnaire results



3.7.1 Baseline SIMS

Participants were more dissatisfied with the information received at the beginning of the study as reported in the initial questionnaire. The lowest satisfaction scores were reported for 'how to tell whether the medication is working', 31 participants (n=85) reported being dissatisfied and 'how long it will take to act', 37 participants (n=86). The highest satisfaction with information received was reported for 'what your drops are for' reported by 82 participants (n=89).

3.7.2 SIMS at completion

In general, participants were more satisfied with information received at the end of the study, reported in the final questionnaire. At this time point, the lowest satisfaction with information given was 'whether eye drops will interfere with other medications' 35 participants (n=81) reporting dissatisfaction. Conversely, the greatest satisfaction was reported by 78 of participants (n=79) with the information received about 'how to receive a further supply of eye drops'.

The most substantial differences were for 'How to obtain a further supply of eye drops', 11 people (12.8%) were not satisfied with this information initially but after two months only 1 participant (1.3%) was not satisfied with this information (no McNemar analysis possible), 'how to apply eye drops', 14 participants (15.6%) were not satisfied with this information but after two months only 3 (3.7%) were not satisfied (p=0.012), and 'what you should do if you forget to take a dose' had reduced from 32 (38.6%) participants to 16 (20.5%) (p=0.007). In a further 4 categories the satisfaction of information increased over the two months but no significant association was shown. Conversely, in 7 categories participants reported being less satisfied about their medication information after two months, but no significant association was evident.

In addition, since there were two different groups of participants (the newly prescribed travoprost group and the follow-up travoprost group), possible

differences in these two groups were analysed. There was no significant relationship (Spearman's correlation coefficient) between the number of days that a patient had reported receiving travoprost therapy and satisfaction with information received (r=0.039, p=0.720).

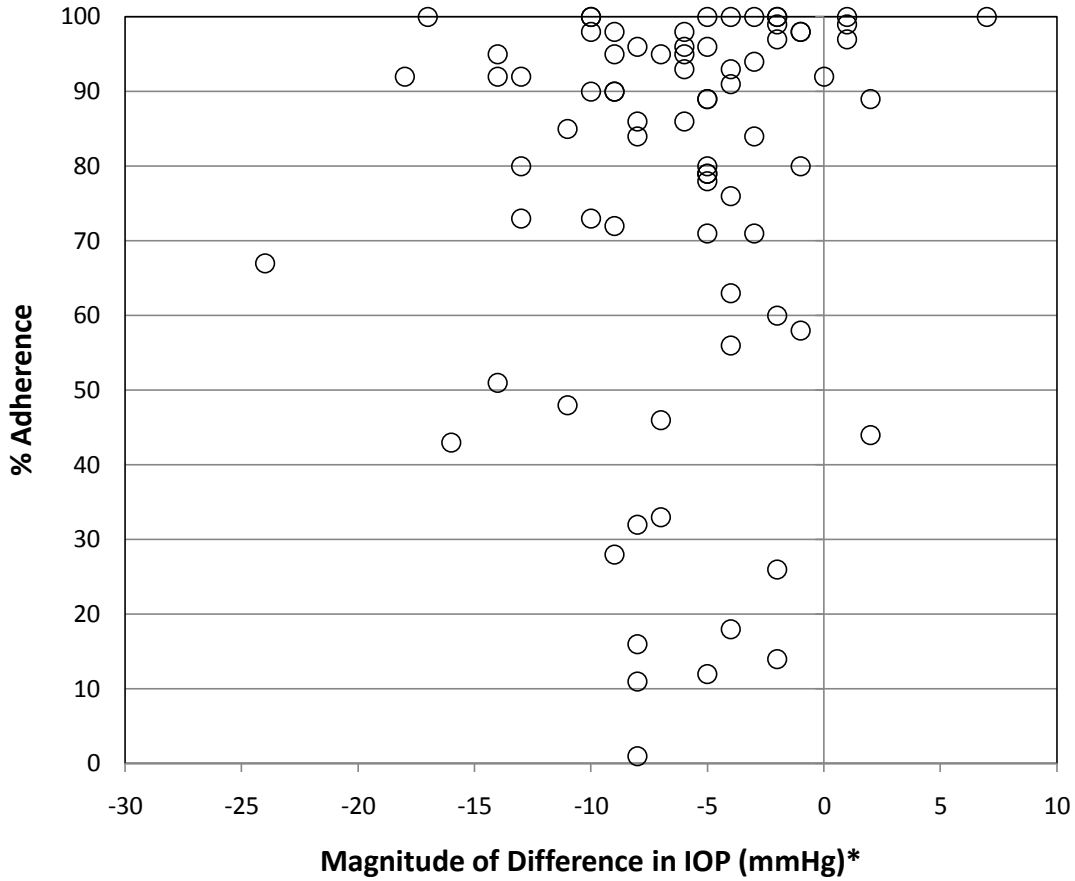
3.8 Association between IOP and adherence

Data were available for 88 participants, 40 from the follow-up group and 48 from the newly prescribed group. Data were missing for the following reasons:

- No baseline untreated IOP available due to switching to travoprost from another IOP lowering eye drop (10, follow-up group)
- No follow-up data (1, newly prescribed group)

Participant baseline untreated IOP (in mmHg) was compared with final IOP measurement to calculate the magnitude of difference. Figure 3.6 shows the correlation between percentage adherence rate and magnitude in IOP difference. A Spearman's rank correlation confirmed a weak, non-significant correlation of r=0.155; p=0.179.

Figure 3.6 Correlation between percentage adherence rate and difference in average IOP at baseline (untreated) and completion (treated).



*Mean IOP of both eyes if both eyes treated or, one eye if only one eye treated.

In order to investigate if period of travoprost use was the reason for the weak correlation, the cohort was split into its two groups. The newly prescribed group difference in IOP measurement was calculated over period of 368 days (IQ range 56, 560) and the follow-up group 646 days (IQ range 197, 918). A Spearman's rho correlation analysis showed a weak positive correlation r=+0.088; p=0.627 for the follow-up group. The weakest positive correlation of the two groups was seen in the newly prescribed group of r=+0.034; p=0.826). The results suggest that the difference in time elapsed between baseline and follow-up measure had no effect on the correlation between IOP reduction and level of adherence.

With evidence to suggest that in some cases, particularly in patients with NTG, the magnitude of reduction in IOP can be an arbitrary measure and because no correlation was found with magnitude of difference in IOP from untreated to treated IOP measure, the final IOP measure was correlated with the percentage adherence rate. A Spearman's rho correlation analysis showed a weak positive correlation of r=+0.106; p= 0.358. The 30 non-adherent participants had a slightly lower mean IOP (15.9 ± 4.1) and the 47 adherent participants had a higher mean IOP (16.4 ± 4.5), this being the opposite of what would be expected. These results suggested that level of IOP and magnitude of reduction in IOP cannot be used as an indicator of adherence.

3.9 Potential problems with the use of the TDA

Data were available for 93 participants, but not all participants answered every question during the discussion. Table 3.6 summarises the comparison between the newly prescribed and follow-up groups. To test for functionality of the TDA on the TDA adherence measure itself, a Chi-Squared test showed that problems with the device, inconvenience and difficulty of use did not have a significant effect on adherence.

Table 3.6 Summary of participant views of TDA use and affect on adherence.

Use of the TDA	New Group	Existing Group	Fishers-Exact	Total Group (n=69)*	
	No n (%)	No n (%)		Non-adherent n (%)	Chi Squared
Were there any problems? (n=84)	29 (66)	29 (66)	(p=0.638)	10 (15)	(p=0.237)
Was it convenient? (n=80)	4 (10)	12 (29)	(p=0.050)	7 (10)	(p=0.134)
Was it easy to use? (n=75)	2 (6)	12 (31)	(p=0.007)	7 (10)	(p=0.134)

*Incomplete data as TDA data only available for 88 participants and not all participants answered every question regarding TDA usage.

The majority of participants had no problems using the TDA and that it was convenient and easy to use. The follow-up group found the device less convenient and less easy to use than the newly prescribed group, but both groups encountered the same amount of problems with the TDA. The problems encountered with the TDA are summarised in Table 3.7. No participants reported any problems with loading the TDA with their travoprost eye drop bottle or changing it after 28 days of use.

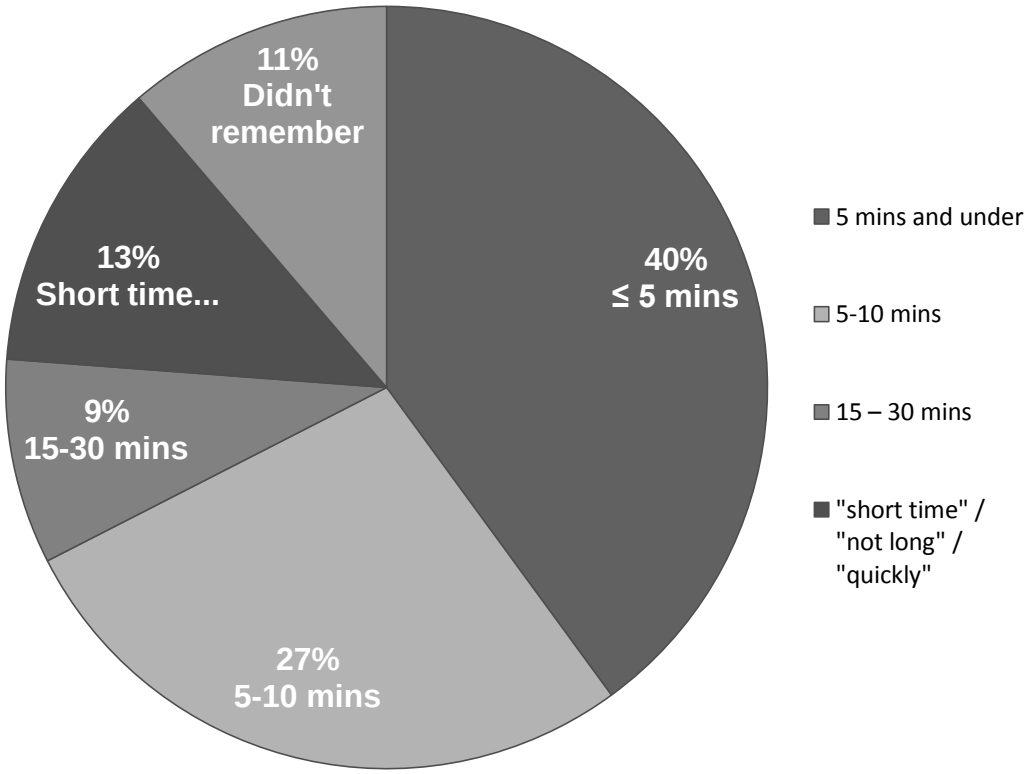
Table 3.7 Summary of problems encountered with the TDA

Dispensing issues n=38	**No (%)**
Didn't dispense drops consistently	18 (47.3)
Sometimes you have to press lever more than once	8 (21.1)
Too slow to dispense drops	3 (7.9)
When bottle becomes empty you need to tap it to release the drop	1 (2.6)
Difficult to know if lever has been pressed properly	1 (2.6)
Device didn't dispense when 2/3 empty so was wasteful	2 (5.3)
Didn't always work when dosing the second eye	2 (5.3)
Had to shake it to get drop out	2 (5.3)
Concerned that maybe too much coming out	1 (2.6)
Reason for non-use n=13	**No (%)**
Stopped using it as felt it didn't work properly	3 (23.1)
Prefers to deliver drops manually	6 (46.2)
Kept poking eye with it so stopped using it	1 (7.7)
Patient never even tried device decided it would be easier by hand	1 (7.7)
No feeling in fingers and had to stop using it	1 (7.7)
Threw device away - didn't like using it	1 (7.7)
Other n=19	**No (%)**
Didn't like using the eye guide	16 (84.2)
Sometimes forgot to remove lid	2 (10.5)
Not convenient when travelling	1 (5.3)

3.10 Potential problems with the use of the questionnaires

Data were available for 85 participants. The time taken for participants to complete the questionnaire is summarised in figure 3.7.

Figure 3.7 Time taken for participants to complete the initial questionnaire



All participants (89%) completed the initial questionnaire within 30 minutes, with 80% reporting achievement within 10 mins or a time frame considered “short”, ‘not long’ or ‘quickly’. The remainder of participants reported that they did not remember completing the questionnaire. The results from the discussion questions found the majority of participants had no problems completing the questionnaire; 70% did not encounter any problems with the questionnaire, 74 % did not find any questions difficult to answer and 74% were sure about what information questions were requesting.

Chapter 4

Discussion

4 Discussion

The relationship between adherence and sociodemographic factors such as age, sex, race, intelligence and education remains complex, and thus a random selection of participants was appropriate. Unfortunately, due to a largely White British cohort the findings of the present study may not be generalisable to all UK populations since ethnicity has been associated with adherence (23). Further studies are needed to investigate the effect of ethnicity on adherence with anti-glaucoma therapy.

Adherence studies may be fundamentally biased by the very selection of patients who attend follow-up care appointments. Non-adherent patients are more likely to drop out of follow-up care and thus be missing from random selection (85). Although it is not possible to account for those patients who had dropped out of care, it can be demonstrated that non-adherent participants had contributed to the findings through some participants' own admission of non-adherence. Theoretically, the sample was made up of more adherent patients (those who attend follow-up care being those more likely to be in the sample and agreeable to taking part in such a study); the magnitude of non-adherence may be even greater in the wider UK glaucomatous population than represented here. Thus, caution must be taken when extrapolating these results.

The TDA is limited to the use of travoprost, and thus this guided our study design to only include participants requiring travoprost. Although this could have been a limiting factor, it was standard practice for all newly prescribed patients to be given travoprost at this out-patient clinic at the time of carrying out this pilot study and thus was of no consequence. However, findings can only be generalised for the patient population using once daily prostaglandins, rather than more complex dosing regimes that some glaucoma patients may be using.

Despite the potential limitations, the sample selected provided a good representation of the UK population demonstrated by an appropriate gender, educational background and employment status distribution. Furthermore, the age range was illustrative of a glaucomatous population (16).

The results were also encouraging in terms of the ease with which the TDA was reportedly used and that there was no demonstrable impact on adherence accepting the limitation of a before and after study. These findings endorse previous reports of TDA use which found that 97% of recordings were accurate in novice TDA users (69).

In pre-study testing, it was thought possible for patients to dose by only partially depressing the lever on the TDA without the TDA actually recording the dose. This has not been reported in any previous literature that has assessed the use of the TDA. To overcome this problem for the present study, participants were instructed to depress the lever all the way down. This 'intervention' might have heightened participant awareness of being monitored, which is a disappointment when the TDA had the potential to be a more discrete monitoring device. Future studies should account for these possible inadequacies and ensure that patients are instructed appropriately to avoid misuse of the adherence recording aspect of the device.

As previous studies have reported that the TDA can make extra erroneous recordings (69), in the present study, if more than one dose appeared to have been taken per day, this was not counted in the percentage adherence calculation. Therefore, it was not reliable in assessing if the correct dosing was applied each day. This is a limitation of using the TDA to assess adherence, since it means over-adherence cannot be reliably recorded. Although the methodology is not fully described, Ajit *et al*. (34) also reported using an adjusted adherence measure for the TDA, treating multiple recorded doses within a 4-hour time period as a single dose.

During the two months of follow-up, missing data were primarily due to participant non-use of the device or not returning the device for data retrieval. Thus, at recruitment in any future studies, it should be made clear to participants that they must be prepared to pursue TDA use during the study period and be encouraged to ensure it is returned for collection of the data. Or, it may be appropriate to screen patients for ability and willingness to use the TDA prior to study inclusion to minimise subsequent drop out.

In addition, the TDA data works on the assumption that the eye drops were successfully dosed, when all that can really be inferred is that the patient attempted a dosing event at a specified time. There is no way of knowing that the eye drop was successfully administered. Indeed, the study by Gupta *et al.* (38) found that 9 out of 10 participants were unable to instil their drops correctly and Robin *et al*. (36) suggested that 60% of experienced glaucoma participants were unable to instil the correct number of eye drops when observed. This is an additional problem, which is virtually unavoidable at present.

The mean adherence rate for the group calculated by the TDA was slightly higher than the findings of previous studies using the TDA. (Okeke *et al.*, 71% (70) and Ajit *et al.*, 80% (34), both over a 3 month period). The lack of agreement with the TDA adherence rate and participant self-report of adherence is consistent with previous studies and revealed that participant reported non-adherence was below that of the TDA in the majority of cases (34, 70). Self-report of adherence is said to be unreliable since patients tend to overestimate adherence (86). The reasons why patients tend to over report adherence are thought to be due to participants feeling uneasy about admitting non-adherence, or simply being unable to report a missed dose (77). If non-adherence is due to forgetfulness, a forgotten dose is unlikely to be remembered for reporting purposes. Thus to reduce memory errors, the length of recall period should be minimal. This study asked participants to recall frequency of missed doses over the past month. A future study should use a one week recall period as suggested by Svarstad *et al.* (77).

No literature has been identified that discusses over-reporting of non-adherent behaviour and therefore, it is of interest that the present study found over-reporting of non-adherence using the MMAS Questionnaire. The MMAS Questionnaire is based on phraseology of the questioning bearing positive answers, since healthcare providers usually phrase their questions in such a way that the answer they want to hear is “yes” (the concept of ‘leading questions’). The MMAS measure has been shown to have 69% accuracy but only 44% sensitivity (53). However, MMAS has been linked to positive clinical outcomes in hypertension studies. The possible lack of sensitivity when used in the present pilot study may be due to a number of reasons. The participants in Morisky’s cohort (53) had previously been on blood pressure treatment for an average of 6 years whereas 50% of our study population were newly prescribed patients. Furthermore, the wording of the questions were adapted for the use of eye drops and referred to eyes rather than asking patients to report on more general feelings and may have contributed to the anomaly. However, it is known that treatment does not aid any symptoms of glaucoma; in fact, the preservative within the drop itself, a subsidiary ingredient, may make the eye feel more dry and uncomfortable, whilst the positive IOP-lowering effect of the drop remains unnoticed. Thus, it may be that the MMAS questionnaire was not a suitable measure of adherence for patients with glaucoma and OH, such as those involved in the present study.

It was of interest that some sections of the questionnaire were not completed by participants. The FMD uses a direct questioning of possible non-adherence (i.e. ‘how many times do you miss a dose’), whereas the MMAS seeks to acknowledge attitudes towards adherence behaviour. Thus, the approach of direct questioning of non-adherence could have caused some participants to omit this question, in order to conceal the adverse information about themselves (87). These reporting errors suggest that questions may need to be worded more carefully to reduce the threat and embarrassment experienced by patients who want to make a good impression. Despite guaranteeing anonymity and allowing completion at home, to help participants feel at liberty to report non-adherence in the present study, it is not possible to determine exactly why these parts of the questionnaire where not completed, but if inferred that those participants who failed to complete these sections of the questionnaire had not

done so due to the potential embarrassment of reporting non-adherence, a greater level of association between self-report and TDA adherence scores may have been reported.

It is likely that the two questionnaires used in the present study did not have the required sensitivity to detect non-adherence, particularly as there was no agreement between the measures, rather than the fault lying with the TDA over reporting non-adherence. However, the comparison of self-reported non-adherence using MMAS before and after monitoring suggested that use of the TDA did not affect patient medication taking behaviour. However, it is suggested that a longer period between reporting the initial and final self-report of adherence should be used in future studies, since in the present study the period of monitoring was shown to have a negative effect on adherence.

Svarstad *et al.* suggest that multiple self-report tools are needed to detect all the different types of non-adherence. The more minor, sporadic dosing errors are more difficult to detect as they are unintentional and thus often erratic when compared to repeated dosage errors which stem from intentional behaviour traits (77). The type of observed adherence is an important factor in understanding patient behaviour and adds complexity in interpreting results that can be useful for clinical use. A recent study by Ajit *et al.* (34) developed the concept of graphically presenting inter-dose intervals of adherence data. Ajit *et al.* used this data in order to categorise types of adherence behaviour patterns that may be useful for clinical management of patient adherence. Although there was only a small sample size (n=37) they concluded that the TDA provided valuable data, which could be used to show the patterns of adherence to therapy with travoprost. Development of a similar computer programme used by Ajit *et al.* should be explored in order to compare the adherence categorisations suggested from their study results with a larger cohort.

The lack of association between simple demographic characteristic and adherence had been commonly cited (23, 59, 62, 88-90) and is further reinforced by the findings of this study. The only significant predictor of adherence was monitoring period. As the first reported study of this duration

and size there, is limited scope for comparison however, the smaller study conducted by Ajit *et al*. (34) reported similar findings.

Previous studies have shown that there is a significant association with knowledge about glaucoma and adherence (59, 62, 89, 90). The present study looked at the effect of SIMS rather than knowledge of glaucoma. It has been recognised that provision of information about medication enables patients to understand the risks and benefits and their appropriate use (80). Although it was not statistically significant, the present study showed that greater adherence correlated with greater satisfaction with information about medication. Participants desired greater information regarding action and usage of travoprost, particularly how long travoprost takes to act and how to know that it is working.

However, this study was not evidencing an educational intervention and thus little variation in satisfaction was expected and therefore significant associations with adherence unlikely to be identified. The results of the present study suggest that use of the SIMS questionnaire in any future adherence intervention study is acceptable to patients and feasible.

Ajit *et al.* found in those completing 75 days of monitoring, the mean average adherence rate was 96% in the first 10 days of monitoring, reducing to and remaining at 86% after 30 days (34). The behaviour of a sample population in any study could be influenced by participation alone; a participant may become more interested in their disease and ask more questions than they would normally do (the Hawthorne effect) (58). Participants of adherence studies may adopt a different medication taking behaviour with the knowledge that they are being assessed. However, it is thought that the Hawthorne effect subsides with time and that patients are unable to keep up this simulated behaviour for long periods with a tendency to revert to habitual behaviour after a certain period of time (56). The latter effect may be the reason for the altered adherence rate seen after 100 days of monitoring in the present study. Reardon *et al.* found

that persistence with glaucoma treatment significantly reduced after one year for newly prescribed patients (91). Thus, the period of monitoring is an important aspect in the design of adherence studies; the longer the study, the more normal characteristic medication-taking behaviour will become evident as the Hawthorne effect diminishes. Future adherence studies should consider longevity in order to study more naturalistic medication-taking behaviour where possible.

Lowering IOP to reduce or halt the progression of glaucomatous disease is the only accepted intervention available to clinicians. Topical medication (eye drops) used to reduce IOP offers an effective treatment and remains the most commonly used first line treatment option for patients with glaucoma or OH requiring therapy. If the eye drop regimen were adhered to, a reduction in IOP would be expected on repeat measurement. However, the percentage decrease would be different for each individual; dependent upon the type of presenting glaucoma (i.e. high or normal pressure glaucoma), efficacy of the particular class of eye drop used (e.g. prostaglandin or beta-blocker) and the response shown by each individual. Measuring the level of IOP to confirm a reduction in IOP is standard practice and it would, therefore, seem logical that a reduced level of IOP would correlate with adherence. However, the results of the present study found no significant difference in mean IOP between the adherent and non-adherent group, and no association between magnitude of adherence and reduction in IOP between untreated and treated IOP. Although there should be a relationship *a priori* between IOP and adherence this has not yet been identified in previous research (23) apart from in the study by Konstas *et al.* (35). Konstas *et al.* found that their non-adherent group of patients had a significantly higher mean IOP than their non-adherent study group. However, their study population consisted of 48% participants with pseudoexfoliation glaucoma, a type of glaucoma known to present with higher IOP and with greater fluctuations in IOP over a 24 hour period than patients with POAG.

It is clear that individual differences and the type of glaucoma will add to the 'noisiness' of the data when trying to correlate adherence with reduction in IOP.

Thus, to eliminate ‘noise’ from the data, it would be beneficial to identify the type of glaucoma and presenting IOP (and its fluctuation) for each participant, particularly as ocular hypotensive therapy not only aims to reduce IOP, but also reduces diurnal fluctuation of IOP.

Another factor introducing ‘noise’ to the data is the time of day that the IOP is measured. It has been suggested that, since IOP has a diurnal variance, participants’ IOP should be measured at the same time point on repeat recordings. However, there is evidence that the diurnal variation (at least in normal eyes) has different patterns from day to day (92) thus adding to the difficulty in utilising ‘random’ IOP measurements as a measure of adherence. In the study published by Konstas *et al.* (35), instead of calculating the difference in IOP between presenting untreated IOP and the follow-up treated IOP, the authors simply measured the treated IOP and calculated the mean IOP level for the adherent group and the non-adherent group.

It is also known that, for reasons yet to be fully explained, that ocular hypotensive medications have a variable degree of effect in individual eyes, a proportion of patients being complete non-responders. Poor responders may, of course, be very adherent with their medication, but measuring IOP will not offer a useful method to determine the level of adherence for such individuals. It is common that patients showing an apparent poor response to initial therapy will be offered a different class of ocular hypotensive, until a medication or combination of medications is found to be effective. The inclusion of patients known to have a poor response to treatment when attempting to analyse for a correlation between adherence and reduction in IOP will produce rogue data. In real life, the situation is compounded by the fact that non-responders to topical medication fall into a number of groups including non-adherers, true non-responders and those whose presenting IOP was at a trough level in their diurnal curve and the treated follow-up IOP at a peak level, making the apparent reduction appear small.

The recommendations for future studies to examine the role of IOP and adherence would follow these guidelines:

- Group patients according to
    1. diagnosis: e.g. POAG/NTG/Pseudoexfoliation glaucoma
    2. Presenting level of IOP (i.e. high and normal)
- Only use patients where drop efficacy has been established

However, after establishing these guidelines, it must still be taken into account that patient dosing soon before the IOP measurement will have the most crucial impact on the level of IOP. An individual could, for example, be adherent in the period leading up to assessment, but not adherent and persistent throughout the whole follow-up period. With respect to travoprost (ideally used the evening before a clinic visit) if a dose is missed on the day prior to assessment it is likely that the IOP will be higher even if the patient has remained 100% adherent for the rest of the monitoring period. Conversely, the poorly persistent patient would have a low IOP if they did administer a dose the night before the clinic visit. The very fact that a patient is due for a clinic visit is in itself a significant reminder to the patient that a drop must be taken the night before. To examine the existence of this phenomenon further, the patterns of dosing frequency using the TDA data could be used to elicit if a correlation existed between increased adherence around the time of follow-up clinic appointments.

An alternative method, would be to measure patients' IOP controlled days within a given time period, as opposed to using single IOP readings from single clinic visits. This would mean taking an IOP reading every day, perhaps at the same time, in order to establish if the IOP were to be at target. This would be more accurate, but logistically less practical, if using the gold standard Goldmann tonometry test that requires topical anaesthetic and an experienced clinician (18). In some chronic conditions, such as diabetes and hypertension, patients have access to self-assessment equipment such as glucose and blood pressure monitors, thus helping patients to have better autonomy with regards to the management of their condition. However, IOP self-measuring devices such as

the ICARE® are expensive and still difficult to operate upon oneself in order to guarantee accurate results. Thus, at present, patient self-regulation of IOP is not a realistic option and may often leave the patient, who would like to be more involved the management of their glaucoma, unable to do so. However, there is potential for researchers to use a device such as ICARE® to obtain measures of IOP controlled days if patients were trained to use such devices themselves.

The technique of self-monitoring of IOP would be particularly useful for patients where fluctuation of IOP is thought to be significant. Adherence to medication would be assumed for these patients were IOP to remain at a constant level without significant diurnal peaks and troughs. For partially adherent patients, the starting and stopping of ocular hypotensives in itself is thought to have the potential to cause greater harm because the fluctuation of IOP would be accentuated by periods of no therapy and unnecessary IOP peaks. Controlled IOP days is thus a better measure of clinical outcome than a measure of IOP at one specific time point within the day. For high pressure glaucoma patients, a better measure of clinical outcome would be to record if the IOP lowering treatment has enabled the patient to reach their target IOP of 30% reduction of IOP from the baseline measure on multiple occasions.

The ultimate device to aid the assessment of IOP control, with the added advantage of offering the potential to assess adherence with respect to IOP, would be a system that would enable continuous IOP monitoring. At present, continuous IOP monitoring devices remain experimental, but in the future these may become extremely useful for routine clinical practice and in research (93).

The complexity of using IOP as a measure of adherence calls into question its current feasibility, particularly when other measures of adherence appear both more practicable and reliable. At present, clinicians must accept that one good IOP measure within the target range reading does not constitute good adherence by any means, nor does a higher than expected reading equate to

poor adherence - drop efficacy, type of glaucoma and frequency of missed doses must all be considered.

4.1 Conclusions

Since adherence has been shown to be affected by the period of monitoring, future studies should aim to measure adherence for more than 100 days to establish if adherence is maintained long term. In addition, the level of adherence needs to be measured against clinical outcomes expected for glaucoma patients. Presently, the 80% adherence goal is based on recommendations for the therapeutic control of hypertension, rather than for glaucoma itself. As reported, robust short-term measures of clinical outcomes are problematic to achieve and thus longer-term studies of adherence to glaucoma medication and its affect on measurable clinical outcomes such as optic nerve damage and visual field loss are required.

This study has provided preliminary evidence that use of the TDA does not significantly alter patient eye drop use behaviour. The TDA, despite its reported limitations, can provide valuable data regarding patient adherence to glaucoma medication. Where previous studies have failed to use effective methodologies, the TDA offers an objective adherence measure for future studies. The TDA offers the additional benefit that it records the exact patient dosing times. It therefore offers clinicians and researchers an exceptional tool for gathering adherence behaviour patterns rather than just being limited to percentage adherence data. Thus, the TDA may be useful as an aid for clinical management decisions, particularly if the data can be represented in a meaningful way, such as a graphical representation of patient adherence.

The educational needs of glaucoma patients in relation to adherence to eye drops still remains poorly understood. Using the TDA for glaucoma educational intervention studies has the potential to provide a greater understanding of

patient drop-taking behaviour and adherence enabling healthcare practitioners to focus information and educational support to glaucoma patients. Furthermore, it may help to identify predictors of poor adherence, enabling identification of vulnerable individuals for additional support.

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Appendix 1 Ethical Committee Approval

National Research Ethics Service

Norfolk Research Ethics Committee
c/o The Norfolk & Norwich University Hospitals NHS Foundation Trust
East of England REC Office [2]
Room 2.08 First Floor
Aldwych House
57 Bethel Street
NORWICH
NR2 1NR

Telephone: 01603 289813
Facsimile: 01603 286573

19 February 2009

Mr David Charles Broadway
Consultant Ophthalmologist
Norfolk & Norwich University Hospital NHS Foundation Trust
Colney Lane
Norwich, Norfolk NR4 7UY

Dear Mr Broadway

Full title of study: **A pilot study to examine the ease of use of the Travalert and identify simple questionnaires to be used in the Glaucoma Adherence Study.**

REC reference number: **09/H0310/13**

The Research Ethics Committee reviewed the above application at the meeting held on 09 February 2009.

Ethical opinion

Pilot study. Members considered that piloting the main study would be a sensible idea and agreed that the proposal will give the research team the opportunity to familiarize themselves with the device, to collect baseline data on adherence and to validate the newly constructed questionnaire.

Time to consider taking part in the study. Members were satisfied with the explanation as to why participants would be invited to consent within a single out patient appointment. However, it was noted that the PIS appeared to contradict this by telling participants to 'take time to decide'. Members were informed that the potential participants would be in the ophthalmic OPD for a considerable length of time as they required to undergo a number of tests prior to commencing treatment. This inevitably leads to patients having periods of 'free time' in which they can consider whether to part in the study.

Exclusion criteria: non- English speakers. Members considered that the researchers justification 'that the ophthalmologists do not see many non-English speakers' or that the translation of the study material may cause 'bias' were unconvincing. Members were informed that glaucoma presents differently in other ethnic groups [e.g. sub-Sahara], which while interesting to the researchers could bias the results. Members considered that as there was no clear prospect of benefit from taking part in the study the exclusion of non-English speakers was not problematic

Concerns regarding the treatment of patients who do not join the study. Members were informed that new patients routinely receive an extensive education and information package on their first visit and would not be disadvantaged by not taking part in the study. This had been explained on the PIS.

Validating the questionnaire. It was noted that the process for validating the questionnaire had not been discussed. It was concluded that that the validation process would be a 'scientific issue' and not a concern for the REC.

Sample size. Concerns were raised that this figure was excessive as the calculation was based on the numbers to pick up different levels of adherence, which is the aim of the main study. Members were advised that the calculations were fine and concluded that there would be no imposition on the participants, as they will not be required to make a manual record. The numbers can be easily met given the high number of referrals to the clinic. The calculation was supported.

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to the research sites listed on the attached form.

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 at NHS sites ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Participant Consent Form: Travalert Pilot Study	1	14 January 2009
Participant Information Sheet: Travalert Pilot Study	1	14 January 2009
GP/Consultant Information Sheets	1	14 January 2009
Questionnaire: Travalert Pilot Study -Final	2	06 November 2008
Questionnaire: Travalert Pilot Study - Initial	2	06 November 2008
Peer Review : NIHR - PB-PG-1207-14119		
Covering Letter	Heidi Cate	14 January 2009

Protocol	2	12 September 2008
Investigator CV : David C Broadway		14 January 2009
Application	12457/21246/1/419	14 January 2009
Checklist		
Questionnaire: Social demographic and medical history	2	12 September 2008
Application	SSIF - NNUH	14 January 2009

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

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.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Website > After Review

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.

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
- 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.

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@nres.npsa.nhs.uk.

09/H0310/13	Please quote this number on all correspondence

With the Committee's best wishes for the success of this project

Yours sincerely

Michael Sheldon MA PhD
Chair

Email: janette.guymer@nnuh.nhs.uk

Enclosures: *List of names and professions of members*
"After ethical review – guidance for researchers, SL-AR2
Site approval form (SF1), Issue 1

Copy to: *Mrs Kath Andrews, R&D office for NNUH*

Appendix 2 Research Governance Committee 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 Charles Broadway
Glaucoma Research Unit
Norfolk & Norwich University Hospital NHS Foundation Trust
Colney Lane
Norwich
NR4 7UY

15 June 2009

Dear Mr Broadway

Re: 2009OPTH03L (11-02-09) A pilot study to examine the ease of use of the Travalert and identify simple questionnaires to be used in the Glaucoma Adherence Study.

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 & 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 **2009OPTH03L (11-02-09)** 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 Social Demographic Questionnaire

Norfolk and Norwich University Hospitals NHS
NHS Foundation Trust

OPHTHALMOLOGY DIRECTORATE
Glaucoma Research Unit

Tel: 01603 288870
Fax: 01603 288261

Colney Lane
Norwich
NR4 7UY

Social Demographic and Medical History Questionnaire

Patient No: .....

Date of Birth: ☐☐ / ☐☐ / ☐☐

Gender: Male ☐ Female ☐

Ethnic Group:

White British..... ☐ White Irish..... ☐

White Other White (specify)..... ☐

Mixed: White and Black Caribbean ☐ White and Black African... ☐

White and Asian..... ☐

Any other mixed..... ☐

Black or Black British:

Black Caribbean ..... ☐ Black African..... ☐

Black Other (specify)..... ☐

Asian or Asian British:

Indian..... ☐

Pakistani..... ☐ Bangladeshi..... ☐

Other Asian (specify)..... ☐

Chinese..... ☐

Other: ☐

Country where born: ☐

Age when moved to UK: ☐☐

Currently in paid employment: Yes ☐ No ☐ Retired ☐ Other ☐

If so, patient's occupation

Please print

Education achieved:

up to age 16..... ☐ up to age 18..... ☐

apprenticeship/certificate/diploma ☐ degree..... ☐

prior to age 16 ..... ☐

Family members affected by glaucoma: (Number affected in each box)

Parent ☐ Brother/Sister ☐ Children ☐

OR (please tick)

Not known ☐ No Brother/Sisters ☐ No Children ☐

Marital status:

Single ☐ Married/Partner ☐

Widowed ☐ Divorced/separated ☐

Medical History:

Diabetes – Type I	Y ☐	N ☐	Years treated? ☐☐
Diabetes – Type II	Y ☐	N ☐	Years treated? ☐☐
Hypertension	Y ☐	N ☐	Years treated? ☐☐
High Cholesterol	Y ☐	N ☐	Years treated? ☐☐
Asthma/wheezing	Y ☐	N ☐	
Bronchitis/emphysema	Y ☐	N ☐	
Heart attack	Y ☐	N ☐	When?
Stroke	Y ☐	N ☐	
Cancer	Y ☐	N ☐	

Type:

Appendix 4 Initial Participant Questionnaire

Norfolk and Norwich University Hospitals NHS
NHS Foundation Trust

OPHTHALMOLOGY DIRECTORATE
Glaucoma Research Unit

Tel: 01603 288870
Fax: 01603 288261

Colney Lane
Norwich
NR4 7UY

Patient No.:.....

Travalert Pilot Study

Initial Participant Questionnaire

Thank you for taking part in this study looking at the use of the Travalert Device and questionnaires which we would like to use in a glaucoma education study in the near future.

This is the first of two questionnaires 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. **Do you currently use eye drops?**
   Yes ☐ No ☐

   If no, please go to question 8

2. **If yes, have you experienced any problems with using eye drops?**
   Yes ☐ No ☐

   If yes, please describe: .....

   .....

   .....

3. **On average, how many doses of your drops do you miss each month?**

☐ 1 dose

☐ 2-3 doses

☐ 4-9 doses

☐ 10-19 doses

☐ 20 or more doses

☐ None

4. **Are you casual at times about using your eye drops?**

Yes ☐ No ☐

5. **When your vision feels better do you sometimes stop using your eye drops?**

Yes ☐ No ☐

6. **If your vision feels worse when you use the eye drops, do you sometimes stop using it?**

Yes ☐ No ☐

7. **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.....

8. **Please rate the information that you have received about each of the following aspects of your glaucoma eye drops.**

Please **tick one box** for each statement.

Have you received enough information about:	**Too Much**	**About Right**	**Too Little**	**None Received**	**None Needed**
How to apply your eye drops	☐	☐	☐	☐	☐
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	☐	☐	☐	☐	☐
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 the medicine will interfere with other medicines	☐	☐	☐	☐	☐
What you should do if you forget to take a dose	☐	☐	☐	☐	☐
How to get a further supply	☐	☐	☐	☐	☐
What glaucoma is	☐	☐	☐	☐	☐

9. **Is there anything that you would like more information about that we have not mentioned?**

Yes ☐ No ☐

If yes, please describe: .....

.....

.....

.....

10. **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 ☐

Haven't used glaucoma medication before today ☐

11. **Do you apply your glaucoma eye drops yourself or does somebody help you?**

Apply by self ☐ Need help ☐

Haven't used glaucoma eye drops before today☐

Many thanks for taking the time to fill out this questionnaire.

Appendix 5 Final Participant Questionnaire

Norfolk and Norwich University Hospitals NHS
NHS Foundation Trust

OPHTHALMOLOGY DIRECTORATE
Glaucoma Research Unit

Tel: 01603 288870
Fax: 01603 288261

Colney Lane
Norwich
NR4 7UY

Patient No.:.....

Travalert Pilot Study

Final Participant Questionnaire

Thank you for taking part in this study looking at the use of the Travalert Device and questionnaires which we would like to use in a glaucoma education study in the near future.

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: .....
   .....
   .....
   .....
   .....

3. **On average, how many doses of your drops do you miss each month?**

☐ 1 dose

☐ 2-3 doses

☐ 4-9 doses

☐ 10-19 doses

☐ 20 or more doses

☐ None

4. **Are you casual at times about using your eye drops?**

Yes ☐ No ☐

5. **When your vision feels better do you sometimes stop using your eye drops?**

Yes ☐ No ☐

6. **If your vision feels worse when you use the eye drops, do you sometimes stop using it?**

Yes ☐ No ☐

7. **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 rate the information that you have received about each of the following aspects of your glaucoma eye drops.

Please **tick one box** for each statement.

Have you received enough information about:	Too Much	About Right	Too Little	None Received	None Needed
How to apply your eye drops	☐	☐	☐	☐	☐
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	☐	☐	☐	☐	☐
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 the medicine will interfere with other medicines	☐	☐	☐	☐	☐
What you should do if you forget to take a dose	☐	☐	☐	☐	☐
How to get a further supply	☐	☐	☐	☐	☐
What glaucoma is	☐	☐	☐	☐	☐

8. **Is there anything that you would like more information about that we have not mentioned?**

Yes ☐ No ☐

If yes, please describe: .....

.....

.....

.....

9. **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: .....

.....

.....

.....

10. **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 ☐

11. **Do you apply your glaucoma eye drops yourself or does somebody help you?**

Apply by self ☐ Need help ☐

Many thanks for taking the time to fill out this questionnaire.

Appendix 6 Discussion Template

Travalert Pilot Study: Patient discussion template

Below are the 3 main areas that will be discussed with the patient in order to determine the suitability of the trial design from the patient's perspective. For 2 questions, additional prompts have been included indicated by the sub categories.

1. Approximately how long did it take you to complete the questionnaire?

2. Did you encounter any difficulties or problems with completing the questionnaire?
    a. Any questions difficult to answer
    b. Were you unsure about what information questions were requesting

3. Did you experience any problems using the Travalert Device?
    a. Was it convenient?
    b. Was it easy to use?