# A practical exploration of the professional, patient and pharmaceutical aspects of medication administration in enterally fed patients

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## Abstract

Medication administration in dysphagic patients or those with an enteral feeding tube (EFT) is complicated with an increased risk of medication errors and complications than the general population. The range of issues that require an evidence base is broad and data are lacking, consequently much of the clinical guidance is consensus based.

Following a literature review to identify the main evidence themes, an exploration of aspects of medication administration in this patient group was undertaken using survey, laboratory and literature review methods. Survey methodology was used to enable description of the reported clinical practice of relevant professionals and patients across the UK. Liquid medications subsequently identified as 'problem' were rheologically evaluated using a clinically derived method focussing on flow properties via EFTs. Crushing methods previously described were evaluated for dose recovery using three model drugs. Finally, a systematic review was undertaken to identify interventions that have been successfully targeted at improving medication related outcomes in this complex group of patients.

Appropriate formulation choice for EFT administration exceeded 80% for both patient and nursing home cohorts. Reported medication administration practices were consistent with consensus guidance in the professional group but were not consistently applied by patient groups. The role of healthcare professionals in informing practice was inconsistent across care settings and warrants further evaluation. Laboratory assessment of liquid medication properties demonstrates a relationship between viscosity and administration difficulties. Tablet crushing methods which significantly reduce dosing accuracy were identified, and calls into question the continued use of equipment currently used for crushing tablets. A systematic review of the literature surrounding intervention strategies to improve medication related practice revealed an education and documentation based focus on preparation and administration steps with minimal evaluation of interventions targeting prescription quality. Retrospective mapping against the Theoretical Domains Framework highlighted a lack of focus on motivational factors which may negatively impact intervention sustainability.

This exploration, from bedside to bench and back again, revealed that potentially suboptimal administration methods are common in clinical practice. New data and insights generated within this thesis should be translated into clinical practice to improve outcomes. However, further research is still required to understand motivations for changing practice, provide pharmaceutical data to support more specific guidance on formulation choice, and an evaluated intervention strategy to change and embed good practice, each of these aspects are a major work in their own right.



Keywords: Dysphagic, dysphagia, enteral tube, nasogastric, swallowing, medicines

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## Glossary of terms

| | |
|---|---|
| *Barrel (of syringe):* | The hollow cylinder of a syringe in which fluids are measured |
| *Catheter:* | A tubular flexible device for removing fluids from, or delivering fluids to, a body cavity |
| *Cue:* | a stimulus or signal to perception, articulation, or other physiological response |
| *Dead space:* | The volume of fluid remaining in the tip of a syringe after the plunger of the syringe has been fully depressed into the barrel |
| *Domain:* | an area of interest; a sphere of thought, action or knowledge |
| *EFT:* | Enteral feeding tube |
| *Fr:* | French, a unit of measurement for enteral devices, 1Fr = 0.33cm |
| *Framework:* | a structure composed of parts framed together |
| *Luer:* | Conical fittings with a 6% taper used for syringes, needles and certain other medical equipment (ISO 594/1:1986) |
| *PEG:* | Percutaneous endoscopic gastrostomy |
| *Plunger:* | The movable part of the syringe which is pushes down the barrel to expel its contents or pulled up within the barrel to fill the syringe |
| *Stimulus:* | an event (whether internal or external to the organism) which elicits a reaction |
| *Theoretical construct:* | a concept specially devised to be part of a theory |
| *Theoretical domain:* | a group of related theoretical constructs |
| *Theory:* | a system of statements or ideas held as an explanation or account of a group of facts of phenomena |

## Acknowledgements

Without the support, encouragement, guidance and most of all patience of my two supervisors Professor David Wright and Dr Christopher Morris this project and thesis would never have made it to completion. I know there were many times when we all felt I was never going to get here.

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This thesis is dedicated to my daughter, Catherine. Mummy has finished her homework now.

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# 1 Introduction

As a clinical pharmacist working within critical care, gastroenterology, surgery and nutrition I was often managing patients with dysphagia related medication management issues in the acute setting whose care would then transfer to a community setting.

Many of these patients could not take medicines by mouth without risk of complication. Every medication review I undertook for these patients required a review of the standard texts and published literature in order to provide guidance on appropriate therapy choices and safe administration. I was frequently required to undertake a risk assessed decision based on scant data.

It was from this continual challenge to deliver evidence based medicine to this specific group of patients within the changing clinical setting that this project was borne.

Regular medication review and optimisation is an essential component of effective medical treatment, it is mandated annually for older patients within the Department of Health National Service Framework for older people (Department of Health, 2001).

Medication review is defined as 'a structured, critical examination of a patient's medicines with the objective of reaching an agreement with the patient about treatment, optimising the impact of medicines, minimising the number of medication-related problems and reducing waste' (Clyne et al., 2008). In the patient population studied within this thesis there is a fine balance between optimisation and minimising risks and complications.

For patients with an enteral feeding tube, medication administration can be complicated and time consuming. If not reviewed and rationalised prior to discharge this complexity can be daunting for self-caring patients or non-nursing carers. In 2003 the British Association for Parenteral and Enteral Nutrition published a range of materials designed to support patients, their carer's and GPs with their medication management (BAPEN, 2003c).

In 2014 NHS England published the NHS 5 Year Forward View (NHS England, 2014). This document presented the collective view of how the health service needed to change in order

to close the widening gaps in the health of the population, quality of care and funding of services.

The embedded principles that overlap with the concepts of this thesis are those of patient empowerment and new models of integrated care.

UK healthcare is faced with the challenge of managing an aging population with increasing levels of frailty and dependence and higher level of managed co-morbidities. One of the many consequences of this is the increasing number of patients in the community with long term dysphagia. The positive impact of good nutrition on disease related outcomes has in turn led to more proactive management of nutrition in these patients.

The increasing use of artificial nutrition via an enteral feeding device, not only in hospital but also in the community, adds a layer of complexity to the management of medication. This thesis explores some of the patient and pharmaceutical aspects of medicines management in these patients in order to inform future models of care.

## 1.1 Dysphagia in clinical practice

In order to understand the rationale behind medication options in patients with dysphagia we must first understand the condition itself and the approach to its management.

### 1.1.1 The swallow reflex

The act of swallowing is essentially a complex reflex which involves 55 muscles, 5 cranial nerves and two cervical nerve roots. The control centre for the swallow reflex is located in the medullary area of the brain stem. It receives sensory signals from the mouth and pharynx as well as signals from the respiratory centre, see figure 1.1.1a (Kendall et al., 2000, Durvasula et al., 2014).

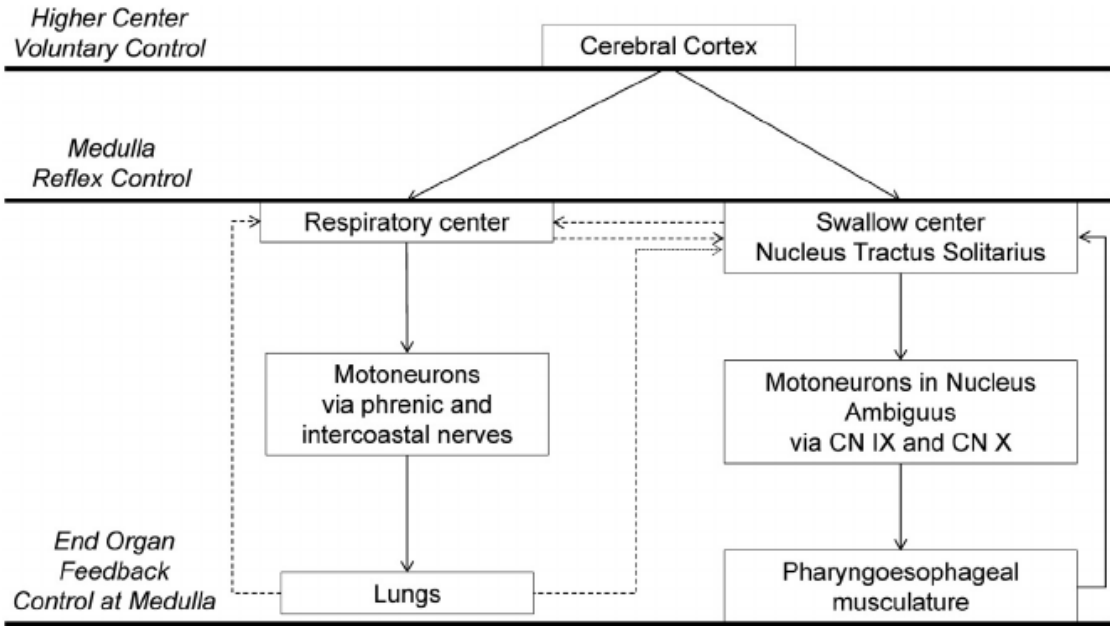



**Figure 1.1.1a The neural regulation of swallow. Reproduced with permission (Durvasula et al., 2014)**

The process of mastication, swallowing and breathing is closely interlinked, with the pathway of swallowed substances and inspired air coinciding in the pharynx, see figure 1.1.1b. Safe passage of the swallowed bolus through the pharynx without aspiration into the trachea is essential to prevent respiratory complications (Matsuo and Palmer, 2009).

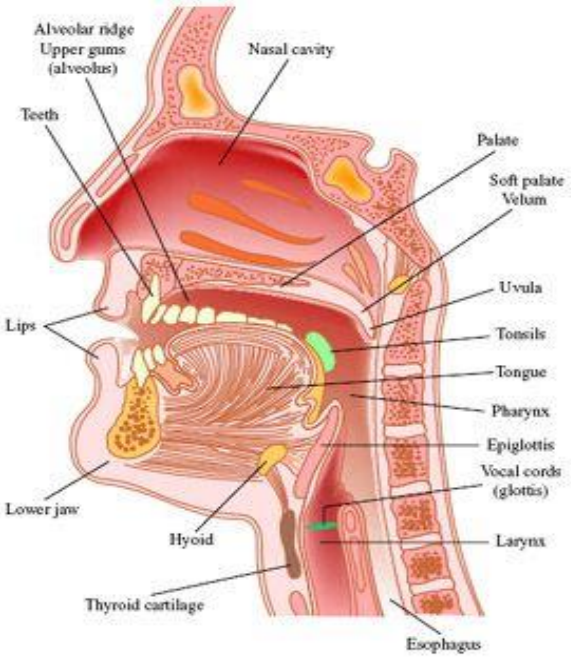



**Figure 1.1.1b Anatomy of the oropharangeal and upper airway system (www.healthhype.com)**

### 1.1.2 Dysphagia

Dysphagia is a symptom, not a diagnosis, of a dysfunctional swallow reflex. It is defined as difficulty or discomfort on swallowing. Signs are linked to the altered timing or delayed passage of the swallowed bolus resulting in tracheal contamination and can include coughing, choking, regurgitation, pain, altered voice or increased chest infections.

The mechanisms of the swallow reflex are complex, however, dysphagia is generally categorised as oropharyngeal dysphagia or oesophageal dysphagia. Broadly due to two distinct causes, an impairment of the swallow reflex due to neurological or muscular problems or a functional obstruction of the upper gastrointestinal tract.

Oropharyngeal dysphagia is when there is difficulty moving a food bolus or fluid from the mouth through the pharynx into the oesophagus.

Certain conditions can weaken the throat muscles, impairing the ability to move food from the mouth backwards into the throat and onwards down the oesophagus. This causes choking, gagging or coughing when trying to swallow or results in the sensation of food or fluids going into the trachea or up into the nasal cavity. There are occasions where the impaired swallow in combination with a reduced sensation can lead to silent aspiration, where the patient is not aware of the passage of fluid or food into the trachea. Neurological impairment can also lead to dysphagia due to the loss of co-ordination of the precise timing necessary for a safe swallow.

Oesophageal dysphagia usually results from an obstruction or altered passage through the oesophagus. This can be due to stricturing or tumour infiltration, or due to a poorly functioning lower oesophageal sphincter resulting in reflux of stomach contents into the oesophagus.

### 1.1.2 Patient groups susceptible to dysphagia

Causes of oropharyngeal dysphagia are many and varied and can be the symptom of a number of clinical conditions and also the side effect of drug therapy. Table 1.1.2 illustrates the range

of conditions and the associated dysphagia type. Incidence and prevalence varies widely across the disease groups, stage of disease and age of patient (Smithard, 2015).

From surveys and self-reported questionnaires it is estimated that between 2.3% and 16% of the general population have oropharyngeal dysphagia (Smithard, 2015), this increases to 35% in the population aged over 75 (Altman, 2013).

**Table 1.1.2 Causes and types of dysphagia (Altman, 2013, Forster et al., 2011)**

| | Oropharyngeal | Oesophageal |
|---|---|---|
| **Neuromuscular** | Stroke<br>Parkinson's Disease<br>Amyotrophic Lateral Sclerosis<br>Multiple sclerosis<br>Myasthenia Gravis<br>Muscular Dystrophy<br>Polio<br>Syphilis | Achalasia<br>Cricopharyngeus/oesophageal spasm<br>Dermatomyositis<br>Scleroderma |
| **Obstructive** | Tonsillitis<br>Tumour | Oesophagitis<br>Zenker diverticulum<br>Webs<br>Schiatzki ring<br>Tumour<br>Extrinsic compression |
| **Medication** | Sedative agents<br>Muscle relaxants<br>Anticonvulsants<br>Any associated with xerostomia<br>Any associated with myopathy | Any associated with oesophageal injury |
| **Respiratory** | Chronic Obstructive Pulmonary Disease | |

Cerebrovascular disease, or stroke, is one of the most common causes of dysphagia. The prevalence of dysphagia following a stroke is between 37% and 78%, the wide variation is attributed to the range of methods used to diagnose dysphagia, the temporal relationship between the stroke and assessment, and the cerebral location of the stroke lesion (Martino et al., 2005). There is potential for dysphagia to improve with rehabilitation.

Neurological disorders such as multiple sclerosis, muscular dystrophy and Parkinson's disease result in a progressive dysphagia. Almost 90% of patients with Parkinson's disease exhibit signs of dysphagia during the course of the disease, however in the majority of patients dysfunction is present before exhibiting clinical signs of dysphagia (Ali et al., 1996).

Cancer and its treatment is another significant cause of dysphagia. The position of the tumour, particularly in head and neck cancers and upper gastrointestinal cancers, the type and extent of surgery and the use of radiotherapy can all lead to swallow dysfunction or the inability to access the GI tract via the oral route. Head and neck tumours are most likely to result in oropharyngeal dysphagia (McIlwain et al., 2014) whereas upper GI tumours are more likely to result in oesophageal dysphagia (Astin et al., 2015).

Drug induced dysphagia is most common in the acute care setting, the most extreme example being in those patients who are sedated or ventilated. However, many other medications can cause dysphagia through their effect on saliva production, and the subsequent swallowing difficulties associated with dry mouth (Villa et al., 2015).

### 1.1.3 The nutritional challenge of dysphagia

Maintaining the nutritional status of a patient with dysphagia presents a number of challenges. The effect on oral intake is dependent on the severity of the condition and mechanism of the dysphagia. Patients with obstructive symptoms usually find that they can tolerate oral fluids but struggle with solid or even semi-solid food whereas patients with impairment of the swallow function can usually tolerate thickened fluids and solids but struggle with thin liquids and can suffer from frequent aspiration and complications such as chest infections.

#### 1.1.3.1 Texture modification and swallow techniques

Maintaining oral nutritional intake is a primary goal in the management of patients with dysphagia. There are two main approaches to achieving this, manipulation of the bolus viscosity or purposeful swallow techniques and compensatory posture adjustments (Cook, 2009).

The alteration of bolus viscosity is particularly effective when patients demonstrate difficulty with thin liquids (e.g. water). Food and drinks can have their texture and viscosity altered through the addition of thickening agents based on gums or starches (Lazarus et al., 1993).

In 2002 the American Dietetic Association published guidance to standardise the terminology and characteristics of diet modification, they described four consistencies of liquids; thin,

nectar-like, honey-like and spoon thick (ADA, 2002). Subsequently researchers have assigned viscosity ranges to these descriptions in order to support further standardisation and facilitate comparison (Leonard et al., 2014), an example is illustrated in table 1.1.3.1 In 2011 the UK National Patient Safety Agency published guidance on diet modification but did not include descriptions for liquids (NPSA, 2011).

**Table 1.1.3.1 Assigned viscosity ranges for thickened liquids as described in the National dysphagia diet by Leonard (Leonard et al., 2014)**

| Designation | Viscosity range (cP)* |
|---|---|
| **Thin** | 1-50 |
| **Nectar-like** | 51-350 |
| **Honey-like** | 351-1,750 |
| **Spoon-thick** | >1,750 |

* at 25$^{o}$C and a shear rate of 50s$^{-1}$.

An increase in awareness of the beneficial effects of adequate nutrition on the clinical outcomes of many conditions has led to an increased use of artificial nutrition for patients who are unable to maintain their nutritional status with the oral route alone.

### 1.1.3.2 Indications for enteral feeding tube use

The British Artificial Nutrition Survey, undertaken by The British Association for Parenteral and Enteral Nutrition (BAPEN) is the largest national prospective survey of artificial nutrition support in the world (Smith et al., 2011). Data from 2010, indicted that an estimated 44,000 adult patients were receiving home enteral feeding in the UK. Of these 75% have a feeding tube placed in their stomach (gastrostomy), 17% have a nasogastric tube and 5% have a tube exiting in the jejunum (jejunostomy). The majority of these patients are independent, with 69% of these patients living in their own homes. However, as would be predicted from the disease types associated with enteral feeding, 63% are over 60 years old.

65% are described as having swallowing difficulties, however the remainder use their tube to improve nutritional intake in addition to oral diet. The predominant indication for home enteral feeding is neurological disorders, accounting for 46% of patients, of which 41% are due

to cerebrovascular disease. The other significant group are those with cancer, this includes gastrointestinal and head and neck, accounting for 39% of patients.

Indications for home enteral feeding in paediatrics are significantly different with only 30% having swallowing difficulties. Supplementing oral nutrition is a significant indication in children with cerebral palsy, cystic fibrosis and general failure to thrive (Smith et al., 2011).

In addition to patients with oropharyngeal dysphagia who through disease progression or failure of diet modification have moved onto enteral tube feeding, there are also several other groups of patients where use of an enteral feeding device could be their only route of nutrition and fluids. These include those with short term dysphagia due to reduced consciousness or acute drug therapy, such as in the intensive care unit.

## 1.2 An introduction to enteral feeding devices

Enteral feeding tubes come in many different types, lengths and sizes, can be inserted using a variety of techniques, and can exit in a variety of places within the GI tract. The choice of type, size, position and material will be influenced by many patient factors.

The external diameter of an enteral feeding tube is expressed using the French (Fr or Ch) unit, where each 'French' is equivalent to 0.33mm. Enteral feeding tubes can be made of silicone, polyurethane (PUR), polyvinylchloride (PVC), or latex. Each of these materials has different physical properties.

### 1.2.1 Nasoenteric devices

The most common type of enteral feeding device use in acute care is the nasoenteric tube. These are most commonly inserted through the nasopharynx and will exit within the stomach (nasogastric), duodenum (nasoduodenal) or jejunum (nasojejunal). See Figures 1.2.1a, b, and c (Reproduced with permission, (White, 2015c))

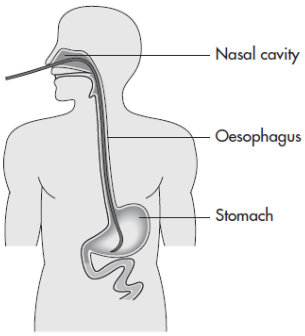



**Figure 1.2.1a Nasogastric tube**

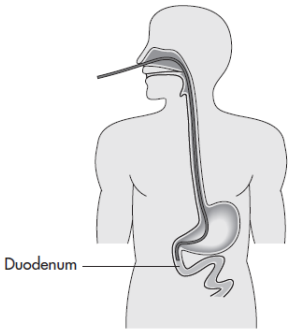



**Figure 1.2.1b Nasoduodenal tube**

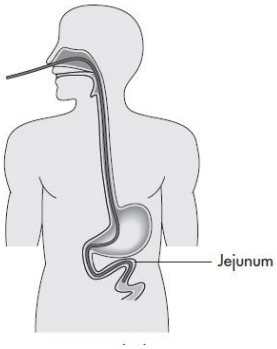



**Figure 1.2.1c Nasojejunal tube**

The nasogastric tube is inserted via the nasal cavity and allowed to pass through the pharynx to the oesophagus and into the stomach, this can be achieved 'blind' in any setting using a sip of water to encourage safe transit of the tube or facilitated using endoscopic or radiological guidance. Confirmation of the correct position has been the topic of several NPSA and NHS Improvement safety notices, and accurate confirmation of safe placement is required before initiation of feeding (Improvement, 2016).

Nasoduodenal and nasojejunal tubes are placed in the same way as nasogastric tubes but are allowed to pass beyond the pylorus into the upper duodenum and onward through to the jejunum. pH testing is not appropriate to confirm position and so radiological confirmation is required for these tubes.

Tubes used via these routes for feeding purposes are typically fine bore (6Fr – 12Fr) and made from silicone or polyurethane. However nasogastric tubes of a wider bore (12Fr – 16Fr) can occasionally also be used for drainage of stomach contents in the acute setting such as critical care and it is important to clarify the purpose of the tube before using for medication administration.

The length of the tube is determined by the distance from entry to exit, a standard adult nasogastric tube is approximately 110cm long, a nasojejunal tube can be up to 170cm long.
Silicone is softer and more flexible than PUR or PVC and as a result requires thicker walls to prevent stretching or collapsing. As a consequence of this difference in rigidity, a silicone tube will have a smaller internal diameter than a PUR tube of the same French size, which has a direct impact on flow rates (Metheny et al., 1988).

Over recent years there has been a trend towards using smaller size feeding tubes for reasons of patient comfort and acceptability. Nasoenteric tubes are not suitable for long term use due to the risk of accidental displacement and nasopharyngeal complications such as ulceration and stricturing.

### 1.2.2 Percutaneous devices

Enteral feeding tubes intended for long term use are placed directly through the skin, via a stoma (ostomy) into the stomach or intestine using either an endoscopic, surgical or radiological technique. These tubes are held in place with an internal balloon, rigid bumper or a suture, the method of retention affects the removal technique. These tubes are commonly referred to as PEGs (percutaneous endoscopic gastrostomies) or G-tubes if exiting in the stomach or Jej tubes if exiting in the jejunum. See Figures 1.1.2d, e, and f (Reproduced with permission,(White, 2015c).

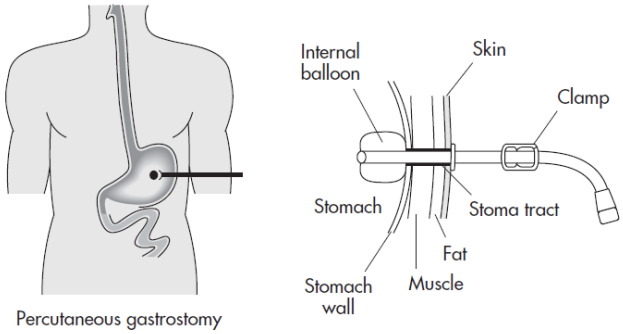



**Figure 1.1.2d Percutaneous gastrostomy**

Percutaneous gastric tubes tend to be of a large diameter, with common sizes being 14Fr - 20Fr. A standard gastrostomy tube may be up to 25cm long, but a skin level device may be only 3-5cm long. Patients have to be measured for a skin level device to ensure that the tract length between the retention bumper and the external bumper is sufficient to prevent pressure sores forming around the device but tight enough to minimise the risk of leakage.

Tubes exiting in the jejunum are more likely to be used in patients who have had gastric or oesophageal surgery or in those with dysmotility issues in the upper GI tract.

Tubes exiting in the jejunum vary on size depending on whether it is a primary placement jejunostomy or inserted through an existing gastrostomy tube.

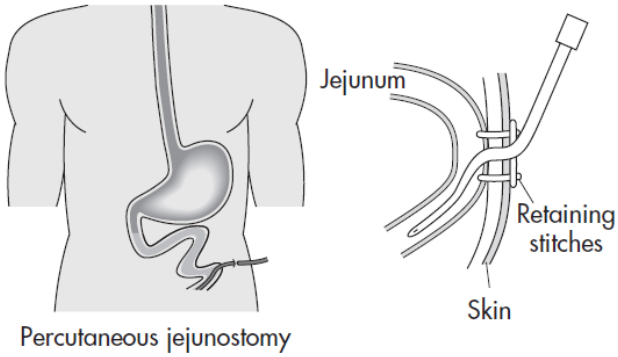



**Figure 1.1.2e Direct percutaneous jejunostomy**

Direct jejunostomy tubes are usually placed either surgically or radiologically, and are typically secured by sutures or a subcutaneous cuff, accidental removal will always necessitate admission to hospital for replacement.

Jejunal tubes can also be placed through an existing gastrostomy. It is important that the most appropriate port is used for medication administration, especially if the gastric port is being used for drainage.

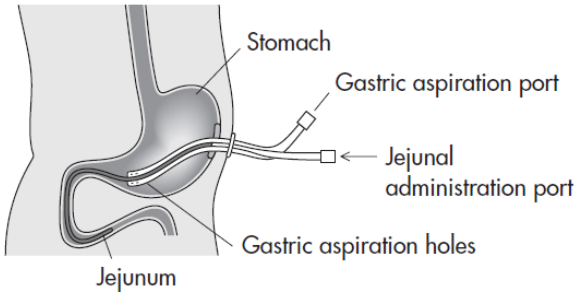



**Figure 1.1.2f Transgastric jejunal tube**

The longevity of any percutaneous device depends on the retention method. Balloon retained silicone devices require replacement every 3 to 6 months, however polyurethane tubes with a rigid internal retention device can stay in place securely for several years.

## 1.3 Medicines management in the dysphagic patient

Patients with dysphagia typically are within a group of patients that already have complex pharmaceutical needs due to the multiple drug therapies that are needed to manage their

underlying condition and other co-morbidities, particularly in the older patient group where polypharmacy is common.

Medication administration to patients with dysphagia, particularly those with an enteral feeding tube provides ethical and legal challenges. Medication administration falls within a specific range of legal and professional legislation and guidelines. Very few medicines are specifically licensed to be manipulated for oral administration and only a handful are specifically licensed for enteral tube administration (Griffith and Davies, 2003).
If the medicine is not licensed for enteral tube administration the manufacturer will not have studied the impact on bioavailability and efficacy of this route of administration. No guidance or instructions for use will be provided within the summary of product characteristics or patient information. As a result patients must be given specific advice from their healthcare professionals (HCP) either within acute care or in the community; alternatively they may seek advice online or through patient support groups which can affect the relationship between patient and HCP(McMullan, 2006).

Ultimately the prescriber is responsible for medication use outside of its product license and must make the judgement of risk versus benefit as they may be liable for any adverse effects suffered as a consequence. However, nursing staff or professional carers are often responsible for administration and pharmacists for supply. Therefore all professionals involved in the supply and administration process are complicit in the use of a medication outside its product license.

The ethical challenge lies in the decision to administer a medication know to provide benefit within the licensed route and indication when there is little or no data indicating the potential risks of altering the dosage form or route of delivery.

### 1.3.1 Oral medication in the dysphagic patient

The approach to medicines management in patients with dysphagia will be dependent on the type and severity of the condition.

There are typically three main options; use of a solid dosage form such as a tablet or capsule placed into a food bolus of a safe texture for the patient, use of a liquid medicine with a high

viscosity or addition of a thickening agent, or use of a thin liquid if assessed as safe to use (Ney et al., 2009).

The first two approaches are frequently used for patients with oropharyngeal dysphagia due to neurological impairment; the use of thin liquids is usually only considered safe in patients with oesophageal dysphagia due to obstruction where rapid transit into the stomach is desirable to minimise risk of regurgitation into the trachea.

### 1.3.2 Mixing medication with food or drink to facilitate oral administration

Mixing medication with any drink or food stuff can be a potential cause of direct drug-nutrient interactions; this should be considered before mixing any medication with food or drink.

The presence of high levels of electrolytes, particularly calcium and magnesium, can significantly reduce the bioavailability of medication susceptible to chelation. This is most commonly seen with the interaction between medication and milk or dairy products. These interactions are generally well documented and standard warnings are included on dispensed items. In the case of tetracyclines and quinolones this interaction is clinically significant with reductions in both peak levels and total dose absorbed being affected (Neuvonen et al., 1991), even by the relatively small amounts of milk added to coffee or tea (Jung et al., 1997).

Likewise the interaction between enteral feeds and medication such as phenytoin, warfarin and ciprofloxacin is well known and written warnings should be available at point of use (White, 2010) .

For patients where a thicker consistency is required, liquid medication is mixed with thickeners or crushed tablets with semi-solids such as yoghurt, applesauce or jam. This latter aspect is also particularly prevalent practice in covert administration practices, in a study of care homes with nursing and special care units 12% of all medicines were routinely mixed with food, only 28% of these occurrences were due to dysphagia (Kirkevold and Engedal, 2005) .

Throughout the literature there are many small studies looking at aspects of compatibility with various food stuffs (Manrique et al., 2014, Johnson et al., 2003, Fleming et al., 2016, Carrier et

al., 2004), however the high variability in both the physical and chemical properties of the food stuffs and also the medication formulations makes any generalisations impossible.

### 1.3.3 Use of an enteral feeding tube for medication delivery

There are differing requirements for the pharmaceutical properties of medication formulations for patients with swallowing difficulties and for administration via a feeding tube. As previously outlined many patients with swallowing difficulties will have an impaired swallow reflex, the use of thin liquid preparations in these patients can increase their aspiration risk and increase the incidence of respiratory complications (Ney et al., 2009). Feeding tube administration, on the contrary, requires a non-viscous, minimally or non-particulate liquid that will flush via the tube with a minimal resistance and low risk of tube blockage.

In areas of clinical practice where dysphagia, reduced consciousness or obstruction are common so too is the use of an enteral feeding tube for medication administration. Phillips (Phillips and Endacott, 2011) highlighted that practice is more common in critical care areas with 59% of ICU nurses utilising this route on a daily basis, this was in contrast to 14% and 11% for surgical and medical nurses respectively.

The practical aspects of EFT medication administration are complicated by variability in medication formulation characteristics, tube materials types and sizes. Therefore general guidance is typically described by formulation type, but with added context for particular types of tubes (BAPEN, 2003b) .

Consideration must also be given to the legal and safety aspects of this route of administration, these aspects will be covered in more detail later in this chapter.

## 1.4 Medication formulation options in dysphagic or enteral tube access patients

The choice of formulation for a dysphagic or EFT patient will be influenced by a number of considerations such as viscosity tolerance for dysphagic patients, or the tube type, size and position for EFT patients.

The cost of a formulation is also considered and may result in inappropriate formulation manipulation rather than using a more expensive formulation (Wright, 2002). This issue is of interest but falls outside of the scope of this thesis.

Each formulation option has its own merits and issues and these must be balanced against the therapeutic needs of the patients. In the majority of cases there will be some compromise between optimal therapy for the clinical condition and the availability of an appropriate formulation.

### 1.4.1 Parenteral formulations

Parenteral administration required medication to be delivered by injection either into the subcutaneous or muscular tissues or directly into the venous system.

The parenteral route of administration is only a considered option for a small number of medications. Its use is limited by the need for appropriate venous access or patient acceptance of continued intramuscular or subcutaneous injections. In the acute setting the intravenous route may be used to initiate medication administration but a move to less invasive methods is considered at the earliest opportunity, this is influenced by the risk and cost associated with this route.

A small number of injectable preparations are suitable for administration via an enteral tube as the drug is already dissolved in a non-particulate solution. However for some drugs the injection is a different salt when compared the oral preparation and therefor the bioavailability will be unknown. There are also practical and cost issues associated with supplying injections for enteral use. However there are some medications where this can be a useful alternative until the oral route can be used, such as in the case of aminophylline injection or hyoscine (Twycross and Wilcock, 2011).

### 1.4.2 Rectal

Despite the potential pharmacokinetic benefits of rectal medication delivery, it remains an unpopular choice within the UK for cultural reasons when compared to other parts of Europe (EMEA, 2006). For this reason there are also fewer medications licensed in rectal formulation

in the UK, particularly for longer term conditions, however it remains a valuable use in the acute setting particularly in acute pain and epilepsy management.

### 1.4.3 Transdermal and intranasal

The transdermal route is particularly valuable for both dysphagic and enteral tube patients. The range of preparations available is still fairly limited but the use of GTN, fentanyl, buprenorphine, rotigotine, rivastigmine, oxybutynin, granisetron and hyoscine patches offer a simple solution in comparison to enteral tube administration. Although cost limits their use as first line preparations in the general population, they should be considered in the dysphagic and enteral tube population.

Intranasal preparations are predominantly used to manage local conditions. However the availability of the triptans as nasal spray offers the dysphagic or EFT migraine sufferer a non-enteral option.

### 1.4.4 Sublingual, buccal and orodispersible medication

The appropriateness of sublingual, buccal or orodispersible formulations in dysphagic patients is very dependent on the underlying condition of the patient. For patients with excess drooling it may not be possible to retain a sublingual or buccal tablet for sufficient duration to allow absorption or active drug may be lost in the saliva. At the other extreme patients who have had extensive head and neck surgery may not produce sufficient saliva to facilitate dissolution of the tablet (Davies et al., 2016), or may have altered buccal blood flow and lymphatic drainage.

For patients with an enteral feeding tube, the same issues apply to sublingual or buccal formulation use, however care should be taken when determining if an orodispersible formulation is suitable for administration through the enteral tube rather than orally. For example, Zelapar® (selegeline) is described as an oral lyophilisate however it is absorbed in the oral cavity and has a higher bioavailability than the oral preparation and therefore only comes in 1.25mg dose units as compared to the 10mg oral formulations.

### 1.4.5 Liquid formulations

Liquid formulations are generally considered the first line choice in dysphagic patients or those with a feeding tube (BAPEN, 2003b), and though there are many pharmaceutical advantages to their use, the cost and impracticability can be a barrier to use and should be borne in mind.

Liquid formulations are typically solutions, elixirs, suspensions and syrups. However due to the wide variation in excipient composition, each drug formulation should be considered individually.

#### 1.4.5.1 Viscosity variation and osmolarity

A solution can contain one or more components (solutes), in a homogenous single-phase system. In medication formulations the solvent in typically water and the solute uniformly present throughout the solution. Most medication solutions contain few excipients and have a low osmolarity. As previously mentioned these may not be suitable for oral administration in dysphagia but are ideal for enteral tube administration.

The one exception is with syrup presentations, technically these are still solutions, the solvent being a saturated glucose solution. This results in a viscous formulation with a high osmolarity, almost 4000mosm/L. Depending on the route of administration and volume of the dose this high osmolarity can cause gastrointestinal side effects. Saturated sugar solutions with both high osmolarity and viscosity found in medication formulations include lactulose and sorbitol.

Typically fluid exiting the stomach into the duodenum has an osmolarity range of 400-600mosm/L, if solutions with a higher osmolarity are introduced directly into the duodenum or jejunum the physiological response of the gut is to increase secretions to dilute this. The consequence of this is osmotic diarrhoea. This is why high osmolarity medication solutions should be diluted before post-pyloric administration (Klang, 2010).

The viscosity range across all formulations of syrups and suspensions is very wide. Some formulations are designed to be shaken before use and hold the suspended material uniformly through the suspending agent for sufficient time to measure the dose, these tend to have a low viscosity and settle on standing. At the other extreme are those suspensions which are

designed to hold the suspended material uniformly throughout the life of the product. These tend to be highly thixotropic, with a very high viscosity on standing which decreases when shaken to facilitate administration.

Highly viscous liquid medication, although challenging to administer via an enteral feeding device particularly a fine bore tube, may not be sufficiently viscous to be safe in a dysphagic patient. Very little information is available in the literature regarding the specific viscosity of liquid medicines; it is not routinely documented in the Summary of Product Characteristics or certificate of analysis.

#### 1.4.5.2 Granule based liquid formulations

Some suspensions form a course granular liquid due to the large size of the suspended granules, in addition palatability or the need to provide a modified release profile has led to the introduction of microgranules in liquid formulations.

Granular liquid formulations carry a high risk of causing tube blockage, particularly in patients with fine bore tubes. There are a number of factors that influence the rate of tube blockage and these are considered in more detail later in this introduction.

#### 1.4.5.3 Excipient issues for liquid formulations

Some formulations contain excipients which themselves can cause unwanted effects. A case report highlights the effect that excipients can have on gastrointestinal symptoms. An increase in dose of a sorbitol containing medication was found to be the cause of a patients bloating and discomfort, crushing and dispersing the tablet formulation was demonstrated to cause the symptoms to resolve (Madigan et al., 2002).

Sorbitol was previously used in large doses as a preservative; however its propensity to cause bloating and diarrhoea in large doses prompted its removal from all but a few preparations. The cumulative dose of sorbitol should be considered for patients on these preparations particularly if abdominal symptoms are troublesome.

A number of formulations include alcohol either as a preservative or as a co-solvent, the quantity in a single dose of medicine is usually small however the cumulative dose across all medications administered during the day should be determined, and any potential drug-alcohol interactions avoided. This is a particular concern for children and neonates, potentially the most vulnerable group of dysphagic patients (Whittaker et al., 2009).

#### 1.4.5.4 Barriers to liquid formulation use

Despite liquid formulations often being considered first choice for enteral tube patients there are circumstances where healthcare professionals, patients and carers resort to altering solid dosage forms to facilitate enteral tube administration in preference to the use of a liquid formulation.

Availability issues can influence choice, in a Brazilian study of nasogastric tube administration, liquid formulations were only available for 23% of drugs being administered via this route (Heineck et al., 2009) demonstrating the impact that medication supply can have on formulation choice (Heineck, 2009).

However, in the study by Phillips (Phillips and Endacott, 2011) 43.9% of respondents said that they would administer a solid dosage form even if the liquid was available in the pharmacy, 26% reporting that this was because it was easier to do so. 15% indicated that they would prefer to use a solid dose form if the calculation to use the liquid was difficult.

Cost may also be a barrier to routine use of liquid medicines; typically they are more expensive than the equivalent dose as a solid dosage form. Data from a survey conducted by Wright (Wright, 2002) identified that nursing home nursing staff perceived 61% of GPs sometimes or always express concern about the cost of liquid medicines when approached about alternative formulations.

### 1.4.6 Solid dosage forms

For many medications the only formulation available is a solid dosage form; as a result crushing tablets was common in clinical practice (Wright, 2002) with 69% of nursing home

nurses crushing tablets on a daily basis. Enteral tube administration was also a common reason for medication alteration (Paradiso et al., 2002).

#### 1.4.6.1 Soluble Tablets

Soluble tablets should mix with water completely to form a clear solution with no particles; they are an appropriate choice for enteral tube administration and can often be dissolved in a very small volume of water which is particularly useful in patients on a fluid restriction (White and Bradnam, 2015). Unfortunately and confusing for prescribers many tablets branded as 'soluble' are in fact dispersible.

#### 1.4.6.2 Dispersible and Effervescent Tablets

Dispersible tablets disintegrate in water to form dispersion; the particle size can be very varied (see Illustration 1.4.6a and b below), most can be dispersed in a relatively small amount of water and are suitable for enteral tube administration, although few are licensed for this route of administration.

Modified release granular dispersible tablets which are licensed for gastrostomy administration, such as Zoton® (lansoprazole) Fastabs and Nexium® (esomeprazole) gastro-resistant tablets, can be dispersed in a small amount of water and flushed down an enteral tube, although there are concerns regarding their use via fine bore tubes and potential risk of blockage (Messaouik et al., 2005, Stewart et al., 2009). There are also other modified release tablets, such as Pentasa® which although dispersible in water are not appropriate for enteral tube administration due to their large granule size (See illustration 1.4.6b).

**Illustration 1.4.6a Voltarol® 50mg Dispersible Tablet dispersion shown with a cross-section of 8Fr enteral tube**

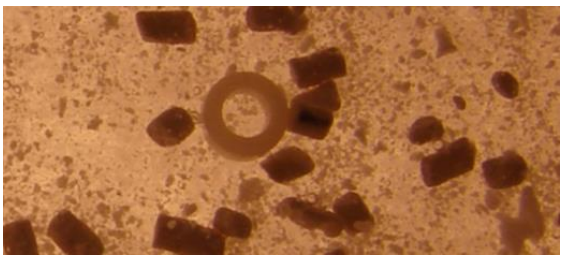


**Illustration 1.4.6b Mesalazine® 500mg Slow Release Tablet dispersion shown with a cross-section of 8Fr enteral tube**

Effervescent tablets are also generally suitable for enteral tube administration, the recommended volumes of water can be quite large, but most will dissolve in a smaller volume than recommended if fluid intake is an issue. The only significant consideration for effervescent tablets is the sodium content, which can be up to 20mmol per tablet.

Due to the reasons described previously, most soluble, dispersible or effervescent tablets will be unsuitable for dysphagic patients due to their low viscosity.

#### 1.4.6.3 Compressed Tablets

The majority of compressed tablets will disperse in water if given sufficient time and agitation (White and Bradnam, 2015), this can be a cost effective option for EFT patients where a liquid preparation is not available. Dispersion may have advantages over crushing with respect to occupational exposure to chemotherapeutic agents (Siden and Wolf, 2013) or minimising loss of dose (Powers and Cascella, 1990), however due to the relatively sparse data this aspect requires further evaluation.

#### 1.4.6.4 Modified release and enteric coated Tablets

Modified release and enteric coated tablets may be suitable for dysphagic patients if they can be taken safely with semi-solid food, however they should not be dispersed or crushed and therefore are not suitable for enteral tube administration. Crushing these preparations will alter the pharmacokinetic profile and may increase side effects or toxicity or decrease effect or prevent absorption at all.

Modified release preparations conventionally contain a larger total amount of drug since they release slowly to maintain therapeutic levels over a prolonged period of time. The potential for overdose if these formulations are crushed is well documented, and yet this practice does occur in clinical practice (Paradiso et al., 2002) perhaps indicating a lack of awareness on this issue. The consequences can be catastrophic, administration of crushed modified release nifedipine via a nasogastric tube contributed to the death of a patient (Schier et al., 2003). Root cause analysis of this incident revealed that the physician failed to realise that solid medication would be crushed for nasogastric administration, the pharmacy did not register the

potential issue when supplying the medication to the critical care unit and the nurse did not understand the pharmacokinetic consequences of crushing a sustained release preparation.

#### 1.4.6.5 Capsules

Some dry powder capsules may be opened and mixed with water, however this should be considered a last resort due to the occupational exposure risks, and this is covered in more detail later.

Gel capsules and modified release capsules are generally not suitable for enteral tube administration, but may be suitable for dysphagic patients if they can be taken safely with semi-solid food.

## 1.5 Safety issues and adverse effects of dose form modification

Altering a dosage form in any way, unless specifically allowed in the products marketing authorisation, is considered as administering the medication outside of its license and therefore the person making the decision to do so is responsible for any adverse effects that may occur to the patient as a direct result of this action (RPSGB factsheet). This legal consideration has been highlighted in the nursing and medical press through the practice of disguising medication in food for covert administration (Haw and Stubbs, 2010), altering a dosage form to facilitate administration through a feeding tube raises the same issues of accountability.

The Royal Pharmaceutical Society published a guidance document in 2011 outlining the pharmaceutical issues associated with dosage form manipulation (RPS, 2011). This was intended to support pharmacists when advising on the appropriateness of formulation manipulation, following the publication of guidance relating to the professional responsibilities when dealing with the supply of pharmaceutical specials (RPS, 2010).

Despite concerns, dose form modification is common in clinical practice a large observational study in Australia (Paradiso et al., 2002), evaluated the data from 1207 observation episodes of medication administration rounds in aged-care facilities, 408 (34%) of these involved alteration of the medication either by crushing tablets or opening capsules. In an observation study of

medication administration errors in a mental health institution (Haw et al., 2007), of the 369 errors observed 30% related to unauthorised tablet crushing. In this study it was noted that 41% of patients had swallowing problems, but there was no record of enteral feeding tube use.

There are several safety and risk issues that should be considered when manipulating formulations; these include increasing the risk of medication errors, dosing inaccuracy, occupational exposure, interaction with food stuffs and professional responsibility. Additionally there are issues that apply specifically to enteral tube administration such as tube blockage, interaction with the feeding tube, wrong route errors, and pharmacokinetic changes and side effects due to non-gastric administration. Each of these issues are considered in turn.

### 1.5.1 Medication errors

An observational study of UK patients in a secondary care facility demonstrated that patients with dysphagia are three times more likely to experience a medication error (Kelly et al., 2011), with an error rate of 21.1% compared to that of 5.9% for patients without, in addition twice the number of dysphagic patients with an enteral feeding tube experienced one or more errors when compared to dysphagic patients without a feeding tube.

The literature is biased towards nursing based observational studies and therefore reporting of preparation and administration errors predominate. The error rates quoted in the literature are varied and difficult to compare directly due to a difference in definition, categorisation and scope but also because each medication may be associated with more than one error, values cited range from 8% to 65% (Kelly et al., 2011, Haw et al., 2007, Sestili. M et al., 2014, Idzinga et al., 2009, van den Bemt et al., 2007).

Prescription errors as the root cause for further errors and issues in this group of patients are underrepresented in the literature; this may be due to the frequency of causality or to underreporting. The predominant focus is on nursing activities at ward level; however several studies allude to the fact that if issues with the prescription had been addressed before the preparation phase the overall incidence of medication errors would be lower. Lohmann et al. (Lohmann et al., 2015) determined that over 90% of wrongly prepared medication on the ICU was inappropriate at the prescription stage. This is in stark contrast to the data from Sestili implicating prescribing in only 10% of the errors detected (Sestili. M et al., 2014).

Effective communication as patients transfer from one care setting to another is a key aspect of medicines management, in a study of discharge communications 18.5% of the errors identified were attributed to recommending crushing an inappropriate formulation (Sestili. M et al., 2014), this study highlights the need to ensure that medication information for patients with dysphagia or EFT is transferred accurately in order to minimise introducing risks and errors at the point of transfer

### 1.5.2 Dosing accuracy and pharmacokinetics

It has been demonstrated that the method used to crush and administer a tablet can lead to dosing inaccuracies, in a study in a critical care environment the investigator observed incomplete dosing due to powder residue from crushed tablets not being transferred to the administration syringe (Al Rakaf and Lababidi, 2009). The effect of technique used to administer tablets was investigated using aspirin as a model drug in a small study comparing crushing in a pestle and mortar; crushing in a medicine cup and dispersing in a syringe. The mean value of actual dose delivered was determined for each method and found to be 74%, 86% and 101% respectively (Powers and Cascella, 1990).

Manipulation of medication in order to administer accurate doses is also prevalent in paediatric practice, splitting tablets and dispersion in water to facilitate administration is commonly undertaken (Nunn et al., 2013). The use of tablet dispersion and proportional administration is used commonly within paediatric practice to facilitate the administration of sub-tablet doses. However, a study undertaken by Broadhurst (Broadhurst et al., 2008) using aspirin have called this practice into question as the dose obtained was highly variable and dependent on both dissolution time and height from within the solution that the dose was taken, with doses as low as 24% being obtained.

Modifying a dosage form can also impact its pharmacokinetic properties, particularly when administered via a feeding tube directly into the jejunum. It is acknowledged that bioavailability from liquid mediation and crushed tablets given directly into the stomach is similar to oral administration (Fish and Abraham, 1999) but may result in slightly faster absorption. When medication is administered further down the GI tract one of two changes may occur; In the case of phenytoin and iron preparations absorption is significantly reduced,

whereas in the case of carbamazepine and diazepam absorption in more rapid resulting in increased side effects (White and Bradnam, 2015). However, there is also some evidence that absorption is unaffected for some drugs resulting in an inability to generalise on the impact of administration further down the G tract. In a case report voriconazole tablets were crushed and administered via a jejunostomy tube, peak and trough levels were comparable to oral therapy (Martinez et al., 2003).

Crushing modified release preparations is not recommended as it may affect bioavailability, time to peak levels, and peak concentrations potentially altering the tolerance to therapy. Cleary et al. (Cleary et al., 1999) evaluated the consequences of administration of crushed pentoxifylline MR tablets; they demonstrated a higher bioavailability, faster time to peak levels and higher maximal concentrations leading to an increase in side effects and reduced tolerability.

### 1.5.3 Inappropriate formulation manipulation and mixing medicines

As previously indicated there are formulations that should not be crushed due the impact on the pharmacokinetics and risk of increased side effects due the damage of protective tablet coating.

The prevalence of crushing inappropriate formulations varies across the literature and are expressed slightly differently in each study, making direct comparison difficult. A study in critical care indicated that 10% of the preparation errors were due to crushing an enteric coated or modified release preparation and 9% of administration errors were due to incomplete administration of crushed tablets (Al Rakaf and Lababidi, 2009). In one of the largest surveys of US critical care nurses, over 21% admitted to crushing enteric coated tablets and 15% crushed sustained release preparations (Belknap et al., 1997).

In addition to inappropriate crushing of formulations there are also concerns regarding mixing formulations together prior to administration this is largely due to the lack of data relating to either impact on bioavailability of the co-adminsitered drugs or the impact on incidence of tube blockage. As there are no data exploring the pharmacokinetic consequences of this activity, recommendations to administer one medication at a time are given (BAPEN, 2003c). Despite this recommendation, mixing medication appears to be common (Al Rakaf and

Lababidi, 2009, Joos et al., 2015a, Kelly et al., 2011). In an observational study of within a residential care facility, 69% of all doses prepared were mixed with at least one drug for administration, of the 165 'cocktails' 28% contained 5 or more drugs (Joos et al., 2015a).

### 1.5.4 Occupational exposure and cross contamination

There is increasing concern relating to the risks to staff when handling and manipulating pharmaceuticals. High risk activities such as preparation the of cytotoxic medication are no longer undertaken at ward level and are carried out under controlled conditions, usually within the pharmacy as it has been long acknowledged that occupational exposure to cytotoxic drugs increases the risk of spontaneous abortions or malformations in the offspring of nurses exposed during routine care of the patient (Hemminki et al., 1985, Dranitsaris et al., 2005).

Crushing tablets in open containers such as mortars or medicine pots, or opening capsules, in a ward environment may increase the risks of exposure by the operator if protective equipment is not used. This could potentially lead to sensitisation, allergies, adsorption and possible adverse effects (Paparella, 2010). An in vitro comparison of crushing methods the open crushing methods produced aerial contamination with particles greater than 5um exceeding 106 particles/$m^3$ (Salmon et al., 2013).

In addition to operator exposure there is also a risk of ward level exposure of other staff and patients to drug powder resulting from such manipulations. If these operations must be undertaken they should be performed in a room with a closed door and traffic through the room should be limited during the manipulation. It is essential that benches and equipment are thoroughly cleaned following such manipulations to remove any drug residues and to ensure the safety of others.

In an observational study in ICU, not washing the pestle and mortar either before or after the preparation step occurred in 20% of the preparation errors (Al Rakaf and Lababidi, 2009). This is lower than an observed rate in aged-care facilities recording evidence of spillage or loss of dose in 70% observations (Paradiso et al., 2002), where shared equipment such as pestle and mortars were used these were not cleaned between administration episodes in 59% of cases.

Contamination of the crushing device can have serious consequences if these traces are not removed by cleaning, this was highlighted in a case report of serious anaphylaxis caused by penicillin contamination of a dose by using an unwashed pestle and mortar (Cohen, 1982).

### 1.5.5 Compatibility with beverages and food

Mixing medication with a safe texture food or drink is a common strategy in medicines management in dysphagia for oral administration, survey work by Wright (Wright, 2002) indicated that 56.5% of nursing home nurses regularly mix medication with food to overcome swallowing difficulties.

Dose form modification is also common to facilitate 'covert' administration of medication, particularly to patients suffering from dementia and psychiatric illnesses. In an observational study in a large psychiatric hospital (Stubbs et al., 2008), of the 1257 doses observed, 25.5% of doses were altered to facilitate administration, 55% were mixed with food to administer. 4% of the altered doses were contrary to the manufacturers recommendations and could seriously influence the effect and side effects of the medication delivered. The researcher also observed that during tablet crushing there was spillage and potential loss of dose. This is also evident in work by Stuijt, in a psychogeriatric care environment where over 80% of medication doses were mixed with food or drink to enable covert administration, as a result between 9.5 and 63.9% of a patient's medication would be crushed (Stuijt et al., 2013).

Despite the fact that mixing food with medication is embedded in routine clinical practice few drugs have been studied with regard to specific stability and interactions with food or liquids (Carrier et al., 2004, Burkhardt et al., 2005, Manrique et al., 2014). Yoghurt and applesauce are the most commonly recommended food stuffs.

Medication is not mixed with food to facilitate administration via an enteral tube as the texture of even blenderised feed can cause issues with administration and tube blockage (Novak et al., 2009).

### 1.5.6 Wrong route errors

There have been a number of case reports in the literature of inadvertent parenteral administration of medication intended to be given orally (Cousins and Upton, 1999, Cousins and Upton, 2000). All of these were the direct result of medication being drawn into a syringe with a connector compatible with i.v. devices. A number of these report serious clinical consequences (Cousins and Upton, 2001, Nicholson Roberts and Swart, 2007) and even fatalities (Cousins and Upton, 1998, Grissinger, 2013). This resulted in the National Patient Safety Agency issuing UK guidance in 2007 on the use of non-leur syringes specifically designed for enteral administration (NPSA, 2007). This initiative was adopted by the global patient safety agencies and an ISO-standard enteral connector, Enfit, was launched in 2016 (ISO Small Bore Connectors Working Group, 2016).

During the global transition to the new connector series there is still a risk of mis-connections and therefore ongoing awareness and training will always be required.

## 1.6 Enteral tube blockage and rupture

Prevention and management of enteral feeding tube blockage is a significant problem. In a recent survey of patients with PEG tubes following head and neck surgery for cancer 18% of patients reported 'quite a bit/very much of a problem' with tube blockage, although interestingly this was considered less of an issue that the psychological and social issues associated with PEG tube use (Rogers et al., 2007).

The exact incidence of tube blockage for the inpatient population is difficult to define as it is frequently not considered a reportable patient care incident (Kenny and Goodman, 2010a). There are several studies reporting tube blockage in the community, but with inconsistent description of incidence and prevalence. This is likely to be due to the different methods to record tube blockage and the variability in the type and size of tube.

In an inpatient study of jejunostomy tubes placed following upper gastrointestinal surgery, only 1 of the 80 patients experienced tube blockage during the postoperative period (Biffi et al., 2000). A long term follow up of 191 patients in Pakistan with PEG tubes found an incidence of tube blockage of only 2.1%, there was no data on cause of tube blockage (Anis et al., 2006).

This is in contrast to a study of home enteral patients in the republic of Ireland (McNamara et al., 2000) where 30% reported tube blockage as a complication of their enteral feeding, although the potential causative factors were not evaluated in this study. Patients in institutional care required more visits to hospital to unblock their tube than patients in the home setting, although the precise figures are not documented in the report.

The consequences of blockage are of concern. Re-admission for tube replacement can be necessary. In a prospective study of complications following PEG placement in 128 patients (Finocchiaro et al., 1997), 8 patients experienced tube blockage during the long term follow up period (mean of 710 days), 3 of these required admission for replacement of the tube.

In addition to the inconvenience of intervention for tube replacement, tube blockage can have serious consequences for patients totally dependent on their tube for their nutritional and fluid intake. In children with glycogen storage disease dependant on overnight tube feeding, tube blockage can result in fatal hypoglycaemia (Evans et al., 2007).

### 1.6.1 Medication and non-medication related causes

Mixing of enteral feed with gastric contents is known to cause coagulation of the feed and cause tube blockage on aspiration (Elia et al., 1984). In a comprehensive in vitro study by Hofstetter (Hofstetter, 1992), based on earlier work by Metheny (1988), reducing pH of milk protein based feeds such as osmolite and ensure increased viscosity until the feed clumped. This occurred at pH 4.6, which is the isoelectric point of milk protein (casein). These researchers demonstrated that gastric acid refluxes back up the feeding tube, particularly when there is no flow through the tube, to decrease the pH of the feed remaining in the tube and cause blockage. They also demonstrated that this effect was reduced if the feeding tube had only one exit point. This research demonstrated that regular flushing with 20mL of water prevented tube blockage due to feed and highlights the need to encourage this in clinical practice. This group also demonstrated that addition of electrolyte such as calcium, magnesium and iron did not affect the viscosity of the feed or increase the incidence of clump formation (Hofstetter, 1992).

In the early 1980's acidic syrup based liquid medicines were demonstrated to be incompatible with standard polymeric enteral feeds (Cutie et al., 1983), direct mixing resulting in clumping, particle or granule formation or alteration of the viscosity.

In a study of children on overnight feeding (Evans, 2007), 45% of the children had at least one episode of tube blockage every 3 months, and 12% had blockages weekly. The researchers attributed this to a number of factors. Several children required corn starch supplements and this could contribute to tube blockage, but medication administration and inadequate tube flushing were also cited as contributing factors. The high incidence in this study compared to others is likely due to the fact that 44% of these children had a nasogastric tube.

Heineck et al. (Heineck et al., 2009) undertook a retrospective chart review and evaluation of tube changes to determine the causes of tube blockage in patients receiving their medication via this route. The researchers determined that patients with more than five enteral drugs, and that had more than 13 doses per day, and received enteral feeding for greater than 10 days had a 4.8, 5.3 and 2.6 greater chance of tube blockage respectively. This highlights the need to minimise and simplify drug therapy in patients receiving their medication via enteral feeding tube.

### 1.6.2 The importance of tube flushing

Adequate tube irrigation is necessary for preventing tube blockage due to enteral feed or medication (Hofstetter, 1992). In the 1980's cranberry juice had become a favoured irrigation fluid for enteral tubes. An in vivo study by Wilson and Haynes-Johnson in 1987 (Wilson and Haynes-Johnson, 1987) demonstrated that regular irrigation using 30mls of water was more effective than cranberry juice for reducing the incidence of tube blockage and thereby increasing the average duration of use of the tube from 5.4 days to 16.8 days.

Methany and co-workers demonstrated that regular flushing with water or Coca-Cola were equally effective at preventing tube blockage, and that as water was cheaper and more readily available it should be used in preference to Coca-Cola (Metheny et al., 1988).

Despite the obvious practical preference for water, this success with a variety of solutions has resulted in their continued usage in common practice with little evidence base (Schmieding and Waldman, 1997).

A small UK survey of 22 ward nurses demonstrated variation in practice in administration methods and flush volumes within a single organisation (Naysmith and Nicholson, 1998). A larger US survey indicated that volumes used to flush feeding tubes varied between 20 and 100mls (Schmieding and Waldman, 1997). This variability in practice may indicate a lack of awareness of the problems associated with this method of drug administration or serve to highlight the categorisation issues of flush volume or hydration volume

### 1.6.3 Risk of tube rupture

Current syringe size recommendations for enteral feeding tube flushing and drug administration are based on perceived wisdom and not evidence base. A recent study (Knox, Davie 2009) aimed to challenge these misperceptions and has demonstrated that small syringes are safe for both administration of flushes and medicines and also for aspiration. In fact aspiration using a large syringe (50ml) should be avoided as this creates a significant negative pressure and could result in tissue damage if the tube is positioned against the stomach wall.

### 1.6.4 Tube – drug interactions

The surface properties of the tube are also thought to influence the rate of adherence of feed and medication. Gaither et al. studied (Gaither et al., 2009), in vitro, the effect of coating polyurethane feeding tubes with PVA (polyvinyl alcohol), demonstrating a reduced adherence of gastric acid coagulated feed. There was no difference with native casein protein, only the acid denatured protein, leading the investigators to conclude that the hydrophobic regions exposed on the denatured protein were adhering to the hydrophobic polyurethane, PVA is hydrophilic, accounting for the apparent resistance to adsorption.

The polymers and plasticizers used in medicine are many and varied, and many are currently being re-formulated to remove DEHP (a phthalate plasticizer). The predominant polymers used for enteral devices, sets and bags are polyurethane, silicone and less often PVC. The potential

for complex interactions exist between medication and plastics, this can result in a subsequent clinically relevant loss of dose. This loss of drug can occur by three mechanisms; absorption, adsorption and permeation, the likelihood and extent being influenced by the properties of both the drug, the excipients in the formulation and the plastic (D'Arcy, 1996). This has been studied extensively for intravenous drugs as the device dwell time can be considerable (container and giving set). A comprehensive study undertaken by Kowaluk et al. (Kowaluk et al., 1982) in the early 1980's studying 45 drugs concluded that several drugs were lost on infusion sets through absorption, a slow time dependant, concentration independent process. The loss was lowest in short lengths of small diameter tubing.

Investigation of this phenomenon with enteral tubes and devices has been undertaken for a limited number of drugs only. However materials used in enteral devices have been evaluated in the context of infusion administration. In a study by Treleano et al. (Treleano et al., 2009) absorption of nitroglycerin and diazepam into different plastics was evaluated, the initial loss of drug was similar for both drugs via soft PVC, polyurethane and silicone, however the absorption of nitroglycerin into silicon decreased over the infusion period of 200 minutes.

In a specific evaluation of crushed tablets via enteral tubes, Klang et al. (Klang et al., 2010) demonstrated a loss of warfarin of approximately 20% when administered through a polyurethane tube, further investigation concluded that this was due to binding to the tube, although no differentiation between absorption or adsorption was made. As most absorption appeared to be related to dwell time, is the author recommended that the drug be administered through the tube rapidly to minimise the contact time and that the tube be adequately flushed (Klang et al., 2010).

Within a single case study a series of errors of both preparation and administration have been documented (Emami et al., 2012), the themes of inappropriate crushing, inadequate flushing and potential interactions with enteral feed resonate with many of the articles cited.

## 1.7 Introduction Summary

As this introduction outlines, medication administration in this patient group is complicated and time-consuming; the increased risk of medication related errors and issues, potentially

resulting in poor outcomes and adverse events, is compounded by a lack of data and, possibly, awareness

As can be seen from the literature, nursing practice has been studied both in acute and community care through survey and direct observation. However there have been no studies investigating the specific advice given by healthcare professionals to patients, or the practice of self-caring patients in the community. This gap in the literature influenced the design of the first research chapter of this thesis, chapter 2.

The research described in chapter 2 had two main objectives; to define the medication advice given by healthcare professionals seen as specialists in this area, and how dysphagic patients in the community and their carers manage their medicines. The primary aim of this research was to identify gaps between the literature, current guidance and reported practice.

The initial literature review highlighted the breadth and scope of medication administration issues in patients with dysphagia. For the purposes of this research the focus was limited to administration issues for patients with enteral feeding devices, as a result pharmaceutical issues relating to mixing medication with food were not investigated in this project.

The second focus of research stemmed from the realisation that the limited range of medication studied with regard to administration via a feeding tube, particularly in the acute setting, may not reflect the most frequently used medication in clinical practice, particularly in community. A secondary objective of the research described in chapter 2 was to more clearly define the medication used by patients with dysphagia in a community setting, this data was used to define the scope of the subsequent two research chapters (chapters 3 and 4), which were conducted in parallel.

Within the current literature it was clear that liquid medicines are preferred in dysphasic and tube fed patients, however the data available on the physical properties of liquid medicines is sparse. This shaped the objective of chapter 3, to define the physical properties of frequently used liquid medicines, with an aim to better understand the range of physical properties and how these may be used to define suitability for enteral tube administration and safe oral administration.

In addition, several studies indicated that medication formulation manipulation is common in this group of patients and yet the limited research looking specifically at this area with regard to the pharmaceutical and safety aspects of this practice raised some concerns about the practice. Research described in chapter 4 utilised the methods used to manipulate medication identified by patients in chapter 2 to evaluate their impact on dose recovery, to determine if concerns regarding dosing inaccuracy was also relevant for other medication.

In order to determine how best to design and evaluate future interventions in this complex medicines management group, a systematic review of the interventions evaluated and their impact on outcomes was determined to be the preferred method. This research is described in chapter 5.

Adverse drug reactions and medication errors have been demonstrated to significantly increase healthcare costs in a variety of healthcare settings (Bates et al., 1997). However, despite detailed analysis of adverse incidents relating to medication administration, enteral drug administration errors rarely feature specifically (Thomas and Panchagnula, 2008). Improving the quality of medicines management in this group of patients may improve outcomes through reduced complications and adverse events, which together will reduce healthcare costs.

# 2 A survey of clinical practice: Professionals and Patients

## 2.1 Introduction to the survey

The research described in this chapter focuses on the start of the journey from "bedside to bench". From the initial literature review it was evident that medication administration in this patient group is complicated and time-consuming with an increased risk of medication related errors and complications.

There were many themes that would warrant further investigation, but the clear gap in the evidence base relating to the relationship between guidelines and clinical practice or advice given by healthcare professionals, and that of practice of self-caring or dependant patients in the community was highlighted for the first part of this research.
The information gap relating to the types of medication administered via enteral feeding devices, particularly in the community, was also identified and in scope for this research.

The literature was focussed predominantly on general nursing staff and it was less clear if the practice of the specialist professionals involved in supporting general nurses in this clinical area, such as nutrition nurses and dietitians, were as varied and a potential source of confusion. What was also missing from the literature was the patient's interpretation of guidance and their practice unsupervised in the community.

The scope of this chapter was limited to drug administration via an enteral feeding tube and not dysphagia in general.

## 2.2 Background

Within the UK, there are key healthcare professionals that are generally part of the clinical team caring for patients with enteral feeding tubes, the nutrition nurse specialist and the dietitian. They may be supported by clinical pharmacists and speech and language therapists.

Education of patients on how to manage their enteral feeding tube, including medicines management, would generally be undertaken by either the ward nurse or one of the specialist

healthcare professionals within secondary care. Specialist professional support is also available for some patients in the community.

The National Nutrition Nurses Group (NNNG) and the Parenteral and enteral nutrition group (PENG) of the British Dietetic Association are founding members of BAPEN (the British Association for Parenteral and Enteral Nutrition) along with PINNT (Patients on Intravenous and Nasogastric Nutrition) a patient support group. Following the publication of the support materials for medication administration via feeding tubes all groups expressed an interest in supporting further research in this area. All of these groups draw their membership from across the UK.

## 2.3 Aims and Objectives

The underpinning research question for this chapter was whether enteral tube drug administration practices in community reflect those of specialist acute care health care professionals and are they in line with current guidance.

The primary objective of this survey based research was to describe aspects of practice in drug administration via enteral feeding tubes amongst professionals, community nursing homes and patients. The secondary objective was to determine which medicines and formulations are commonly used in this patient group, which of those are associated with administration issues, and what specific methods are used to manipulate medication.

The overarching aim being to determine the areas, if any, of variability both in advice and practice between the groups and to review this in the context of the available evidence.

## 2.4 Method

Three groups of potential respondents were targeted for the survey; the specialist nursing and dietetic professionals advising and training on enteral drug administration, patients in the community receiving medication via this route and Oxfordshire community care homes with nursing providing care for patients receiving medication via this route.

The objective to describe aspects of practice required a sample that represented a number of geographical localities to avoid sampling from a group that were all potentially influenced by the same local guidance or influence.

The secondary objective required the collection of data from a large number of responders, for this reason observational study of clinical practice was excluded, although it would have provided a large enough patient cohort to be confident that frequently used or problem medication were representative.

For the reasons above a survey design was considered the most appropriate method for obtaining the required information on clinical practice and experience from a large number of patients and professionals across the whole of the UK. Community nursing home information was focussed on local practice in Oxfordshire as a follow up observational study was planned. In addition to practice and experience data, information on medication types and formulations administered was also collected to inform the focus of subsequent guidelines.

From the literature review several issues were identified, these were: tube flushing practice before, during and after medication administration, administration techniques for different formulations, tube blockage and sources of information or advice.

Content validity was assured through the use of the literature and the researchers own experience, this was further assured through the pilot process (Bowling, 2002). A mixture of closed questions with a subsequent free text option provided clarity for analysis with the free text option allowing the respondent to provide a more in-depth response without being directed by multiple choice responses, this provides rich data but can be difficult to interpret (Rattray and Jones, 2007). The application of Cronbach's alpha was not applicable to this survey as a scoring system was not being applied and correlations were not being drawn between questionnaire items.

Ethical approval for this study was granted by the Mid and South Buckinghamshire Research Ethics Committee in January 2009.

Survey distribution took place between May 2010 and January 2011.

### 2.4.1 Questionnaire design, pilot and review

The response rate for postal surveys is inherently low (Cook et al., 2009) therefore all possible options for increasing response rate were utilised. For all questionnaires the graphic design included both academic and NHS logo and use of colour as this has been demonstrated to improve response rate. A covering letter, information leaflet, free-post reply envelope and pen were included with all surveys (Edwards et al., 2002). The professional survey also included a reply card to allow for anonymous reply. The community nursing home covering letter included the incentive of a textbook for responders, a monetary incentive was considered inappropriate (Edwards et al., 2005).

#### 2.4.1.1 Professional questionnaire

A 15 item questionnaire was formulated around the themes identified from the literature. Two items relating to the area of clinical practice of the respondent, 3 items relating to clinical practice in relation to enteral tube flushing, 8 relating to clinical practice in medication administration via feeding tubes and 2 items on personal experience of medication administration problems and tube blockage. The majority of the questions were focussed on the specifics of medication administration as the main topic of interest.

The survey was designed using mix of closed questions and free text explanation of response.
The initial survey was piloted by 8 nutrition nurses and 4 dietitians. On review, minimal changes to grammar of questions was made, there were no fundamental question changes. A 'not applicable' response was added to some questions to accommodate variation in scope of clinical practice of respondents. This pilot confirmed the time taken to complete questionnaire.

#### 2.4.1.2 Patient questionnaire

A 15 item questionnaire was designed to explore patient's experience of drug administration via enteral feeding tubes incorporating the themes identified from the literature and specific questions relating to medicines and formulations.

Basic demographic data and tube information was collected; no personal information or patient identifiers were requested. Three items related to the patients/carers own practice around tube flushing. One section was specifically targeted to collect information on medication, formulation and administration of the patient's current medication regimen. Three questions targeted the patient's method(s) of administering their medication, two questions specifically related to problems with medication administration, two questions about tube blockage and their management. A further comments section was included to allow patients/carers to comment on any of the themes identified in the questionnaire.

The questionnaire was reviewed anonymously through the charity PINNT, a small selection of minor comments and suggestions were returned with a general endorsement of the survey. The patient reviewers confirmed that none of the questions were intrusive or inappropriate. Minor amendments to grammar and wording were made to improve the accessibility of the survey.

#### 2.4.1.3 Nursing home questionnaire

A 20 item semi-qualitative questionnaire was designed to determine the number of patients in community nursing homes within Oxfordshire who have medication administered via an enteral feeding tube. The questions were designed to ascertain the methods used to administer the medication, the type and size of tube in use, the specific medications being administered, the problems encountered and the resources available. No patient identifiable data was requested. Respondents were asked to consider participation in an observational study.

The first 5 items of the questionnaire related to general information about the organisation and their client group. Nine items related to the respondent's clinical practice, two related to experience of tube blockage and medication problems. A large section of the questionnaire required information relating to the type of tube the clients had in situ and the details of specific medication being administered through the tube. No client identifiers were requested.

The questionnaire was reviewed by a 3 nursing home managers. No changes were recommended. The quantity of data requested was considered to potentially negatively

impact on response rate but all reviewers felt that there was no other method for obtaining this data.

### 2.4.2 Sample population, distribution and follow up

#### 2.4.2.1 Professional Survey

The sample population for the professional survey was non-pharmacy healthcare professionals who advise on aspects of medication administration via feeding tubes. A purposive sample was identified through two relevant professional groups, the National Nurses Nutrition Group (NNNG) and the Parenteral and Enteral Nutrition Group (PENG) of the British Dietetic Association. The chairs of these two groups were approached to support the survey. 260 NNNG members and 160 PENG members were sent the questionnaire, with a pre-paid envelope and reply postcard. The prepaid reply post card was included for return independently of survey, this allowed for identification and follow up of non-responders but maintaining anonymity of reply. Follow up questionnaire was sent 6-10 weeks following initial mailing.

#### 2.4.2.2 Patient Survey

To achieve a geographically varied sample the patient support group PINNT was identified as a potential response group. PINNT members are patients or carers of patients on artificial nutrition, either parenteral or enteral, from the whole of the UK. The committee of PINNT had been involved in the initial project proposal and agreed to support questionnaire dissemination. This allowed for an anonymous mailing.

The survey was sent to the 130 members of PINNT who had an enteral feeding tube or who were caring for a patient with an enteral feeding tube. The survey was sent directly to members by PINNT on behalf of the researcher in December 2010, to maintain anonymity of patients. Due to the method of survey dissemination the researcher could not identify recipients and therefore was no follow up for non-responders.

#### 2.4.2.3 Nursing home survey

Organisations, within Oxfordshire, providing community based care were identified though online care home, nursing home and telephone directories. Each organisation was contacted by telephone to determine if they provided care for patients with enteral feeding tubes, and a named individual identified within each organisation that the questionnaire should be sent to. Within Oxfordshire 152 care organisations were identified , 61 of which provide care for patients with enteral feeding tubes, all of these provided nursing services, 10 had never had or did not currently have patients with enteral feeding tubes. Of the remaining 51 homes, 50 agreed verbally to complete the survey and to consider participating in the observational part of the study.

Questionnaires were number coded when sent to a named contact at the nursing home to allow identification of non-responders. A follow up questionnaire was sent 6-10 weeks following initial mailing.

### 2.4.3 Analysis

All responses were transcribed into Microsoft Excel 2010. Simple mathematical analysis was undertaken for numerical responses using the maximum and minimum values given if a range was provided.

Quantitative content analysis was undertaken for the free text responses using a conventional content analysis technique (Hsieh and Shannon, 2005), these were consolidated into theme based groups where possible.

## 2.5 Results

### 2.5.1 Professional Survey Results

Completed questionnaires were received from 175 respondents giving an overall response rate of 41.6%, there was a lower response rate from the nurse group compared with the dietetic group, 33.8% and 48.8% respectively.

Respondents were 71 nutrition nurses, 77 dietitians, 23 other nurses and 4 classified as other professions. Regarding scope of practice, 141 worked in adult practice, 3 in paediatrics, 29 worked in both sectors (23 in community, 12 in secondary care), with 2 nil response. Regarding place of work, 46 worked in community practice only, 107 worked in secondary care only, 15 worked in both areas, 7 nil response. See table 2.5.1a for a breakdown of area of practice by profession.

**Table 2.5.1a Breakdown of area of practice by profession**

| | Secondary Care | Community Practice | Both areas | Nil response | Total |
|---|---|---|---|---|---|
| **Adult Practice** | 48 Dietitians<br>41 Nutrition Nurses<br>1 Other<br>8 Other Nurse | 20 Dietians<br>3 Nutrition Nurses<br>2 Other<br>4 Other Nurses | 1 Dietitian<br>8 Nutrition Nurses | 1 Dietitian<br>4 Nutrition Nurses | 141 |
| **Paediatric Practice** | 3 Nutrition Nurses | | | | 3 |
| **Adults and Paeds** | 3 Dietitians<br>3 Nutrition Nurses | 4 Dietitians<br>4 Nutrition Nurses<br>1 Other<br>8 Other Nurses | 3 Nutrition Nurses<br>3 Other Nurses | | 29 |
| **Nil response** | | | | 2 Nutrition Nurses | 2 |
| **Total** | 107 | 46 | 15 | 7 | |

All 175 respondents responded to the question about tube flushing when the feed is stopped. 173 respondents indicated that they flush or recommend flushing when the enteral feed is stopped, 2 respondents felt that this question was not applicable. Specific flush volumes were provided by 141 respondents. The volumes varied with the majority of respondents indicating a minimum flush volume of 50mL and a maximum of 100mL, the full distribution is detailed in Figure 2.5.1a. Several reasons were given why flush volume may vary, the most common reasons relating to fluid balance either increased needs or fluid restriction, this highlights the interplay between flushing to maintain patency and the need to provide hydration. The full range of reasons are summarised in table 2.5.1b.

**Table 2.5.1b Reason given why flush volume may be varied**

| Reason | Post feed volume | | Pre-medication volume | | Between medication flush | |
|---|---|---|---|---|---|---|
| | Number N=141 | % | Number N=105 | % | Number N=76 | % |
| Dependent on fluid requirements | 83 | 58.9 | 55 | 52.4 | 25 | 32.9 |
| Fluid restriction | 30 | 21.3 | 25 | 23.8 | 10 | 13.2 |
| As directed by dietitian | 20 | 14.2 | 7 | 6.7 | 3 | 3.9 |
| Dependent on number or type of medicines | 17 | 12.1 | 24 | 22.9 | 21 | 27.6 |
| Dependent on medical condition | 15 | 10.6 | 8 | 7.6 | 3 | 3.9 |
| Varies if adult or child | 13 | 9.2 | 9 | 8.6 | 8 | 10.5 |
| Depends on type of tube | 10 | 7.1 | 9 | 8.6 | 4 | 5.26 |
| Tolerance | 9 | 6.4 | 6 | 5.7 | 5 | 6.6 |
| Depends on oral intake | 6 | 4.3 | 2 | 1.9 | 2 | 2.6 |
| Depends on feed regimen | 5 | 3.5 | 5 | 4.8 | 1 | 1.3 |
| As directed by referring hospital | 1 | 0.7 | 1 | 0.9 | 0 | 0 |
| Dependent on ambient conditions e.g. hot weather | 1 | 0.7 | 0 | 0 | 0 | 0 |
| History of tube blockage | 0 | 0 | 2 | 1.9 | 0 | 0 |
| Dependent on viscosity of medication | 0 | 0 | 0 | 0 | 5 | 6.6 |
| Enough to ensure medication reaches stomach | 0 | 0 | 0 | 0 | 5 | 6.6 |
| As recommended by pharmacist | 0 | 0 | 0 | 0 | 1 | 1.3 |

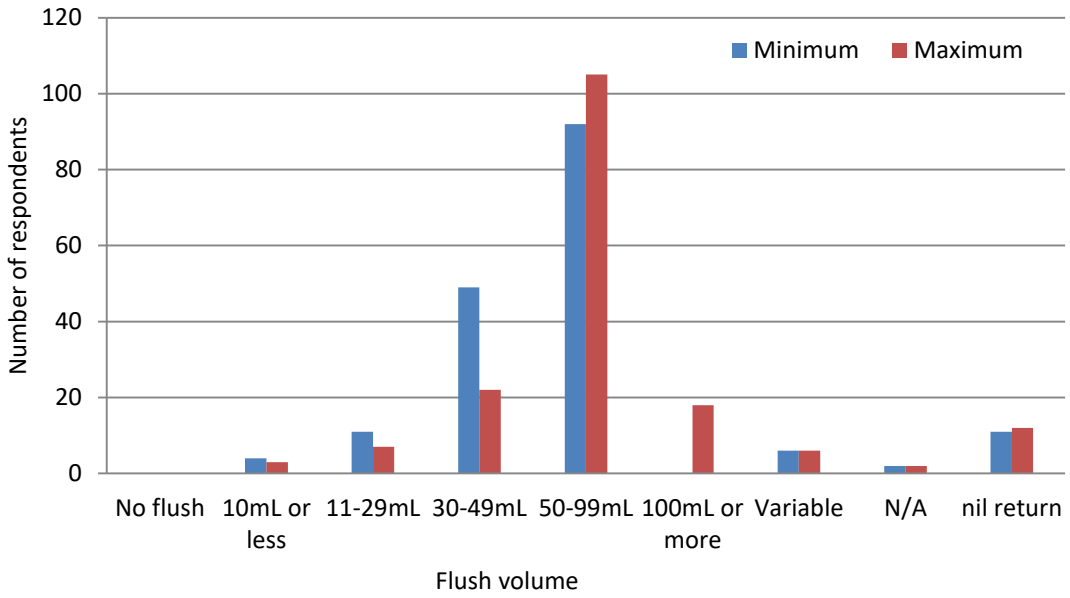



**Figure 2.5.1a Maximum and minimum post-feed flush volume**

Volumes used for flushing the tube prior to medication administration were provided by 105 respondents. The trend was towards a smaller volume when compared to the post-feed flush. The distribution of volumes used or recommended are detailed in figure 2.5.1b. Six respondents indicated that they did not flush the tube at all prior to giving medication. Reasons for varying the flush volume were similar to those given for the post-feed flush, however the number of medications as a reason was cited more often, a history of tube blockage was a new reason cited in response to this question. The full range of reasons are detailed in table 2.5.1b.

Volumes used to flush the tube between medications were provided by 76 respondents, with a further trend towards smaller volumes, the most frequently cited volume being 10mL. The distribution of flush volumes are detailed in figure 2.5.1c. Eight respondents indicated that they did not flush the tube between medications. Reasons for varying the flush volume were similar to those given previously but with medication specific reasons being cited more frequently. The distribution of responses are detailed in table 2.5.1b, three new themes were identified.

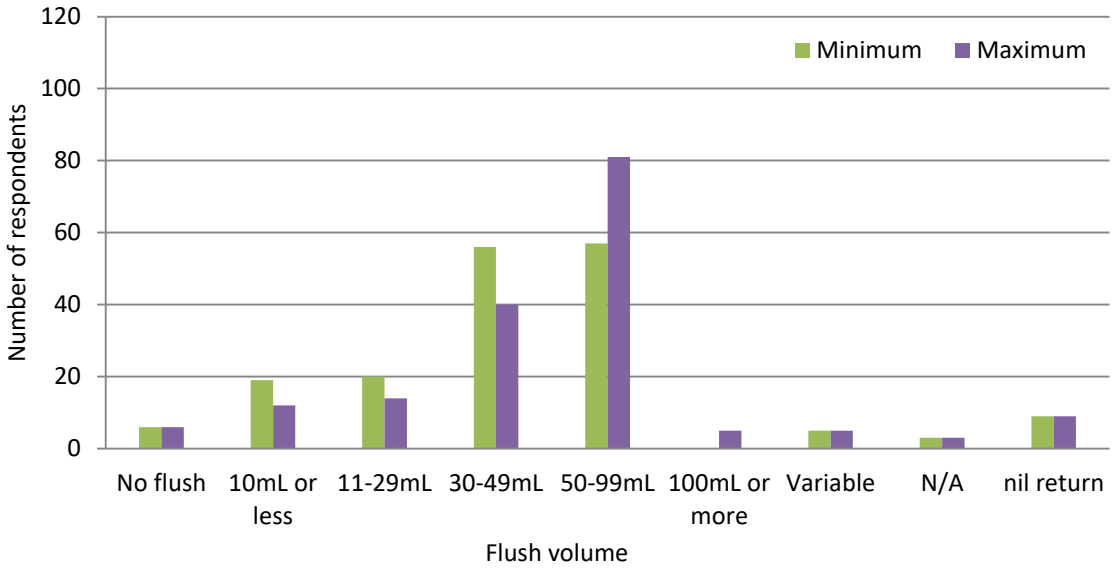



**Figure 2.5.1b Maximum and minimum pre-medication flush volume**

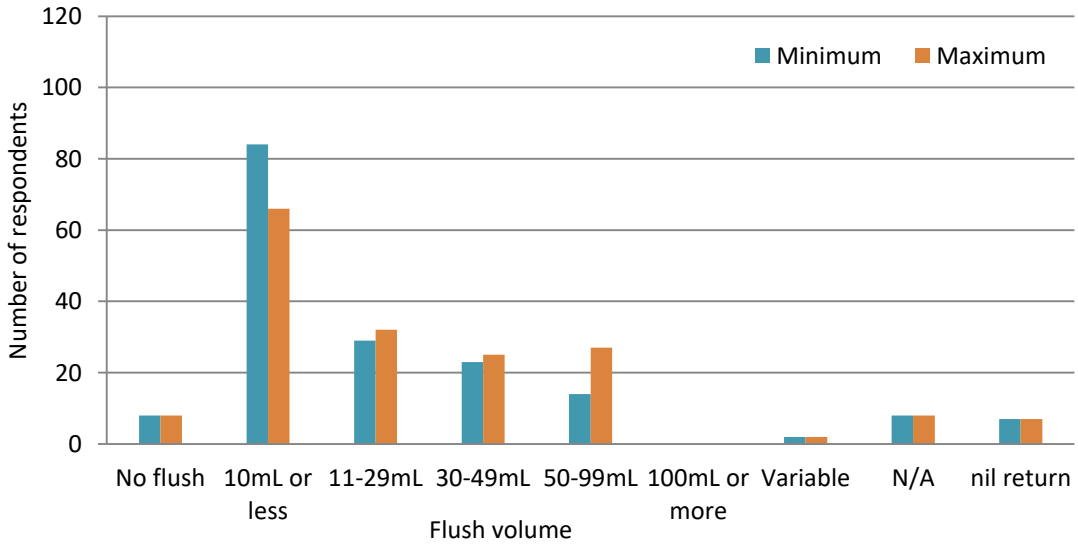



**Figure 2.5.1c Maximum and minimum between-medication flush volume**

When specifically asked about liquid medicines, 2 respondents indicated that they did not administer liquid medicines; 35 respondents felt this was not applicable to their role, all of which were dietitians. 138 respondents indicated that they administered liquid medicines however a significant number did not supply information on the specific method they used. The most frequent detail provided related to dilution prior to administration. All responses related to methodological detail are listed in table 2.5.1c.

**Table 2.5.1c Liquid medication administration methods**

| Response | Number n=138 | % |
|---|---|---|
| Refer to reference source or other healthcare professional | 35 | 25.4 |
| Comments unrelated to method of administration | 29 | 21.0 |
| Dilute with water before administration | 28 | 20.3 |
| Nil response | 17 | 12.3 |
| Use a 50ml syringe | 7 | 5.1 |
| Administer by gravity | 4 | 2.9 |
| Administer using flush/push | 4 | 2.9 |
| Use appropriate size syringe | 3 | 2.2 |
| Use separate syringes for each dose | 1 | 0.7 |

The question relating to administration of tablets had only 78 positive responses. 48 respondents did not administer tablets, 18 dietitians (23.4%), 21 nutrition nurses (29.6%), 1 other profession (25%) and 8 other nurses (34.8%). 43 felt that it was not applicable to their practice, this consisted of 36 dietitians (46.8%) , 4 nutrition nurses (5.6%), 1 other profession (25%), 8 other nurses (34.8%). 6 did not give a response (3 dietitians, 3 nutrition nurses). 8 respondents indicated a specific volume of water to mix tablets with, the volumes ranged from 2ml to 50ml.

The specific crushing methods identified from the descriptions were: use of a pestle and mortar, a pill crusher, between two spoons and a crushing syringe (a specifically designed syringe with an inbuilt crushing tip).

Thirty respondents indicated that they would check with a pharmacist, however this may be heavily biased as the information provided to responders indicated that the researcher was a pharmacist.

Methods used to administer tablets and descriptive themes identified by the 78 positive respondents are detailed in table 2.5.1d.

**Table 2.5.1d Tablet medication administration methods**

| | Number n=78 (20 dietitians, 43 nutrition nurses) | % |
|---|---|---|
| Crush and mix with water | 39 | 50.0 |
| Only use if liquid preparation not available or suitable | 34 | 43.6 |
| Check with pharmacist | 30 | 38.5 |
| Only if soluble or dispersible | 15 | 19.2 |
| Do not crush mr/ec/cr | 9 | 11.5 |
| Volume of water specified | 8 | 10.3 |
| Use pestle and mortar | 8 | 10.3 |
| Use pill crusher | 8 | 10.3 |
| Crush using spoons | 3 | 3.8 |
| Crushed using clean equipment | 2 | 2.6 |
| Put powder into syringe and then draw up water | 1 | 1.3 |
| Push/pause flush after dose | 1 | 1.3 |
| Capsules opened and mixed with water | 1 | 1.3 |
| Put tablet into barrel of syringe and draw up water | 1 | 1.3 |
| Crushing syringe | 1 | 1.3 |

122 respondents indicated problems and specific medications they associated with blockage, analysis of these responses identified 51 medications and types of formulation. The full details of specific medication are listed in table 2.5.1e, non-specific comments are detailed in table 2.5.1f.

The most commonly cited medications, omeprazole and lansoprazole, are available as granular dispersible preparations, these were expected to be identified as problem formulations. However, the number of liquid medicines associated with problems was higher than expected with viscosity or stickiness being a recurring problem. Interactions with medication were also frequently cited for a range of medicines and indicate an additional dimension to what professionals perceive as a problem.

**Table 2.5.1e Medication associated with problems or blockage**

| Medication /formulation type | No. associating with problems | No. associating with blockage | Other comments/problems |
|---|---|---|---|
| **Omeprazole** | 55 | 53 | Timing of dose for overnight feeds 1<br>Small granules block tube 4<br>No liquid preparation 2<br>Need to administer with sodium bicarbonate to prevent blockage 1<br>Doesn't dissolve 3<br>Works best in put into the barrel of a syringe and administered quickly 1 |
| **Lansoprazole** | 55 | 50 | Very granular 1<br>Usually not mixed and flushed properly 2<br>Timing of dose with overnight feeds 1<br>Small granules stick in tube 2<br>No liquid available 1<br>Large granules in the suspension formulation 1<br>Difficult to dissolve 5<br>Blocks if Fastab ® not used 2 |
| **Baclofen** | 20 | 8 | Block if not mixed with enough water 4<br>Has to be diluted 2<br>Viscous/thick 9<br>Can result in large volume of water to dilute 1<br>Difficult to administer 1<br>Patients reluctant to dilute 1 |
| **Lactulose** | 19 | 14 | Viscous 2<br>Sticky 2<br>Needs large volume of water to dilute 2<br>Problem if fluid restricted 1<br>Blocks if not diluted 3 |
| **Phenytoin** | 15 | 1 | Interaction/break required in feeding 12<br>Need to nix with water 1<br>Thick and sticky takes a long time to give 3 |
| **Creon ®** | 8 | 6 | Difficult to crush 1<br>Have to get prescription changed 1<br>Electrostatic nature of medication 1 |
| **Clarithromycin** | 7 | 7 | |
| **Paracetamol** | 7 | 4 | Very thick liquid sticks to tube 1<br>Particles block tube 2<br>Blocks if not dissolved properly 1<br>Too fizzy 1 |
| **Ciprofloxacin** | 6 | 5 | Interaction / feed breaks difficult in ITU 1<br>Need to use tablets to avoid blockage 1 |
| **Multivitamins** | 5 | 0 | Lack of suitable formulation 1<br>Forceval thick and sticks to syringe 1<br>Forceval not easy to administer 1<br>Sanatogen gold difficult to give/crush 2 |

| Medication /formulation type | No. associating with problems | No. associating with blockage | Other comments/problems |
|---|---|---|---|
| | | | Have to change prescription to dalivit 1 |
| **Co-amoxiclav** | 4 | 4 | |
| **Antacids** | 4 | 2 | Gavison advance turns feeds to 'mashed potato' if mixed 1<br>Viscous 2<br>Sticky 1 |
| **Iron Supplements** | 3 | 3 | Ferrous fumarate blocks 1 |
| **Fybogel ®** | 3 | 2 | Sticky 1 |
| **Sodium Valproate** | 3 | 2 | Very thick and sticky 1 |
| **Carbamazepine** | 3 | 1 | Interaction with feed 2<br>Thick and viscous 1 |
| **Vitamin B Co Strong** | 3 | 0 | Difficult to crush 2<br>Have to change to injection 1<br>Have to change to vigranon B 2 |
| **Metronidazole** | 2 | 1 | Interaction results in feeds breaks on ITU 1<br>Suspension blocks tube 1 |
| **Sucralfate** | 2 | 1 | Interaction results in feed breaks in ITU 1 |
| **Warfarin** | 2 | 0 | Not suitable for crushing 1<br>Interaction results in feed breaks in ITU 1 |
| **Mesalazine** | 1 | 1 | Granules block tube 1 |
| **Sando K ®** | 1 | 1 | Blocks if mixed with feed 1 |
| **Pyridostigmine** | 1 | 1 | Dissolves but leaves powdery residue 1 |
| **Asasantin ®** | 1 | 1 | Very difficult to dissolve 1 |
| **Aciclovir** | 1 | 1 | |
| **Metformin** | 1 | 1 | Tablets block tube 1 |
| **Magnesium Hydroxide** | 1 | 1 | |
| **Cardiac Medicines** | 1 | 0 | No suitable form 1 |
| **Ramipril** | 1 | 0 | No liquid 1 |
| **Thiamine** | 1 | 0 | Doesn't dissolve well 1 |
| **Rifampicin** | 1 | 0 | Interaction 1 |
| **Magnesium Glycerophosphate** | 1 | 0 | Difficult to get syrup 1 |
| **Riluzole** | 1 | 0 | Difficult to get liquid 1 |
| **Nimodipine** | 1 | 0 | Limited formulations available 1 |
| **Flucloxacillin** | 1 | 0 | Interaction results in feed breaks in ITU 1 |
| **Penicillin** | 1 | 0 | Interaction results in feed breaks in ITU 1 |
| **Levofloxacin** | 1 | 0 | Interaction results in feed breaks in ITU 1 |
| **Digoxin** | 1 | 0 | Interaction results in feed breaks in ITU 1 |
| **Theophylline** | 1 | 0 | Interaction results in feed breaks in ITU 1 |
| **MST ®** | 1 | 0 | Not suitable for crushing 1 |
| **Codeine Syrup** | 1 | 0 | Viscous 1 |
| **Movicol** | 1 | 0 | Difficult to administer 1 |
| **Zopiclone** | 1 | 0 | Coating a problem, have to use an alternative 1 |
| **Levothyroxine** | 1 | 0 | Small and difficult to crush 1 |
| **Levetiracetam** | 1 | 0 | Thick and oily 1 |

**Table 2.5.1f Non-drug specific comments on problem medication**

| Medication /formulation type | Number of respondents associating this with problems | Number of respondents associating this with blockage | Other comments/problems |
|---|---|---|---|
| **Solid dosage forms not crushed properly** | 12 | 12 | Takes too long to crush tablets 1 |
| **Viscous Liquids** | 10 | 8 | Needs diluting to avoid blockage 1<br>Prone to block if not flushed 1 |
| **Some antibiotics** | 4 | 4 | Thick if not diluted will block 1<br>Thick syrups 1 |
| **Chalky textured medication** | 1 | 1 | |
| **Capsules with granules** | 1 | 1 | |
| **Enteric coated tablets** | 1 | 1 | |

68 respondents indicated that mixing medication was not applicable to their practice, 59 dietitians (76.6%), 5 nutrition nurses (7%), 1 other profession (25%) and 3 other nurses (13%). 101 respondents indicated that they would not mix medication together prior to administration. There were 5 (4.7%) respondents (2 nutrition nurses, 3 other nurses) who indicated that they mixed medication together prior to administration via a feeding tube. 3 of these indicated that they would mix other medication with paracetamol, 2 indicated that they would only mix medication if advised by pharmacy/formulary, 1 indicated that they would mix crushed tablets together and 1 indicated that they would mix many medication together.

Decisions relating to formulation choice can be influenced by several members of the healthcare team. 169 respondents indicated which professionals were responsible for deciding on the choice of formulation used within their practice. Multiple responses were permitted. Pharmacists were the most cited professional group; however social desirability may have introduced bias here potentially inflating this response. See figure 2.5.1c for distribution of responses.

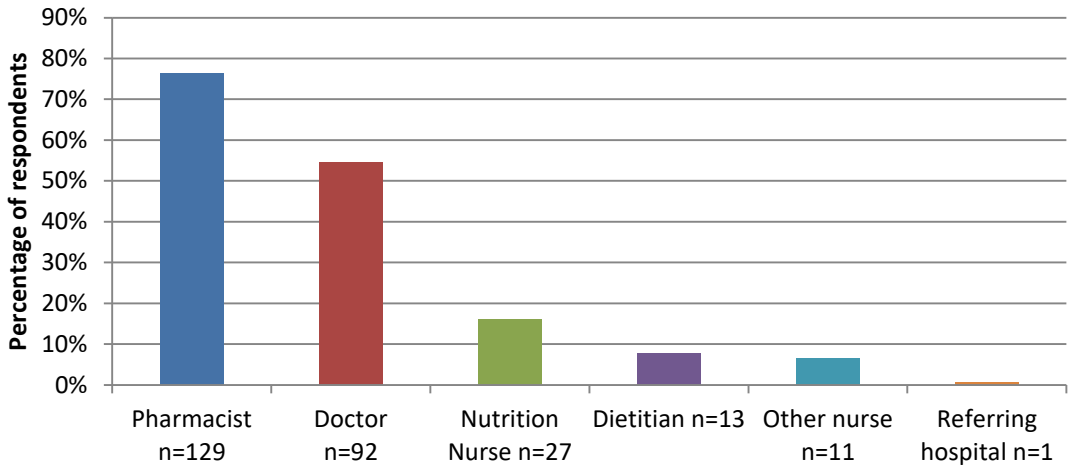



**Figure 2.5.1c Profession responsible for deciding formulation used**

A wide range of methods were described for clearing blocked tubes. 170 responses were returned and multiple responses were permitted. The most frequent response was warm water flush. In general dietitians favoured enzymatic clearance methods such as clogzapper®, pancreatic enzymes and carbonated solutions, whereas the nursing approach favoured tube manipulation methods such as push/pull techniques, small syringes, aspiration and direct manipulation. Figure 2.5.1d details the range of methods used to unblock tubes.

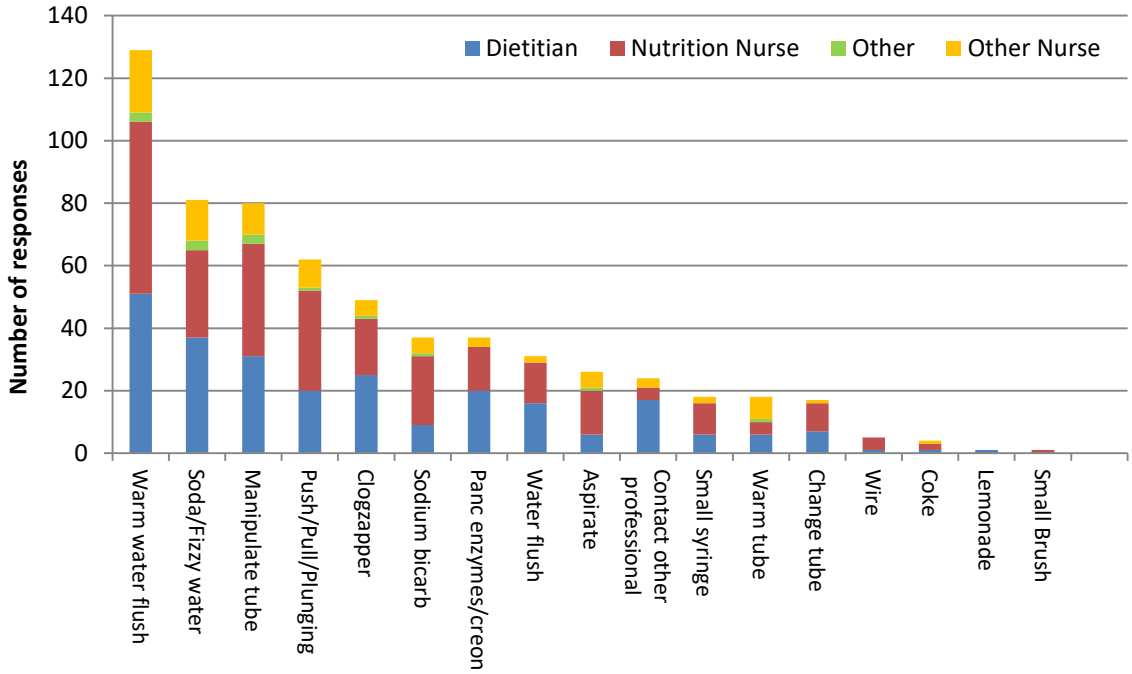



**Figure 2.5.1d Methods used or recommended by professionals for unblocking enteral feeding tubes**

The majority of respondents confirmed that they used or recommend the use of specific enteral syringes (172 of 175). 81 respondents provided comments on the problems associated with the use of these syringes. The themes and frequency are identified in table 2.5.1g, most comments relating to poor fit, print rubbing off and sticking plunger relate to one brand.

**Table 2.5.1g Problems reported with enteral syringes**

| | **Responses n=81** |
|---|---|
| Poor fit or leaking | 37 |
| On-going supply problems | 11 |
| Sticking plunger | 11 |
| Initial supply problems | 10 |
| Confusion over product codes for ordering/wrong product frequently requested | 9 |
| Encouraging staff to use them | 6 |
| Cost | 6 |
| Print on tubes rubbing off | 2 |
| Inadequate supplies ordered for patient | 1 |
| Awkward connections due to angle of port/tip | 1 |

A specific size of syringe recommended for flushing was provided by 152 respondents, 138 (90.1%) recommended a 60ml syringe, other respondents recommended a choice of syringe size influenced either by tube type, age of patient or flush volume being used. 98 respondents recommend a specific size of syringe for medication, 58 recommend a 60ml syringe, a range of syringe sizes were indicated by other respondents, 16 indicating that it should related to the dose or volume of medication being given. Within the free text section of the survey seven respondents described measuring the medication dose accurately in a small syringe and then transferring to a larger syringe for administration, additionally four respondents expressed concerns over the lack of clarity on the syringe size associated with tube rupture.

Fifty three respondents included information or insights in the free text section of the survey, the majority were providing clarification or justification for their responses within the survey. However, several additional insights were derived from the free text section of the survey. Despite not being specifically asked, eight respondents indicated that cost influenced

formulation choice, particularly on transfer to primary care. Three respondents specifically called out the transfer to primary care as a reason for formulation changes or a change in administration practice.

### 2.5.2 Patient survey Results

71 completed responses were received (54.6%), 6 returned uncompleted (4.6%).
The age distribution and tube type are indicated in table 2.5.2a. Tube size range is indicated in table 2.5.2b, there was no relationship between tube type or size and age of the patient. 7.1% of patients did not know what type of tube they had, 35.7% did not know what size the tube was.

**Table 2.5.2a Age distribution and tube type of respondents**

| Age Range | Tube type | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Gastrostomy** | **Low profile device** | **Jejunstomy (JEJ or PEGJ)** | **Naso-gastric** | **Naso-jejunal** | **Unknown** | Total no. patients |
| **0-18 years** | 6 | 6 | 4 | 4 | 0 | 2 | **22** |
| **19-40 years** | 1 | 5 | 3 | 2 | 0 | 1 | **12** |
| **41-65 years** | 8 | 3 | 9 | 1 | 1 | 0 | **22** |
| **66+ years** | 6 | 4 | 1 | 1 | 0 | 3 | **15** |
| Total | **21** | **18** | **17** | **8** | **1** | **6** | **71** |

**Table 2.5.2b Enteral tube size distribution**

| **Tube Size** | **Number of patients** |
|---|---|
| 8Fr | 9 |
| 12Fr | 5 |
| 14Fr | 18 |
| 15Fr | 5 |
| 16Fr | 6 |
| 18Fr | 1 |
| 20Fr | 1 |
| Unknown | 26 |

Respondents were asked to describe the volume of water they used to flush the tube after the feed was stopped, the volume flush before medication was given and the volume flushed between medications. 2 of the 21 paediatric patients did not flush or have their tube flushed after the feed was stopped, 1 of 21 only sometimes flushed the tube after the feed was stopped. 15 patients did not flush the tube before giving medication, 13 did not flush between medications. Figure 2.5.2a illustrates the range of flush volumes used in paediatric patients.

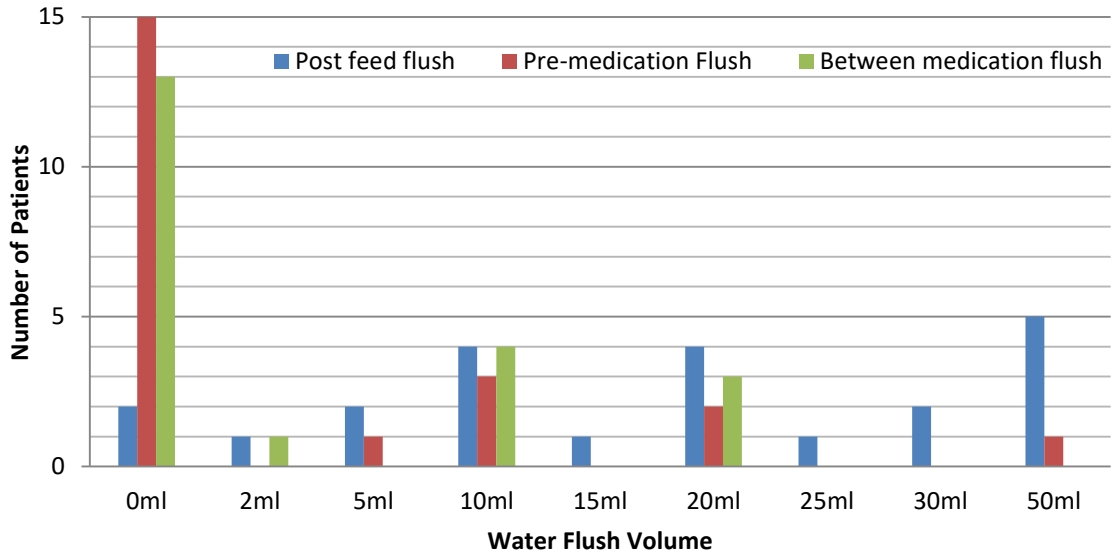



**Figure 2.5.2a Tube flush volumes used in paediatrics**

All adult patients flushed their tube after the feed was stopped, there was wide variation in flush volume used, the most common volume was 50mL, however the average volume was 71ml due to the small number of respondents using very large volumes. The large volumes are most likely to represent hydration fluid volumes rather than tube clearance flushes as indicated in the reasons for varying volume as described below. Figure 2.5.2b illustrates the flush volumes used in adult patients.

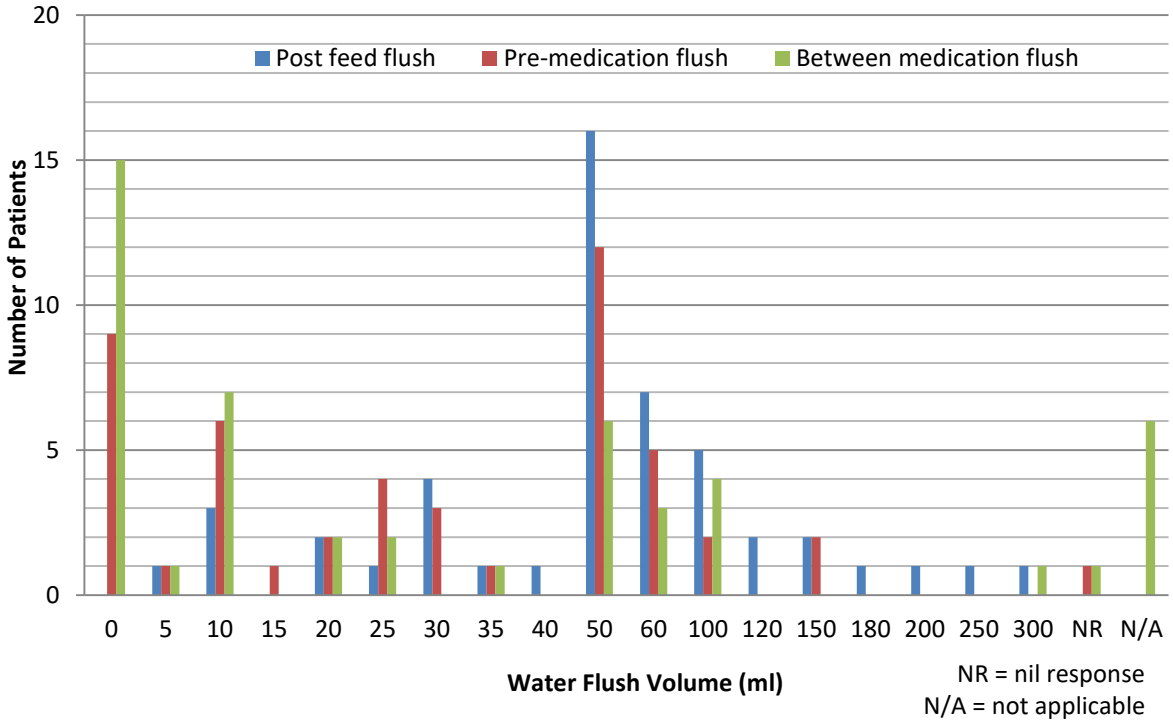



**Figure 2.5.2b Tube flush volumes used in adults**

Respondents were asked if there were any reasons for varying the volume they used to flush their tubes. 15 respondents described factors that affected the volume they used to flush their tube after administering feed; these are detailed in Table 2.5.2c. 10 respondents described factors that affected the volume they used to flush the tube prior to giving medication, see table 2.5.2d. Nine respondents described factors affecting the volume they used to flush the tube between medications, see table 2.5.2e. Medication related reasons are more prominent in the pre-medication and between medications flush.

**Table 2.5.2c Factors affecting post-feed flush volume**

| Description | Number of respondents |
|---|---|
| Depends on volume of feed | 2 |
| Too much volume causes vomiting | 1 |
| More needed in hot weather | 1 |
| Depends on fluid volume needed during the day | 4 |
| More needed if tube is 'sluggish'/feed sticking to tube | 6 |
| Use less if I'm out and don't have access to sterile water | 1 |
| Depends on the volume of medication | 1 |

**Table 2.5.2d Factors affecting pre-medication flush volume**

| Description | Number of respondents |
|---|---|
| Depends on duration of feed | 2 |
| Increase to meet fluid requirements | 2 |
| Increase if tube is 'sluggish' | 1 |
| Don't give extra water if 'feeding' water before meds | 1 |
| Reduce volume if feed is running at the same time | 1 |
| Depends on medication | 3 |

**Table 2.5.2e Factors affecting between-medications flush volume**

| Description | Number of respondents |
|---|---|
| Increase if tube is 'sluggish' | 1 |
| Depends on medication volume | 1 |
| Depends on number of medication | 2 |
| Flushing between each medication would be too much volume | 1 |
| Use less if I'm out and don't have access to sterile water | 1 |
| Depends on medication viscosity | 3 |

From the 71 patients returning completed questionnaires, 10 did not use their tube for medication or were not taking any medication, 3 patients were not on regular medication but occasionally used the tube for liquid antibiotics. For those patients administering medication via their tube, a total of 237 medicines were administered, an average of 4.1 medicines per patient per day. Of the 237 medicines administered daily, 192 (81%) were an appropriate formulation, 19% (45) of doses required manipulation, 21 of these were available as a licensed formulation not requiring manipulation (8.9%), See figure 2.5.2c for the number of medications administered daily. 86 individual medicines were identified, see table 2.5.2f for medicines being administered by 2 or more patients.

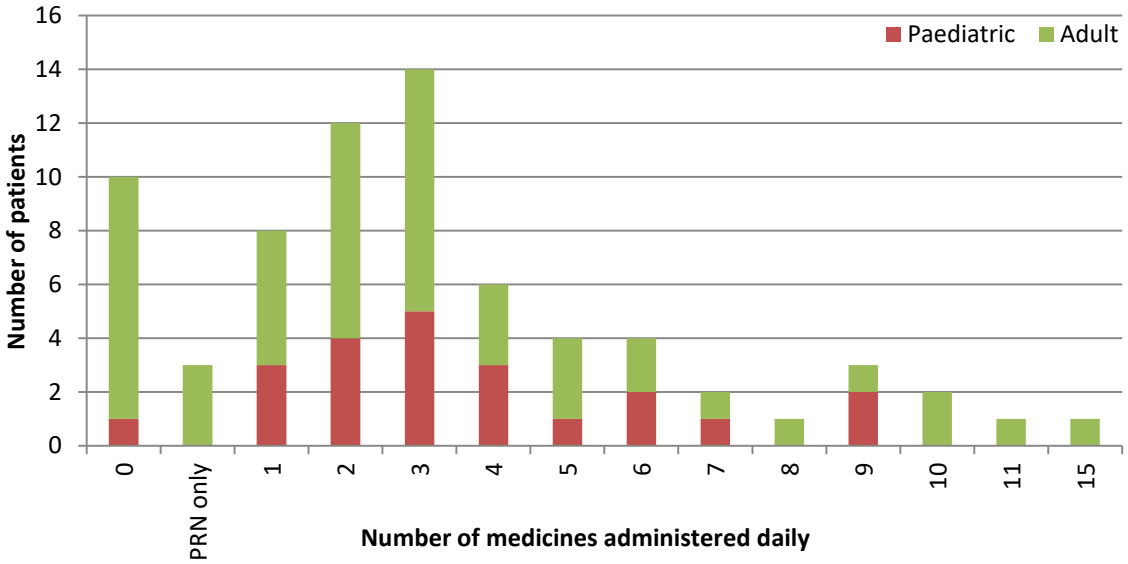



**Figure 2.5.2c Number of medicines administered daily**

**Table 2.5.2f Number of patients recieving each medicine**

| Number of patients receiving these medication | Medication (s) |
|---|---|
| 36 | Paracetamol |
| 13 | Omeprazole |
| 9 | Movicol® Powder |
| 7 | Domperidone, Lactulose, Ranitidine |
| 6 | Baclofen, Co-codamol, Fluoxetine, Lansoprazole, Morphine |
| 4 | Cetirazine, Levothyroxine, Loperamide, Metoclopramide, Prednisolone, Senna |
| 3 | Aspirin, Carbamazepine, Clonazepam, Ibuprofen, Ondansetron, Sodium valproate, Oxybutynin |
| 2 | Amoxicillin , Azithromycin , Hyoscine butylbromide, Ciprofloxacin, Clonidine, Diazepam, Ferrous fumarate, Gabapentin, Levetiracetam, Nifedipine , Pancreatic enzymes, Potassium, Propranolol, Simvastatin, Sulfasalazine, Sytron ®, Tramadol, Trimethoprim |

The responses relating to the administration method for liquid medicines were reviewed, the detail provided was very varied, 51 patients provided some information, eight clear aspects of

administration were defined in the descriptions provided by patients. The descriptors are detailed in table 2.5.2g.

**Table 2.5.2g Liquid medication administration**

| Description | Number of respondents |
|---|---|
| Administer in small syringe / 10ml syringe | 8 |
| Administer in 50/60ml syringe | 7 |
| Medication diluted before administration | 6 |
| Medication administered undiluted | 1 |
| Administered under gravity | 6 |
| Administered by pushing/flushing | 4 |
| Use the same syringe to flush with water after administering dose | 2 |
| Administer slowly | 1 |

25 patients provided details of administration of tablets or capsules via their feeding tubes. Several themes were identified. See table 2.5.2h for details provided. 7 patients specifically mentioned the volume they used to mix with the crushed tablets these were, 3-5ml, 10ml, 10-50ml, 2 used 20ml, 30mL, and a 'cup' of water.

**Table 2.5.2h Administration details for solid dosage forms**

| Description | Number of respondents |
|---|---|
| Only used tablets if liquid was not available | 2 |
| Gave soluble tablets using syringe | 2 |
| Dissolved tablets in water | 10 |
| Dissolved in warm water | 1 |
| Opened capsules and mixed with water | 1 |
| Crushed tablets (no method specified) | 8 |
| Crushed between 2 spoons | 1 |
| Crushed using pestle and mortar | 1 |
| Crushed using pill crusher | 1 |
| Crushed and added to liquid medicines | 1 |

Ten patients provided information on mixing medicines, they described mixing all the medicines they were prescribed together prior to administration.

Patients identified the following medications as being associated with tube blockage:

Omeprazole (7), Lansoprazole (4), Sodium valproate (2), Sulphasalazine (2), Liquid antibiotics (2), nitrofurantoin (1), Ciprofloxacin (1), Antacids/Gaviscon (1), Baclofen (1), Clopidogrel (1), Salbutamol (1), Magnesium (1), tablets that don't dissolve easily (1).

Respondents were asked who recommended the medication formulation they used and who they got advice about medication from. 3 patients responded that they advise the prescriber on the formulation which was used. Figure 2.5.2e indicates the profession who recommended the formulation used and who the patient would ask for advice about their medication. Figure 2.5.2f shows the number of professionals that the patient would approach for advice.

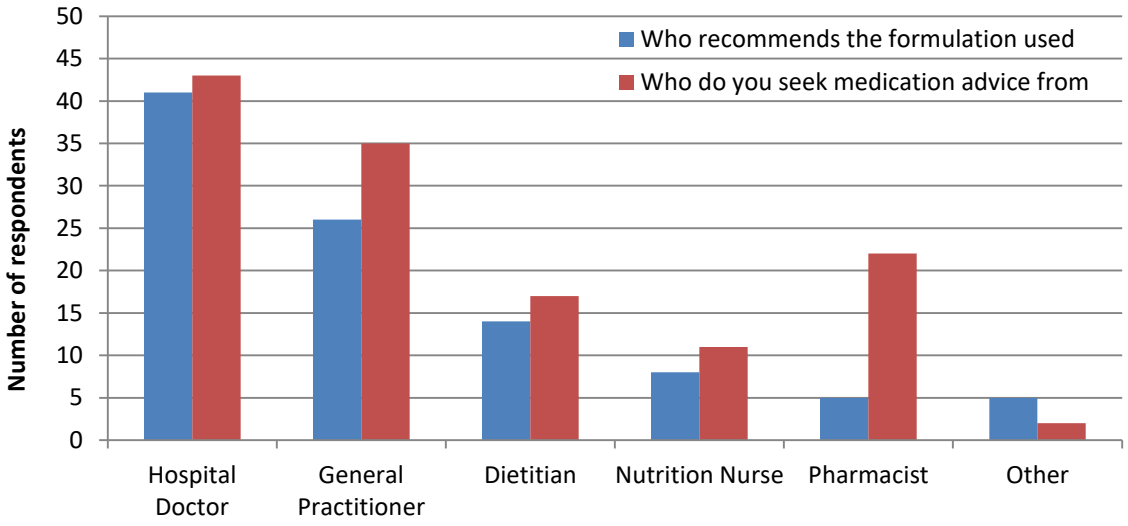



**Figure 2.5.2e Professionals influencing formulation choice and giving medication advice**

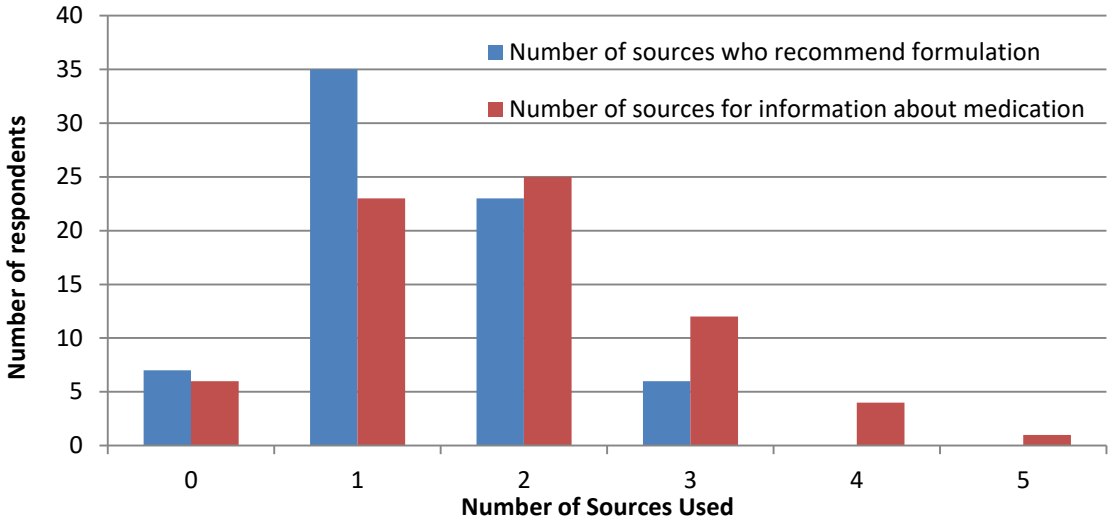



**Figure 2.5.2f Number of information sources**

47 patients provided details of the action taken when tube blockage occurred, 18 reported never having a tube blockage and 6 did not respond. See figure 2.5.2g for the range and frequency of responses.

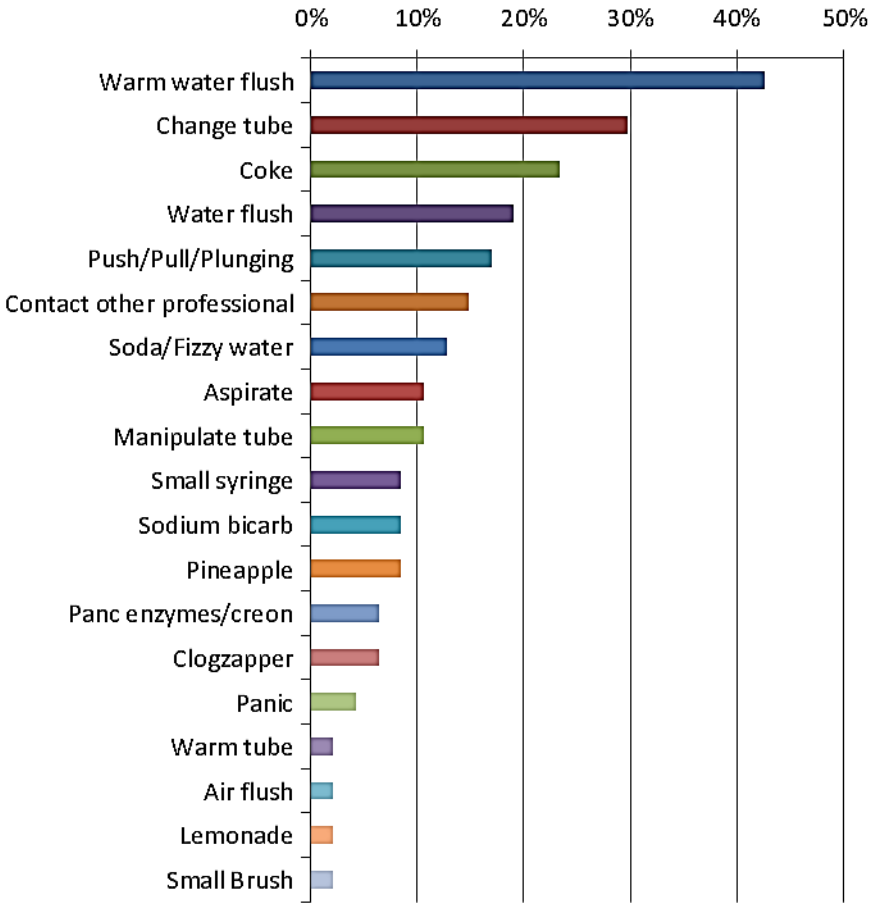



**Figure 2.5.2g Method(s) used by patients to unblock a feeding tube**

8 of the 71 patients did not use the enteral syringes, 2 patients commenting that they had difficulties obtaining supplies in community. Of the 63 patients that used enteral syringes, 29 had not had any problems with them, 16 did not comment. 18 patients commented on the enteral syringes, the themes identified are detailed in table 2.5.2i.

**Table 2.5.2i Enteral syringe issues**

| Issue | N=18 |
|---|---|
| Become stiff and difficult to flush quickly | 7 |
| Difficult fit to tube/poor seal | 4 |
| Supply is an issue | 2 |
| Need lots of them | 1 |
| Does not fit tube without an adapter | 1 |
| 50/60mL syringes difficult/painful to push | 1 |
| Problems getting them prescribed | 1 |
| Port on syringe tip is difficult to remove air bubbles due to position | 1 |

In the general comments section at the end of questionnaire there were several comments relating to medication formulation and availability, professionals knowledge of medication administration and information sources. These provide valuable insights into the patient experience.

Three comments specifically related to preference for liquid formulations and concerns about availability and cost.

> *Respondent 22 "Over time there have been occasions when a liquid is unavailable. Sometimes this is permanent so I have no choice but to crush tablets. Other times, as has been the case with oxybutynin elixir 2.5mg/5mL, I have been forced to use the tablet form for a period of time as the liquid form was not available. I have never found this satisfactory and I am sure that I do not get a full dose with tablets, however well I rinse the syringe and put the contents through my PEG. Liquid medicines are far more efficient and I know I get a proper dose every time."*

*Respondent 19 "We would always remind any prescribers that medication needs to be liquid".*

*Respondent 46 "Why do pharmaceutical companies charge such exorbitant prices for the same drug in liquid form?."*

Five free text responses specifically related to the patients experience of advice from healthcare professionals, four of these imply that the patient has no confidence in their healthcare professional to give correct advice.

*Respondent 3 "GPs, Doctors and Pharmacists have no idea about medication for tube fed patients. All just scratched their heads when I asked if it can go down the tube. So I have to go by trial and error. My GP ask me if it can go in the tube before doing a prescription."*

*Respondent 42 "Dietitian has no understanding at all. Pharmacist has no idea about giving medication through a PEGJ tube."*

*Respondent 19 "If any doubt about new medications we would seek advice from the pharmacist (we use the same one when we can) or community nurse – who may seek advice from the hospital pharmacists."*

*Respondent 46 "Antibiotics are administered, when necessary, in liquid form. Pharmacists usually use tap water – should be sterile water if patient has a jejunostomy."*

*Respondent 24 "There is very little awareness amongst doctors, nurses, GPs etc that medication can be put through feeding tubes, especially jejunostomies. I have had to become the expert and tell doctors which medication should be delivered when I'm not well it disheartens and scares me when medical professionals don't know what to do."*

Two free text comments specifically related to the availability and access to information, one indicating that they took their own resources with them.

*Respondent 37 "Not enough info about which meds to put down PEG and which not to readily available."*

*Respondent 24 "I take it [The Handbook of Drug administration via Enteral Feeding Tubes] with me to doctors, hospitals etc so that they can use it as a reference tool when prescribing medicines."*

### 2.5.3 Community Nursing Home Results

21 community care homes with nursing returned completed questionnaires (41%). These 21 respondents provided care for a total of 882 patients, 41 of which had enteral feeding tubes (5%), all were using these tubes for medication delivery.

Only four care homes with nursing agreed to participate in the observational study, each having only one patient with a feeding tube. Due to the low number of patients at each centre and the time required for each observation of medication administration it was decided that there was insufficient patient numbers or available time resource to proceed with an observational second phase at this time

Specific medication and tube data was provided for 39 patients, patients received an average of 10.2 doses per day. Analysis of the medication data identified 65 medicines and a total of 399 doses. See Table 2.5.3a for Top 20 medication.

Of the 399 identified doses, 68 (17%) required manipulation to facilitate enteral tube administration. 18 (4.5%) of these were available in an appropriate formulation.

**Table 2.5.3a Commonly administered medication in responding care homes with nursing**

| Medicine | Number of patients | Total number of administrations | % of patients |
|---|---|---|---|
| Paracetamol | 23 | 83 | 59.0% |
| Baclofen | 13 | 40 | 33.3% |
| Lactulose | 13 | 23.0 | 33.3% |
| Lansoprazole | 13 | 13 | 33.3% |
| Aspirin | 9 | 9 | 23.1% |
| Sodium valproate | 8 | 17.0 | 20.5% |
| Movicol | 8 | 8.5 | 20.5% |
| Gabapentin | 7 | 23 | 17.9% |
| Metoclopramide | 6 | 20 | 15.4% |
| Omeprazole | 6 | 7 | 15.4% |
| Citalopram | 5 | 5 | 12.8% |
| Simvastatin | 5 | 5.0 | 12.8% |
| Levothyroxine | 5 | 5 | 12.8% |
| Senna | 4 | 5 | 10.3% |
| Levetiracetam | 3 | 6 | 7.7% |
| Phenytoin | 3 | 8 | 7.7% |
| Cetirizine | 3 | 3 | 7.7% |
| Diazepam | 3 | 5 | 7.7% |
| Amlodipine | 3 | 3 | 7.7% |
| Ramipril | 3 | 3 | 7.7% |

A variety of enteral tube sizes were identified, all were permanent gastrostomy devices. See table 2.5.3b for size distribution. The most common size and device was the Fresenius 15Fr PEG device, this is the device of choice for the local acute trust.

**Table 2.5.3b Size of enteral feeding tube (NH patients)**

| Enteral tube size | Number of patients (n=47) |
|---|---|
| 12 french | 3 |
| 14 french | 5 |
| 15 french | 18 |
| 16 french | 1 |
| 20 french | 3 |
| Size unknown | 7 |

21 respondents provided data relating to administration techniques. All 21 flush the tube when the feed is stopped; volumes used ranges from 50-200ml. Mean volume was 86.8ml, median and mode are 50ml, the median is skewed upwards due to a low number of very high flush volumes, as seen with other group responses this most likely represents hydration volume rather than tube clearance volume per se. See table 2.5.3c for flush volume distribution.

**Table 2.5.3c Tube flush volume when feed is stopped**

| Volume | Number of responses (n=21) |
|---|---|
| No response | 1 |
| Varies | 1 |
| 50-60ml | 1 |
| At least 50ml | 1 |
| 50ml | 9 |
| 100ml | 5 |
| 200ml | 3 |

All 21 respondents flush the EFT with water before medication is administered; volumes ranged from 20ml to 200ml. Although the median and mode were 50ml, the mean value was 70mL. See Table 2.5.3d for distribution of flush volumes.

**Table 2.5.3d Tube flush volume before drug administration**

| Volume | Number of responses (n=21) |
|---|---|
| Varies | 1 |
| 20ml | 2 |
| 50ml | 10 |
| At least 50ml | 1 |
| 60ml | 1 |
| 100ml | 4 |
| 150ml | 1 |
| 200ml | 1 |

Six respondents indicated that they did not flush the tube between medication administrations. Of those that did flush the tube the volumes ranged from 10ml to 150ml. The

median and mode were both 50ml, the mean value was 37.1mL. These volumes are much higher than those in the professional and patient group and may indicate a misinterpretation of the question, perhaps indicating the volume of water given between medication administration episodes rather than between each individual medication. See table 2.5.3e for distribution.

**Table 2.5.3e Tube flush volume between medications**

| Volume | Number of responses (n=21) |
|---|---|
| 0ml (no flush) | 6 |
| 10ml | 2 |
| 20ml | 1 |
| 30ml | 1 |
| 50ml | 7 |
| At least 50ml | 1 |
| 60ml | 1 |
| 100ml | 1 |
| 150ml | 1 |

20 respondents confirmed that they administered liquid medicines via EFTs. 9 specifically mention administration using a syringe to plunge the medication through the tube, there was no mention of administration via gravity. 3 specifically describe diluting liquids prior to administration.

17 respondents confirmed that they gave tablets via EFTs. 11 describe dissolving or dispersing the tablets prior to administration, 8 specifically describe crushing tablets, no details were given regarding the equipment they used to achieve this. 3 describe opening capsules. Only 4 respondents specify the volume of water that the tablets were mixed with, 2 use 10ml, 1 use 20ml and 1 use 30ml.

Medication identified by respondents as causing problems or blockage were omeprazole (1), lansoprazole (2), felodipine MR (1), ranitidine tablets (1), and Zomorph® capsules (1). The use of modified release preparations such as felodipine and zomorph® are a concern as these must have been crushed to be administered potentially resulting in adverse effects.

Two respondents confirmed that they mixed medicines together prior to administration. One mixed all medicines together, the other respondent mixed the liquid medicines together. Neither respondent gave specific details of the medicines involved.

The medication formulation for use was decided by the Doctor (20), Nurse (6), Dietitian (4), and/or Pharmacist (3). Advice was sought from the Pharmacist (10), Dietitian (10), Doctor (9) and/or Nurse (6).

Several methods were described to unblock tubes, 6 respondents had not had this occur, three of these described what they would do in the event of a tube blockage. See table 2.5.3f for breakdown of responses.

**Table 2.5.3f Methods used for unblocking tubes**

| Methods | Number of respondents (n=21) |
|---|---|
| Soda water/carbonated water/fizzy water | 9 |
| Warm water | 5 |
| 'milk' tube | 5 |
| Push/pull water flush | 6 |
| Cola | 3 |
| Pancreatic enzymes | 1 |

All respondents had a policy for administration and all used enteral syringes, no respondents had problems with the syringes.

## 2.6 Discussion

This series of survey data, through the UK wide sample used, provides evidence that the current consensus based guidance (BAPEN, 2003a, Dougherty and Lister, 2008) is generally followed in the UK healthcare environment across acute and community care, in both nursed and self-caring patients. It is the first data to provide insights into the current practice of patients using their enteral feeding tube for medication administration. Through this approach the themes identified from the literature can be explored in more depth across these patient groups and care settings.

### 2.6.1 Enteral tube flushing practice

#### 2.6.1.1 Tube flushing frequency

Enteral tube flushing advice from the professionals surveyed was largely consistent with the recommendations published by BAPEN in 2003 (BAPEN, 2003a) and adopted in the nursing procedural textbook (Dougherty and Lister, 2008), with over 96% of professionals recommending flushing after feed, before medication and between medications, this is also reflected in the nursing home population where 100% of respondents said they flushed after feeds and before medication, although the practice of flushing between medications was lower at 71%, however it is acknowledged that this was not a direct observation of practice and reported procedural compliance may not accurately reflect practice as social desirability bias may result in an inaccurate picture (Van de Mortel, 2008).

These recommendations do not appear to have translated into practice by self-caring patients in the community, the majority of patients flushed the tube after the feed was stopped however the proportion of patients flushing the tube before medication was lower at 66% and the number flushing between medications lower still at 56%. Despite the lower number patients flushing the tube in accordance with current accepted guidance, these values are still higher than those found in the literature for other patient groups(Evans et al., 2007) however there remains a potential benefit in reinforcing guidance.

Three observational studies undertaken in care homes with nursing in Belgium (Joos et al., 2015a), the Netherlands (Stuijt et al., 2013) and Australia (Paradiso et al., 2002) focussed on formulation manipulation for patients with dysphagia. The Belgian research group were the only one to specifically look at tube flushing; they observed very low frequency of pre and post medication tube flushing with less than 2% of administrations having appropriate tube flush. The between medication flushing was very difficult to interpret due to the large proportion of medications mixed together and administered as a single dose. This is clearly much lower than that expressed by both the nursing home group and patient group in this study.

A UK based questionnaire study of carers of 34 children with inherited metabolic disorders dependant on overnight enteral feeding indicated that 91% flushed the tube after feeds and

medication but only 19% flushed before meds (Evans et al., 2007); this practice is more consistent with the findings from this study.

The literature relating to hospital practice is largely survey based, a review of these studies suggest that only 5%-43% of practitioners flush tubes before or between medications (Bankhead et al., 2009). In an Australian survey of nursing practice undertaken at the same time as this survey work 28% of respondents claimed to flush the tube before medication, 47% flushed between medication and 96% flushed after meds (Phillips and Endacott, 2011).

In an observational study in ICU of 310 enteral medication administrations to 65 patients, 514 errors were reported (Al Rakaf and Lababidi, 2009). Inadequate flushing, either before, during or after administration was the most common error, accounting for 27% of the administration errors.

#### 2.6.1.2 Tube flushing volumes

The volume recommended by professionals to flush tubes was fairly consistent with the guidance, being generally between 30-50mL either after feeds or before medications, with a smaller volume recommended between medications (BAPEN, 2003a), this is also borne out in the nursing home practice, although volumes are slightly larger. In addition to UK consensus guidance, 30ml is common pre-and post-feed and medicine flush volume appearing in several references in the literature as far back as the 1980's (Bourgault et al., 2007, Wilson and Haynes-Johnson, 1987, Schmieding and Waldman, 1997, Keithley and Swanson, 2004).

This consistency of advice from healthcare professionals has not translated into practice by self-caring patients in the community where the flushing volumes at all stages vary widely.

From the specialist healthcare professional responses the post-feed flush volume was more likely to be changed due to fluid requirements than the between medication flush, whereas the between medication flush was more likely to be influenced by the number of medications being administered. For patients the factor affecting post-feed flush was if the tube was becoming 'sluggish', whereas number of medications or liquid viscosity was more likely to influence between medication flush volumes.

Some very large flush volumes were reported by all groups of respondents and reflects the use of tube flush volumes to all also provide hydration, the survey did not make a distinction between volumes for tube clearance and those for hydration and therefore this may have led to an increase in the declared volumes used.

A recent focus group, by a Belgian research team, explored reasons why nursing staff do not adhere to guidelines; lack of time influenced adherence to guidelines especially not mixing medicines but a lack of understanding of the consequences also affected attitudes to mixing medicines, use of protective equipment and flushing practice. Concern about fluid needs and restrictions also affected flushing practice (Joos et al., 2015b).

During the observational period of a recent service evaluation study conducted on a UK stroke rehabilitation unit (Bennett et al., 2013), inadequate or absent tube flushing prior to medication was observed, this was despite guidance being available within the organisation. Unfortunately no specific values are provided in the publication.

In a case report of a catalogue of errors in enteral medication administration, a lack of pre- and post-medication flush was highlighted. (Emami et al., 2012)

### 2.6.2 Formulation appropriateness

In both the nursing home survey and the patient survey a high percentage of the medication in use was of an appropriate formulation, 83% and 81% respectively. Of the inappropriate formulations in use, over a third of the nursing home medication and almost half of the patient medication were available in a more appropriate formulation.

Several respondents in the professional group commented that cost can sometimes influence the formulation choice and adversely impact on the use of appropriate liquid medication. This may account for the higher use of solid dosage forms in the community settings.

This compares very favourably to the literature. In the Belgian nursing home study 55% of medication was supplied as solid dosage forms (Joos et al., 2015a). In a Brazilian study of inpatients with enteral feeding tubes, over 95% of patients had at least one medication in a solid dosage form, however only 23% of these would have been available as a liquid

preparation, highlighting the impact that medication formulation availability can have on clinical practice (Heineck et al., 2009).

Lack of a suitable formulation for administration can lead to variability in the product recommended or supplied. Captopril was not available as a licensed liquid product, a survey of UK paediatric cardiac specialist and referring centres revealed that there was variation in the product supplied with 4 hospitals recommending that the tablets be crushed and dissolved and the other 22 centres using nine different unlicensed liquid specials. Most centres provided information on discharge to ensure continuity of supply in the community, however 3 hospitals recommended formulations that were different from that supplied by the hospital (Mulla et al., 2007).

### 2.6.3 Liquid medicine administration practice

Liquid medication formulations are preferred for enteral tube administration. There is consensus within the published recommendations that liquid medication may need to be diluted further prior to administration (White and Bradnam, 2015, Bankhead et al., 2009, BAPEN, 2003a, Wohlt et al., 2009), particularly viscous liquids or those being administered directly into the jejunum (Adams, 1994), although there is a lack of consensus on the volume of water to be used.

From this survey research 20% of professionals recommend diluting liquid medication prior to administration, 14% of care homes with nursing and 12% of patients do so. The need to dilute liquid medication prior to administration was cited by some as a problem, particularly when large volumes are necessary. Phenytoin was given as a specific example.

In the study by Philips and Endacott in Australia,(Phillips and Endacott, 2011) liquid medication was diluted routinely by 58% of nurses, 71% citing viscosity as a reason to do so. The information relating to liquid viscosity in the literature is sparse, particularly in relation to enteral tube administration. This area requires further evaluation.

### 2.6.4 Solid dosage forms

#### 2.6.4.1 Crushing methods

From the professional survey 43.5% respondents specifically commented that they would only recommend crushing a solid dose form if a liquid was unavailable. Methods described in the survey responses included pestle and mortar, pill crusher, two spoons, barrel of syringe and a crushing syringe. Patients also described using pestle and mortar, spoons and pill crushers, the nursing home respondents did not specify a particular method.

The use of a pestle and mortar for tablet crushing is most frequently referred to method in the literature (Paradiso et al., 2002, Phillips and Endacott, 2011, Mota et al., 2010), however concerns have been expressed over their shared use between patients due to the risk of cross contamination if not cleaned properly (Paradiso et al., 2002, Cohen, 1982).

#### 2.6.4.2 Crushing inappropriate formulations

Although some of the patients surveyed were crushing tablets for enteral tube administration, none of them were modified release or coated preparations. This was not the case for the medication being administered to the nursing home patients, where felodipine MR and potentially Zomorph® were being crushed. the two additional medications may have caused concern from an occupational exposure depending on the specific method used for that medication, they were finasteride and azathioprine.

Within the literature crushing inappropriate formulations is frequently described by nursing staff with many being unaware of the formulations that they should not crush. In their survey of Australian acute care nurses Philips and Endacott (Phillips and Endacott, 2011) identified that 21% would give MR and 34% would give EC via an enteral tube. In a Brazilian study only 29% of respondents agreed that modified release dosage forms should not be crushed (Mota et al., 2010).

A survey of discharge communications for enterally fed patients in Italy revealed 86 errors in 50 summaries (Sestili. M et al., 2014), almost 70% of the errors were due to the supply of an

incorrect formulation on discharge, 18.6% were due to necessitating the crushing of an inappropriate formulation.

In the study by Paradiso (Paradiso et al., 2002) 18% of medication that was altered was considered to be of concern either due to effect on pharmacokinetics, risk of toxicity or side effects. In a small study of geriatric inpatients in Ireland, 30% of patients with an enteral tube were prescribed sustained or modified release preparations (Lonergan et al., 2010).

### 2.6.5 Problem medicines and tube blockage

#### 2.6.5.1 Medication associated with administration problems

Within the survey respondents were asked about medication that they associated with administration problems. Three key themes emerged: difficulty in administration due to liquid viscosity, complicated administration process due to risk of drug-nutrient interactions or concern about tube blockage.

Liquid medication is generally considered the first line formulation for patients with enteral feeding tubes, however there are several liquid medications which due to their viscosity are associated with difficulties in administration, particularly via fine bore tubes, the specific medication identified by the professional and patient groups were baclofen, lactulose, phenytoin, sodium valproate, paracetamol and sulphasalazine. No specific information could be located in the literature in relation the specific rheological properties of these formulations to enable any comparison.

Granular formulations, either dispersible tablets such as omeprazole and lansoprazole or suspensions such as clarithromycin and ciprofloxacin were cited by all groups as being associated with blockage. The issues with omeprazole, lansoprazole and esomeprazole are widely accepted (Lonergan et al., 2010)and there are numerous publications demonstrating that, with the right technique, it is possible to administer these formulations without blockage (Sharma, 1999, Taubel et al., 2001, DiGiacinto et al., 2000, Ponrouch et al., 2010).

A research group in Brazil (Heineck et al., 2009) undertook a retrospective chart review and evaluation of tube changes to determine the causes of tube blockage in patients receiving

their medication via an enteral tube route in an inpatient setting. They determined that tube blockage was associated with both the number of medicines and the administration episodes per day. Patients that used more than five drugs enterally and that had more than 13 drug administrations per day were more likely to experience tube change due to blockage.

#### 2.6.5.2 Tube blockage

The range of methods used to attempt clearance of a blocked enteral tube was quite extensive with 12 different methods described. Warm water flush was the first line approach by both the professionals and the patients, the nursing home staff would use carbonated water first. Within the professional group more nursing staff recommended physical methods for clearance such as tube warming, manipulation and push/pull/plunging, whereas the dietetic staff more frequently recommended enzymatic approaches such as creon or clogzapper®.

Interestingly the second most frequent response by patients was to change the tube, the third response being to use coke suggested by 23%. The use of coke was also suggested by 14% of nursing home staff but only 2.3% of specialist professionals.

Coca-cola was demonstrated as being no more effective at maintaining tube patency than water by Methany in 1988 (Metheny et al., 1988) and yet both HCPs and patients advocate its use in unblocking enteral tubes. In the survey by Philips and Endacott (Phillips and Endacott, 2011) 62% of respondents favoured flushing with coke for tube blockage, compared to 38% with water. In the Belgian residential care facility study the researchers noted that one centre routinely flushed enteral tubes with coke (Joos et al., 2015a) and in the descriptive survey of nursing care of enteral feeding tubes undertaken by Schmieding et al. (Schmieding and Waldman, 1997) solutions used to unblock the tube included water, normal saline, ginger ale, warm coffee, orange juice, cola, cranberry juice, meat tenderiser and pancreatic enzymes.

### 2.6.6 Mixing medicines

Mixing medication together for enteral tube administration is not recommended in most consensus guidelines, and yet it is common practice illustrated in a number of publications with the most extreme situation being seen in the Belgian nursing home study where 69% of medicines were mixed together prior to administration. In the Brazilian inpatient study, (Mota

et al., 2010) 51% of nurses mixed medication in the same syringe and only 18% prepared each drug separately and flushed between each dose as recommended.

Data from this survey indicates that practice is more aligned to guidelines, only 4.7% of healthcare professionals would mix or recommend mixing medication together before administration, 14% of patients mix medication together and 19% of the nursing home staff indicated that they mixed medicines. These rates are more in line with those seen in the observational study in ICU (Al Rakaf and Lababidi, 2009) where mixing medication occurred in 11% of instances. However it would appear that there is some increase in mixing when there is potentially less input from specialists.

Communication at discharge is important to transfer instructions across care settings, however a survey of discharge communications for enterally fed patients revealed 86 errors in 50 summaries, (Sestili. M et al., 2014) 8.1% were due to mixing the medication with the enteral formula. This highlights the need for specialist review of this information prior to discharge.

In the development and evaluation of an evidence based practice guide in the United States for enterally fed patients in a military hospital, Kenny and Goodman established that baseline knowledge and practice was poor, however after protocol implementation the practice of mixing medicines decreased and there was anecdotal reports of a reduction in tube blockages (Kenny and Goodman, 2010a).

### 2.6.7 Equipment issues

This survey work was undertaken before the transition to ISO compliant enteral syringes (EnFIT) which is currently ongoing.

The use of appropriate enteral syringes was mandated in the UK by the NPSA in 2007 (NPSA, 2007) , following a number of serious incidents relating to wrong route errors (Cousins and Upton, 2000, Cousins and Upton, 1999, Cousins and Upton, 2001, Cousins and Upton, 1998). Despite this there are still patients in the community using non-compliant syringes. Risk issues likely to be lower than acute care setting as likelihood of having both central access and enteral access is low.

The main issues identified with enteral syringe use, particularly in the community, were that the syringes became more difficult to use (stiff) if they were washed and re-used.

### 2.6.8 Reference sources and health care professional knowledge

From the survey responses it was clear that there was a difference in the role of the pharmacist between the acute and community setting. Within the hospital environment 77% of respondents indicated that the pharmacist is the most likely to influence formulation choice, this is mirrored in the literature with several nursing studies indicating administration practice and formulation choice is influenced by the pharmacist (Phillips and Endacott, 2011, Schmieding and Waldman, 1997).

It is clear that the input from the pharmacist is substantially less in the community environment; this could be due to a number of reasons such as knowledge or patient access however this is unknown at present.

The free text responses provided some insight into the lack of confidence that patients have in their healthcare professionals with regards to enteral tube medication administration. To date there has not been an evaluation of UK community pharmacist's knowledge about this route of administration. A survey of community pharmacist's knowledge in Belgium indicated that knowledge of drug via tube issues was too limited to be able to provide good advice to patients or their caregivers (Joos et al., 2015c), this online survey had an exceptionally low response rate of only 2%.

In a survey of Irish home enteral patients (McNamara et al., 2000) only 19% of patients expressed confidence in their GPs knowledge of enteral tube feeding. In this study population over 78% of patients received their medication via their enteral tube.

### 2.6.9 Risk Profile and Problem Medication Predictability

High risk drugs are considered to be those with a narrow therapeutic range; they are well defined and include medication such as digoxin, warfarin and phenytoin. Three nursing home patients were receiving phenytoin, the liquid being associated with difficulty in administration due to the need to dilute because of the viscosity, only twelve (6.9%) of the professional group

respondents indicated that the interaction with feed was a problem. It is possible that more were aware of the issue but did not see it as a problem.

As expected there were a range of medication where problems in administration could be predicted, such as the case with granular formulations such as omeprazole, lansoprazole and creon®. It was surprising that two patients within the nursing home were receiving modified release preparations via a feeding tube as crushing would destroy the slow release properties and increase the risk of overdose; this is of particular concern for morphine, although the preparation specified was Zomorph® which are fine granules in a capsule. If the tube is a wide enough bore it may be possible to administer the granules whole without risk of blockage (White and Bradnam, 2015).

What was surprising was the large number of liquid medication associated with administration problems, the most commonly cited ones being phenytoin, lactulose, baclofen and paracetamol, these also being among the more common medication in this group of patients. Issues with viscosity, stickiness or granular properties were highlighted as the cause of problems.

A wide variety of medication were identified as associated with drug-nutrient interactions, however each was only identified by one professional indicating that awareness of this particular issue in enterally fed patients may be low.

### 2.6.10 Limitations

The use of survey methodology for this initial research provided the means to access both professional and geographical breadth; however this is at the expense of depth of study. The potential impact that a more comprehensive survey would have had on response rates was considered and a more generalised approach was used.

By definition the professional and patient groups are self-selecting, they are already engaged enough with the clinical area or their therapy to have joined a specialist interest group and therefore will more likely be exposed to good practice guidance in this area. The nursing home group are not affected by this but as a geographically limited group practice is likely to reflect local influences.

Self-reported practice has been shown to be more compliant than observed practice in other areas of healthcare (Al-Wazzan et al., 2011) and therefore it is highly likey that, although anonymous, the act of returning responses to a pharmacist may have influenced either consciously or unconsciously the honesty of the responses. The desire to be seen to be compliant with best practice is inherent in all self-reported surveys however this assumes that the respondent is aware of what best practice should be.

## 2.7 Conclusions

Despite potential social desirability bias it is encouraging that practice recommended by UK healthcare professionals is reported to be broadly in line with the existing consensus guidance, and although the validity of the nursing home and patient data is limited by the survey approach it is also encouraging that described practice is close to the guidance and markedly better than that seen in the literature. The data reveal areas where advice or practice is not consistent with the evidence, such as before medication and between medication flushing and the practice of mixing medication, this insight should be used to shape future focussed interventions to improve practice.

The focus of the specialist healthcare professional aspect of this survey was on the advice that they would give in addition to their practice. It would be interesting to explore the local dynamic between advice and practice in more depth.

The availability and use of appropriate formulations is higher than that cited in the literature and may be related to both awareness and availability. There is possibly further scope to increase use of appropriate formulations; however it appears that formulation manipulation remains both common and necessary.

The specific medications associated with tube blockage or administration issues was consistent across all groups and warrants further investigation to determine if the physical characteristics of these medications can be defined and appropriate advice offered. This data does provide insights into medication that may be associated with problems and sharing this information proactively though targeted resources may support informed therapy choices.

The range of methods used for solid dosage form manipulation is varied and this also warrants further investigation to determine the most appropriate method for use to optimise dose delivery.

The comments from patients and the indication of which profession decide on formulation choice and offer advice provide valuable insights into target groups for supportive materials but also indicate the patients lack of confidence in their healthcare professionals knowledge in this area. This does raise concern and should be addressed.

There are several themes emerging from this chapter that could be further evaluated. Liquid medication are traditionally considered first choice of tube administration and yet there are several liquid medicines associated with administration issues, this will be explored in more detail in the next chapter.

Tablet crushing is a recurring theme in both the introductory chapter and this survey chapter, further evaluation of the range of methods used and their impact on dose recovery is warranted and this forms the basis of the fourth chapter of this thesis.

The community aspect of this survey work focussed on nursing staff and patients, further research into the knowledge, skills and confidence of community and practice based pharmacists to provide advice on medicines management in this group of patients is warranted.

The final theme that would benefit from evidence to inform practice is to assess the impact of mixing medicines together to facilitate administration on bioavailability and pharmacokinetics; however this would be a complex in vivo study and it outside of the scope of this research project

Future intervention design should take into account the potential low baseline knowledge in areas such as drug-nutrient interactions and good tube flushing practice. Future guideline updates should place particular emphasis on the consequences of inappropriate formulation manipulation and give clear guidance on medication specific formulation choice where data exists. Aspects relating to direct and indirect cost of formulation choice should also be included.

In addition, intervention design should place a particular focus on the transitions between care providers and the risks of ineffective communication or adverse medication changes at these points.

Patient support groups and professional platforms provide a potential platform for dissemination of guidance; particular consideration should be given to disease specific support groups where dysphagia and enteral tube use are prevalent such as Parkinson's disease, Motor Neurone Disease and Stroke.

# 3 Impact of liquid medicine rheological properties and enteral tube physical properties on medication administration under gravity

## 3.1 Introduction

The literature review in the introduction to this thesis and the consensus guidance published thus far (BAPEN, 2003a, Dougherty and Lister, 2008) indicated that liquid formulations are generally preferred for patients with an enteral feeding tube. This is primarily due to the lower incidence of tube blockage associated with liquid formulation use and the ease of administration when compared to crushed tablets.

Within the previous chapter we identified a range medication that were associated with administration issues due to their physical properties, the most common being the granular dispersible formulations, however a surprising number of them were liquid formulations.
Liquid formulations were traditionally developed for the paediatric population and therefore formulation development was focussed on taste and texture to improve palatability and adherence as a result formulations represent a diverse range of physical properties, many of which may impact on their suitability for enteral tube administration. Very few liquid medicines are licensed for enteral tube administration and therefore no information is provided within the licensing information regarding suitability for use or physical properties such as granularity or viscosity. This lack of objective information makes it more difficult to determine if any given liquid formulation is suitable for enteral tube administration.

Current guidelines recommend diluting thick/viscous liquids before administration (Dougherty and Lister, 2008), a practice which was also seen in the survey results in the previous chapter, however there does not appear to be a sound evidence base for this advice which raises questions regarding the volume of dilution required and for what purpose.

This chapter evaluates the pharmaceutical properties of the liquid medicines identified as being associated with administration difficulties and considers if a more scientific approach to identifying and describing the characteristics of formulations associated with administration issues is possible. This information can then be used to assess other formulations for enteral tube administration suitability and also provide information to manufacturers of liquids intended for this route of administration.

## 3.2 Background

Rheology is the study of the flow properties of materials; this can be liquids or semi-solids. Within pharmacy it has been used to characterize and classify medication formulations and excipients. As a science it has developed into a hugely complex area as the understanding and implications of the nuances of the flow properties of a material have been investigated and new methods and descriptions defined.

### 3.2.1 Rheology of liquid medication

The viscosity of a liquid is simply its resistance to flow or movement. Fluids which have a direct relationship between flow and applied stress are referred to a Newtonian Fluids, these can be assessed using methods which apply a single stress value and determine viscosity at a single shear rate. Non-Newtonian fluids are those that have a non-linear relationship between flow and applied stress; the viscosity change must be measured over a range (Aulton and Taylor, 2013).

There are several coefficients used to describe the flow of fluids, dynamic viscosity being the most simple consisting of only two variables, rate of flow and applied stress. Dynamic viscosity is expressed in centipoise (cP) or pascals per second (Pa.s), the viscosity of water at $20^{o}C$ is 1cP or 1mPa.s.

The kinematic viscosity is also used and is defined as the dynamic viscosity divided by the density of the fluid; this is expressed in $m^2s$-1.

Very dilute aqueous medicine liquid formulations tend to exhibit Newtonian or near Newtonian properties as the fluid properties of water predominate, more complex formulations particularly those with gelling agents such as gums exhibit thixotropic (pseudoplastic) properties, being either shear thinning or shear thickening.

At the interface of solid material and liquid medication complex intermolecular forces occur effectively reducing the flow rate at the interface to zero, the distance from the surface to the maximum flow rate is known as the boundary layer. The rate of flow of a fluid over an even

surface is dependent on the distance from that surface, the viscosity of the fluid and the force applied; therefore in the context of enteral tube administration a wider tube will permit a faster flow rate.

### 3.2.2 Flow properties through enteral feeding tubes

As described above it is known that liquid flow rate through a tube is influenced by the characteristics of both the tube and the fluid. This was evaluated for feed solutions through nasogastric tubes in the 1980s (Skidmore, 1980) and a relationship demonstrated between flow rate and viscosity and flow rate and internal diameter of the tube. A relationship between the length of the tube and the flow rate has also been shown (Elia et al., 1984). Further work undertaken by Metheny (Metheny et al., 1988) demonstrated that the material of the nasogastric tube may also influence feed flow rate however this compared tubes with the same external diameter rather than internal diameter.

Traditionally nasogastric tubes are manufactured from PVC, PUR or silicone. These materials have different surface properties; however the potentially complex surface interaction between medication and feeding tube material has not been studied.

It is known that liquid medicines with a high osmolarity are associated with increased GI side effects particularly if administered via the jejunal route (Adams, 1994). Nurses and patients associate thick or viscous liquids with difficulty in administration via these tubes.

Limited physical testing is completed on liquid medications as part of their QC release and therefore little is known of the properties of liquid medicines used in routine clinical practice. Availability of this information would allow pharmacists to determine if a particular liquid medicine required dilution prior to administration in order to reduce the osmolarity or viscosity to an acceptable level to minimise administration difficulties and potential gastrointestinal side effects.

A range of medications were identified in the previous chapter which represented all those which nurses associate with administration difficulties and those which were most commonly administered to patients with enteral feeding tubes.

To date there are no data exploring the impact of viscosity on flow properties of liquid medicines through enteral feeding tubes and no validated methodology recommended for testing pharmaceutical solutions for this route of administration. As described above the methods used for evaluating not only the rheological properties but also the impact of interface factors is an evolving science.

Existing methods available for evaluation of viscosity and flow properties do not take into account the interaction between the tube material and the liquid and also the impact of the tube diameter and the potential significant impact of the width of the boundary layer in relation to the internal diameter of the tube.

## 3.3 Aims and Objectives

The aim of this research was to better understand if there are specific rheological properties that influence the administration practicalities of liquid formulations through enteral feeding tubes, how these relate to enteral feed delivery and if they are affected by tube material, diameter or dilution practices.

The main objectives were:

1. To develop a simple method replicating clinical practice to understand and describe liquid medicine flow properties through enteral tubes of the problem liquid medicines and a range of liquid medicines not associated with problems.
2. Evaluate the viscosity of these liquid medicines using standard techniques and relate these characteristics to the observed flow properties of 'problem' medicines from the developed model.
3. To describe the impact of tube material, tube size and medication dilution on flow rates through enteral tubes, using the developed models.

## 3.4 Methods

In order to meet the objectives for this research three approaches were required; direct observation of the flow properties of a range of liquid medicines through a feeding tube, determination of viscosity as a basic rheological property using an accepted method, and observation of flow through tubes of differing material.

As previously outlined a number of factors affect the rheological properties of liquids, this includes viscosity and density (both affected by temperature), pressure applied, diameter of the tube and material properties, affecting the boundary layer width. Each model developed aimed to minimise confounding factors by limiting some of these variables, however this does impact on the transferability of this data.

The range of liquid medication was selected for evaluation based on the data obtained from the survey responses in the previous chapter. The selection was focussed on liquid medication identified as 'problem' by the professionals and commonly administered medication from the patient and nursing home responses with additional liquids included if they were available for purchase from pharmacies or if the usual dosing volume was large. A pragmatic approach was taken regarding very expensive liquid formulations, those where the normal dose was less than 5mL (e.g. citalopram) and controlled drugs. A decision was made not to test any penicillin containing liquids due to one of the laboratory teams allergy status.

Four standard enteral feeds were also evaluated for flow comparison purposes; these were chosen from the hospital formulary based on frequency of use.

### 3.4.1 Model development and liquid medicine flow under gravity

It was decided that a single brand of syringe would be used throughout to minimise any interference from equipment variation. There are four brands of enteral syringes on the UK market; Baxa, Medicina, Enteralock and Nutrisafe. In order to minimise the impact of syringe choice on the flow rates the syringe with the least impact was selected. This was determined by removing the plunger from the syringe, attaching it vertically to a clamp, filling to 50ml graduation with water and determining the time taken for the syringe to empty. Although minimal difference in time taken, the Medicina syringes were marginally faster and so were chosen for the rest of the experiments.

Likewise for the flow evaluations a single tube type was evaluated. There are primarily two materials used for enteral feeding tubes, polyurethane (PUR) and silicone, the size of tube being described in French units (Fr or Ch) which is 0.33mm/French unit. Polyurethane has a larger internal diameter than an equivalent French size silicone tube due to the different

properties of silicone and PUR. There are also different designs for the exit tips of the tube, some have a single terminal eyelet others have multiple eyelets, this has been shown to impact on the flow through the tube and the risk of blockage (Hofstetter, 1992), therefore a single eyelet 8Fr polyurethane nasogastric tube, as an example of a commonly used tube in acute care, was chosen for evaluation.

#### 3.4.1.1 Model development

A simple model using a nasogastric tube support frame was designed intended to mimic the position and shape of a nasogastric tube within a patient recumbent at 30 degrees, the recommended incline for patients on continuous enteral feeding (Metheny et al., 2002). All experiments were undertaken at ambient room temperature to reflect a ward environment.

There is no published data on the range of pressures that can be applied by the human hand with a syringe in clinical practice, no mechanical method for controlling this could be developed within the resources available and as a result the decision was taken to use a gravity method for administration to minimise any variability introduced by the variable application of pressure from the syringe by the operator.

Liquid medicines identified from the 'problem' group from the survey were evaluated, in addition a range of other commonly used liquid medicine were included to provide a range of possible viscosities and comparators that were not associated with administration problems.

The following equipment was required: 50ml enteral syringe with barrel removed (Medicina, UK), Enteral feeding tube (Corflow 8Fr Polyurethane adult nasogastric tube), Tube clamp, Glass beaker and the nasogastric tube support frame. See Image 3.4.1

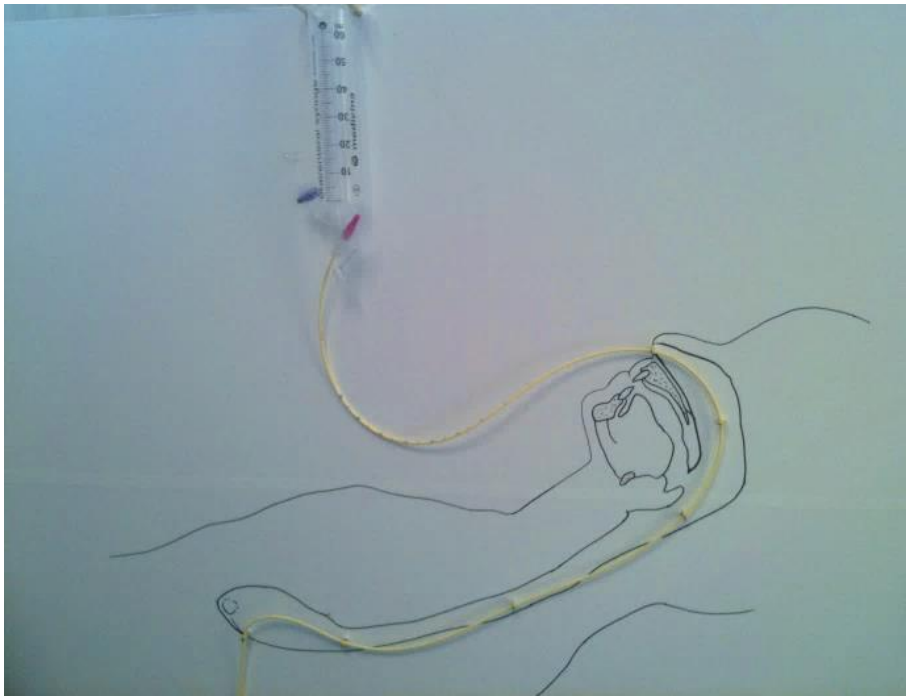


**Image 3.4.1 Flow model nasogastric tube holder**

Procedure steps for simulated nasogastric administration flow property assessment

1. Record ambient temperature
2. Place clamp onto nasogastric tube about 10-20 cm from top end of tube
3. Thread nasogastric tube through eyelets
4. Attach enteral syringe to tube, ensuring all ports not in use are closed
5. Place syringe onto holder at top ensuring syringe is level
6. Place beaker below end of syringe
7. Pour 35mls of liquid to be tested into the syringe (this is sufficient to prime tubing)
8. Record time taken for fluid volume to drop from 30ml mark to 10ml mark (record time in seconds to two decimal places)

Five test runs were completed for each liquid medicine; a clean syringe and tube were used for each run. See table 3.4.1 for medication details.

**Table 3.4.1 Detail of liquid medicines**

| Medication | Strength | Manufacturer | Rationale |
|---|---|---|---|
| Aciclovir | 200mg/5mL | GSK | Pr, |
| Amantadine | 50mg/5mL | Alliance | Dose up to 20mL |
| Amiloride | 5mg/5mL | Rosemont | Dose up to 20mL |
| Atenolol | 25mg/5mL | Thame | NH |
| Baclofen | 5mg/5mL | Focus | Pr, Pa, NH |
| Carbamazapine | 100mg/5mL | Novartis | Pr, Pa, |
| Cetirazine | 5mg/5mL | Pinewood | Pa, NH, OTC |
| Chlorphenamine | 2mg/5mL | Sandoz | OTC |
| Clarithromycin | 125mg/5mL | Sandoz | Pr, |
| Clonazepam | 0.5mg/5mL | Rosemont | Pa, NH |
| Codeine | 25mg/5mL | Thornton & Ross | Pr, |
| Co-trimoxazole adult | 80mg/400mg/5mL | GSK | Example antibiotic |
| Co-trimoxazole paed | 40mg/200mg/5mL | GSK | Example antibiotic |
| Docusate | 50mg/5mL | Typharm | Dose up to 20mL |
| Domperidone | 5mg/5mL | Winthrop | Pa, |
| Ensure | 2kcal/mL | Abbott | Enteral feed comparator |
| Ferrous Fumarate | 140mg/5mL | Thornton & Ross | Pr, Pa, |
| Fluoxetine | 20mg/5mL | Chemidex | Pa, |
| Furosemide | 40mg/5mL | Rosemont | Dose up to 20mL |
| Furosemide | 50mg/5mL | Rosemont | Dose up to 20mL |
| Haloperidol | 5mg/5mL | Rosemont | NH |
| Ibuprofen | 100mg/5mL | Teva | Pa, |
| Jevity | 1.1kcal/mL | Abbott | Enteral feed comparator |
| Lactulose | 3.35g/5mL | Teva | Pr, Pa, NH |
| Levetiracetam | 100mg/mL | UCB | Pr, Pa, NH |
| Loperamide | 1mg/5mL | Janssen | Pa, |
| Lorazepam | 1mg/5mL | Rosemont | Dose up to 20mL |
| Metoclopramide | 10mg/5mL | Rosemont | Pa, NH |
| metronidazole | 200mg/5mL | Rosemont | Pr, |
| Mirtazepine | 15mg/mL | Rosemont | Pa, NH |
| Osmolite | 1 cal/mL | Abbott | Enteral feed comparator |
| Osmolite | 1.5kcal/mL | Abbott | Enteral feed comparator |
| Paracetamol | 250mg/5mL | Rosemont | Pr, Pa, NH |
| Paracetamol | 120mg/5mL | Edict | Pr, Pa, NH |
| Phenytoin | 30mg/5mL | Pfizer | Pr, NH |
| Propranolol | 5mg/5mL | Rosemont | Pa, |
| Ranitidine | 150mg/5mL | Rosemont | Pa, |
| Senna | 7.5mg/5mL | Reckitt Benckiser | Pa, NH |
| Sodium Picosulfate | 5mg/5mL | Boehringer Ingelheim | OTC |
| Sodium Valproate | 200mg/5mL | Sanofi Aventis | Pr, Pa, NH |
| Sulphasalazine | 250mg/5mL | Rosemont | Pa, |
| Warfarin | 1mg/mL | Rosemont | Pr, NH |

Rationale for selection : Pr-problem, Pa – patient, NH – nursing home, OTC – can be purchased

#### 3.4.1.2 Rheological evaluation

An AR1000 Rheometer (TA instruments), with thermal control, was used to determine the rheological properties of the non-granular liquid medicines.

All shear rate and viscosity evaluations were undertaken using an incremental shear stress application from 0 to 25 Pa applied using a 6mm diameter flat plate sensor. Temperature was controlled at 25 degrees centigrade using a temperature controlled base plate.

### 3.4.2 Impact of dilution on flow properties

Dilution of liquid medication is recommended in the literature for viscous medication, specific volume recommendations vary. Eight of the problem medicines were also evaluated using the simulated administration flow model to determine the effect of dilution on flow. A range of dilutions were evaluated, starting with the recommendation of 50:50 (White and Bradnam, 2015)and then adjusted according to run times to achieve a flow rate in the same range as the flow times for standard enteral feeds.

Five runs for each dilution of each medication were completed.

### 3.4.3 Impact of tube material on flow rates

In order to assess the impact of tube diameter and tube material on flow rate, tubes of the two most commonly used material, polyurethane and silicon, were chosen. A range of sizes commonly used for nasogastric tubes in acute care clinical practice were selected, see table 3.4.3a.

**Table 3.4.3a Enteral tube material evaluation – tube details**

| Material | Manufacturer | French size | Internal Diameter (cm) (CorpakMedsystems, 2014) |
|---|---|---|---|
| Polyurethane | Corpak | 6 | 0.137 |
| Polyurethane | Corpak | 8 | 0.196 |
| Polyurethane | Corpak | 10 | 0.254 |
| Polyurethane | Corpak | 12 | 0.267 |
| Silicone | Medicina | 6 | 0.1 |
| Silicone | Medicina | 8 | 0.15 |
| Silicone | Medicina | 10 | 0.2 |
| Silicone | Medicina | 12 | 0.25 |

Three of the liquid medicines previously evaluated in the initial phase of this research chapter were chosen as the test liquids. One problem medication, lactulose, and two arbitrarily selected non-problem liquids. The details are included in table 3.4.3b.

**Table 3.4.3b Enteral tube material evaluation - Liquid formulation details**

| Medicine | Strength | Manufacturer | Max viscosity (cP) | Min viscosity (cP) | 20mL flow time (s) via 8Fr NG tube |
|---|---|---|---|---|---|
| Chlorphenamine | 2mg/5mL | Sandoz | 12.1 | 9.7 | 120.64 |
| Loperamide | 1mg/5mL | Janssen | 15 | 13.9 | 160.78 |
| Lactulose | 3.35mg/5mL | Teva | 276 | 192.8 | 974.28 |

A shortened length of enteral tube attached to a 50mL enteral syringe with the barrel removed (Medicina, UK) was clamped to a retort stand at 60cm above a glass beaker to provide a simple vertical drop model.

Procedure steps for tube material flow impact evaluation

1. Record ambient temperature
2. Cut the enteral tube at 50cm from the port
3. Attach enteral syringe to tube, ensuring all ports not in use are closed
4. Place syringe onto clamp with bottom of syringe 60cm from the workbench
5. Place beaker below exit of tube
6. Pour 35mls of liquid to be tested into the syringe

7. Record time taken for fluid volume to drop from 30ml mark to 10ml mark (record time in seconds to two decimal places)

Five runs were completed for each liquid via each tube type.

## 3.5 Results

### 3.5.1 Liquid medicine flow under gravity

Simulated administration times (run times) of medicines varied widely, all 'problem' liquid medicines, with the exception of levetiracetam, flowed slowly under gravity with an administration time more than twice that of enteral feeds. Most of the 'problem' medication had a flow rate under gravity that would preclude this method of administration in clinical practice. The range of values are illustrated in table 3.5.1, medicines annotated * were associated with tube blockage or administration difficulties by respondents to the survey in chapter two.

Medication identified with negligible flow under gravity and excessively long run times were not fully evaluated using this method, these included sulphasalazine, warfarin, paracetamol 120mg/5mL, paracetamol 250mg/5mL, ibuprofen 100mg/5mL and co-trimoxazole. Clarithromycin was found to be a granular suspension and blocked the tube. Administration of all these medications was abandoned after one hour if negligible flow was observed.

**Table 3.5.1 Liquid medication delivery times (under gravity)**

| Drug | Time to deliver 20mL under gravity (s) | SD | Number of samples tested |
|---|---|---|---|
| **Water** | 17 | 0.39 | 6 |
| **Haloperidol** | 17 | 0.41 | 6 |
| **Ranitidine** | 26 | 0.24 | 6 |
| **Atenolol** | 37 | 1.26 | 6 |
| **Metoclopramide** | 38 | 0.92 | 6 |
| **Furosemide** | 71 | 0.49 | 6 |
| **Levetiracetam*** | 71 | 1.41 | 6 |
| **Furosemide** | 73 | 1.43 | 6 |
| **Propranolol** | 82 | 1.62 | 6 |
| **Fluoxetine** | 88 | 4.4 | 6 |
| **Cetirizine** | 89 | 1.93 | 6 |
| **Amiloride** | 96 | 2.31 | 6 |
| **Chlorphenamine** | 121 | 1.68 | 6 |
| **Osmolite 1cal/mL**** | 135 | 10.09 | 6 |
| **Loperamide** | 161 | 6.65 | 6 |
| **Amantadine** | 163 | 3.34 | 6 |
| **Senna** | 180 | 15.38 | 6 |
| **Sodium picosulphate** | 219 | 22.72 | 6 |
| **Mirtazepine** | 225 | 15.35 | 6 |
| **Jevity (fibre)**** | 257 | 11.75 | 6 |
| **Clonazepam** | 264 | 3.15 | 6 |
| **Ensure 2cal/mL**** | 355 | 5.37 | 6 |
| **Osmolite 1.5kcal/mL**** | 406 | 18.04 | 6 |
| **Docusate** | 434 | 18.49 | 6 |
| **Domperidone** | 454 | 60.93 | 6 |
| **Lactulose *** | 974 | 22.56 | 6 |
| **Carbamazepine*** | 979 | 63.25 | 6 |
| **Ferrous Fumarate*** | 1487 | 107.07 | 6 |
| **Codeine*** | 1629 | 136.37 | 6 |
| **Sodium Valproate*** | 3348 | 332 | 6 |
| **Aciclovir*** | 4998 | 478 | 6 |
| **Lorazepam** | 8400 | | 1 |
| **Phenytoin*** | 12000 | | 1 |
| **Baclofen*** | 38250 | | 1 |

### 3.5.2 Rheological properties

Evaluation of the rheological properties of the liquid medication was determined using the AR1000 temperature controlled at 25 degrees centigrade. A summary of the maximum and minimum viscosity of the liquid medications is provided in Table 3.5.2. The problem medicines

identified from the previous chapter all have an initial maximum viscosity of above 100cP, this value may serve as a guide when initially reviewing medication for enteral tube use, providing this data is available from the manufacturer.

**Table 3.5.2 Viscosity and flow properties of liquid medication**

| Medication | Strength | Max Viscosity (cP) | Min Viscosity (cP) | Shear rate/stress linear correlation (r) | 20mL delivery time >15 mins (900 seconds) |
|---|---|---|---|---|---|
| **Paracetamol** | 250mg/5mL | 211,000 | 321 | 0.78 ST | Yes * |
| **Paracetamol** | 120mg/5mL | 134,033 | 39.6 | 0.71 ST | Yes * |
| **Ibuprofen** | 100mg/5mL | 22,360 | 44.0 | 0.74 ST | Yes |
| **metronidazole** | 200mg/5mL | 13,336 | 503 | 0.92 | Not tested * |
| **Sulphasalazine** | 250mg/5mL | 8,136 | 15.0 | 0.81 ST | Yes * |
| **Warfarin** | 1mg/mL | 7,622 | 23.0 | 0.81 ST | Yes * |
| **Baclofen** | 5mg/5mL | 5,332 | 1,431 | 0.90 | Yes * |
| **Co-trimoxazole** | 40mg/200mg/5mL | 2,916 | 410 | 0.92 | Yes |
| **Co-trimoxazole** | 80mg/400mg/5mL | 1,649 | 52.7 | 0.96 | Yes |
| **Phenytoin** | 30mg/5mL | 1,578 | 415 | 0.95 | Yes * |
| **Clarithromycin** | 125mg/5mL | 1,037 | 70.9 | 0.96 | Yes * |
| **Sodium Valproate** | 200mg/5mL | 440 | 114 | 0.92 | Yes * |
| **Ferrous Fumarate** | 140mg/5mL | 434 | 157 | 0.98 | Yes * |
| **Aciclovir** | 200mg/5mL | 388 | 73.3 | 0.94 | Yes * |
| **Lactulose** | 3.35g/5mL | 276 | 193 | 1.00 N | Yes * |
| **Codeine** | 25mg/5mL | 275 | 197 | 1.00 N | Yes * |
| **Carbamazapine** | 100mg/5mL | 206 | 36.9 | 0.96 ST | Yes * |
| **Domperidone** | 5mg/5mL | 101 | 19.3 | 0.96 ST | |
| **Senna** | 7.5mg/5mL | 56.7 | 5.4 | 0.98 ST | |
| **Mirtazepine** | 15mg/mL | 26.2 | 25.5 | 1.00 N | |
| **Docusate** | 50mg/5mL | 26.1 | 25.4 | 1.00 N | |
| **Sodium Picosulphate** | 5mg/5mL | 16.9 | 10.4 | 0.99 N | |
| **Amantadine** | 50mg/5mL | 16.7 | 14.8 | 1.00 N | |
| **Loperamide** | 1mg/5mL | 15.5 | 13.9 | 1.00 N | |
| **Osmolite** | 1 cal/mL | 14.8 | 12.2 | 1.00 N | |
| **Chlorphenamine** | 2mg/5mL | 12.1 | 9.5 | 1.00 N | |
| **Cetirazine** | 5mg/5mL | 11.5 | 7.5 | 0.98 | |
| **Fluoxetine** | 20mg/5mL | 11.1 | 8.0 | 0.98 | |

* Identified as 'problem' medication in Chapter 2. N=Newtonian, ST=shear thinning

The liquid medications exhibited a range of fluid properties, primarily either Newtonian or shear thinning (thixotropic).

The relationship between shear rate and shear stress for shear thinning formulations is shown in figure 3.5.2a. This relationship was most pronounced for paracetamol, ibuprofen, sulphasalazine and warfarin liquids, all of these formulations have xanthan gum as the suspending agent which is known to be shear thinning; however without specific knowledge of the exact composition the viscosity variability could not have been predicted.

Several preparations exhibited Newtonian behaviour with a linear relationship between stress and flow with a correlation coefficient of 1, this is shown in figure 5.3.2b using codeine and lactulose as examples. These two formulations both have saturated sugar solutions as their base, sucrose and lactulose respectively, all other formulations that exhibited Newtonian properties had water as the primary solvent with very few additional excipients.

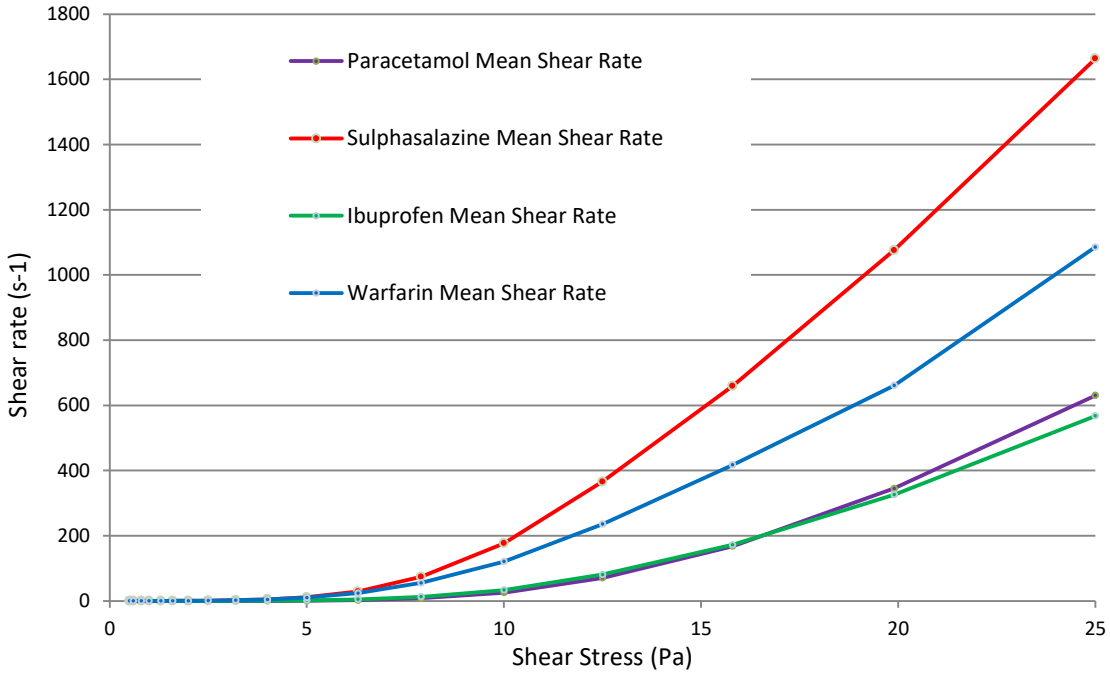



**Figure 3.5.2a Flow behaviour of shear thinning medicines**

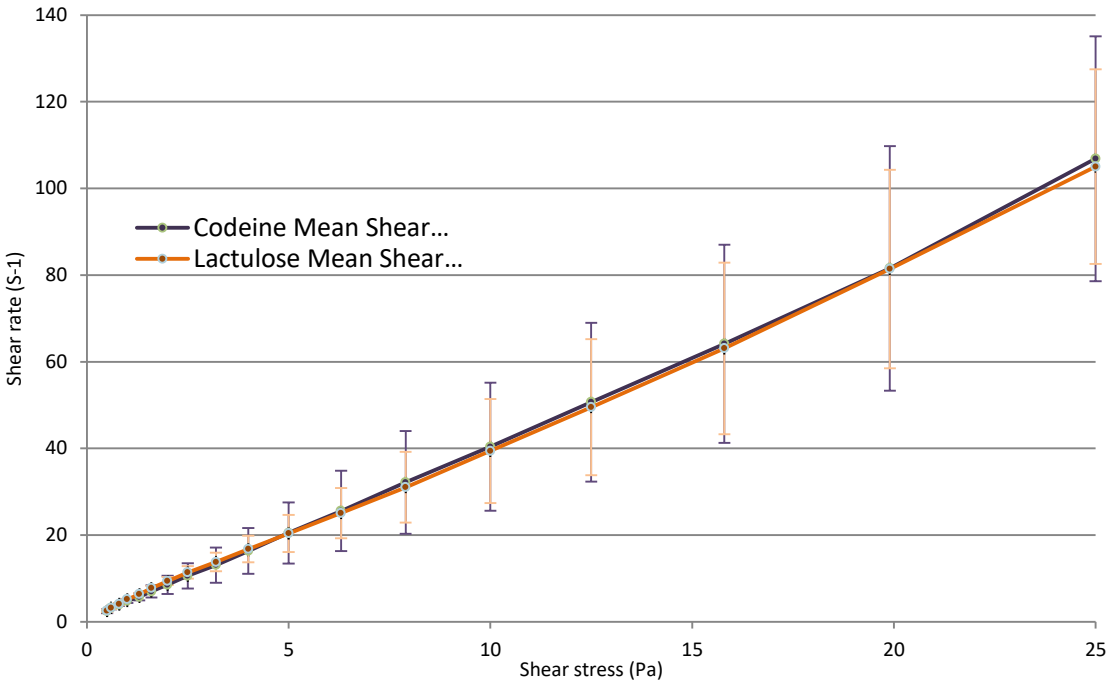



**Figure 3.5.2b Flow behaviour of medicine with Newtonian character**

### 3.5.2.1 Relationship between viscosity and flow properties

Almost all the medicines with a high initial viscosity were associated with problems by healthcare professionals and patients; however there was no direct relationship between viscosity and administration rate indicating that other factors must have a major influence.

In order to explore this further the flow behaviour of medicines with very similar viscosity profiles were compared. The difference in run time was most evident for codeine and lactulose which have almost identical viscosity profiles, exhibiting Newtonian characteristics, but the run time of codeine is 40% longer, as shown in figure 3.6.3a.

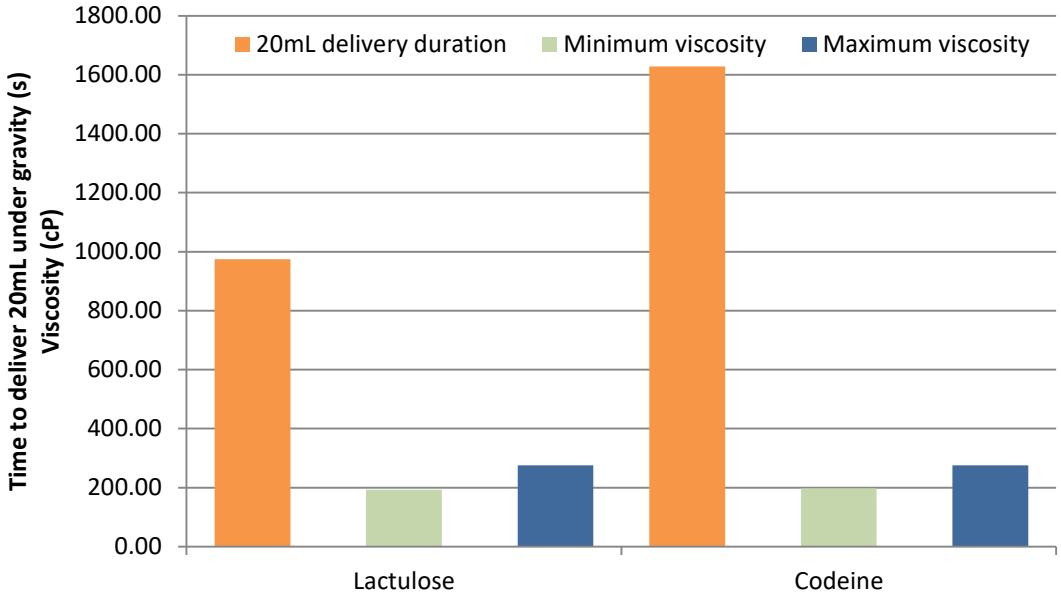



**Figure 3.6.3a Viscosity and run time comparison of lactulose and codeine liquid**

The base of both codeine and lactulose formulations are saturated sugar solutions, lactulose consists of only lactulose dissolved in water, codeine has a saturated sucrose solution as its base with ethanol and sodium methyl hydroxybenzoate as additional excipients.

Likewise mirtazapine and docusate have very similar minimum and maximum viscosity values however the delivery time of docusate is almost twice as long. Docusate and domperidone have very similar minimum viscosity, but the maximum viscosity of domperidone is almost 4 times higher, and yet the delivery time is almost the same. This is illustrated in figure 3.6.3b.

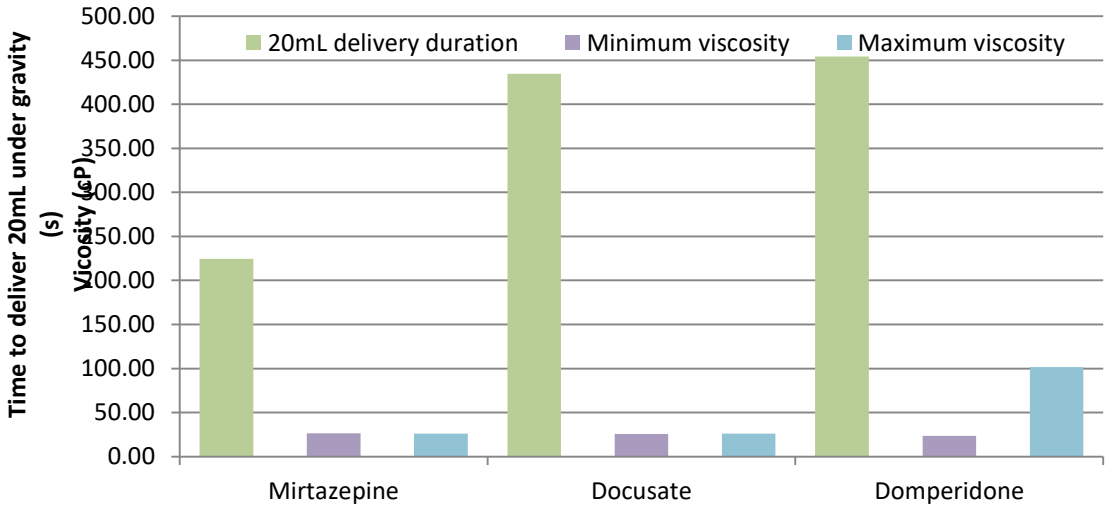



**Figure 3.6.3b Viscosity and run time comparison of mirtazepine, docusate and domperidone liquid**

These examples alone serve to demonstrate that viscosity alone may provide an indication of the suitability of a liquid formulation for enteral tube administration but does not provide a robust method to derive administration time.

### 3.5.3 Diluted liquid medicines

In Chapter Two the practice of diluting 'thick' liquid medicines was reported in both the professional and patient groups, this is consistent with the published guidance. However, as previously discussed there are no published data on the degree of dilution necessary for individual medicines and therefore non-specific recommendations are made (White and Bradnam, 2015).

When using the simulated nasogastric model, several liquid medicines evaluated were found to be too viscous to evaluate undiluted. A range of dilutions were evaluated for these medications to determine the degree of dilution that would deliver the medication under gravity at the same rate as enteral feed. The same model and parameters were used as in the undiluted gravity evaluation. Run times of medicines are illustrated in figure 3.5.3.

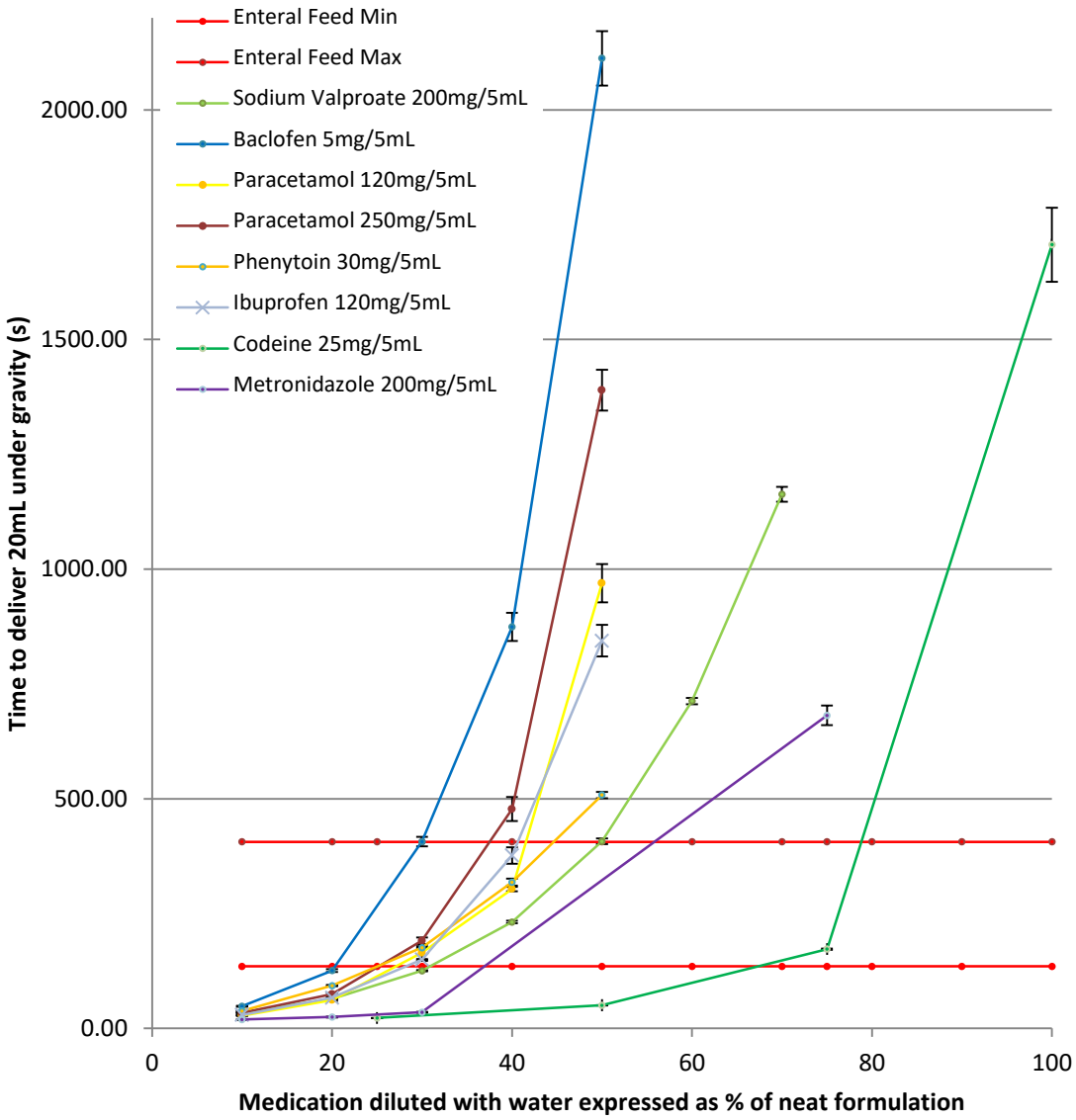



**Figure 3.5.3 Run times for undiluted and diluted viscous liquid medicines**

The enteral feeds with the fastest and slowest run times are indicated in red on figure 3.5.3. The data from table 3.5.2 may indicate that a delivery time of less than 15 minutes is acceptable. This data indicates that a dilution with an equal volume of water (50%) as recommended in the literature is a valid recommendation for codeine, sodium valproate, metronidazole and phenytoin liquids. It does indicate that a 50% dilution may be insufficient for the paracetamol, ibuprofen and baclofen formulations and that further dilution may be necessary.

### 3.5.4 Tube material comparison

Loperamide and chlorphenamine were chosen as fast running formulations and lactulose was chosen as a slow running formulation. The undiluted formulations were run through the vertical 50cm lengths of enteral tube (n=5). When comparing enteral tubes of the same external diameter, polyurethane delivered an equivalent volume in a shorter period of time. The 20mL delivery times are shown in figure 3.5.4a. This result was predicted as it was known that the internal diameter is larger for the polyurethane tubes.

This is highly statistically significant, with a p value below 0.0003 for all medications in all tube sizes. For lactulose this would be a clinically relevant difference in delivery times with the exception of the 12fr tube size, for loperamide and chlorphenamine this would only be clinically relevant at the 6Fr tube size.

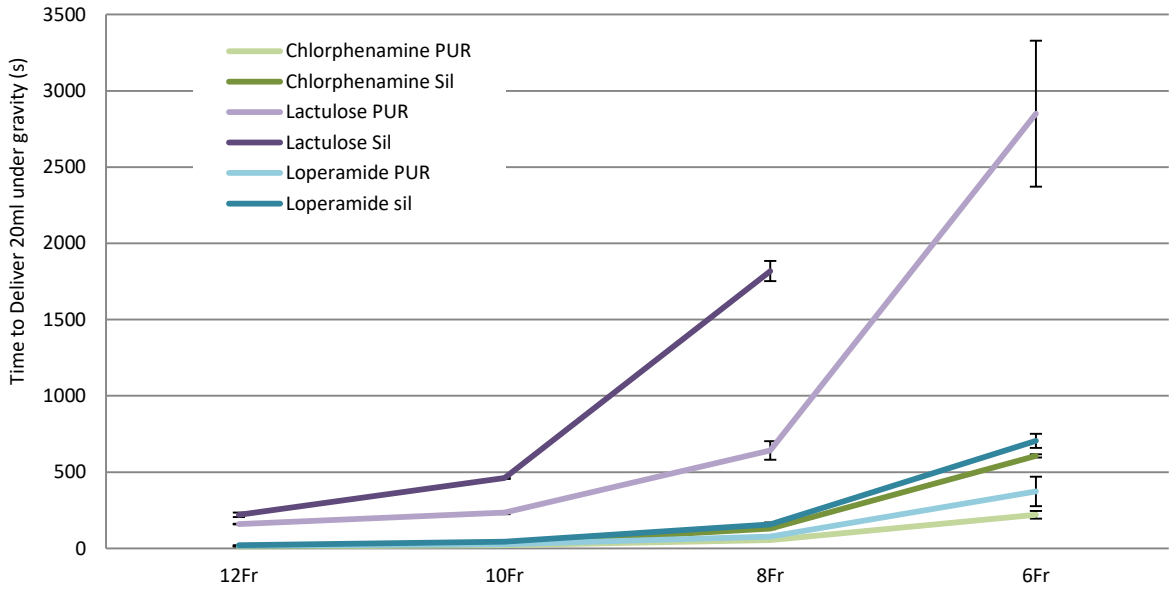



**Figure 3.5.4a Impact of Enteral Tube size (Fr) on dose delivery time under gravity**

When the flow is evaluated by internal diameter, silicone tubes permit a faster flow rate the difference becoming potentially clinically relevant with smaller internal diameters. The effects of tube material become clinically insignificant with internal diameter above 2.5mm, as can be seen in Figures 3.5.4b and c.

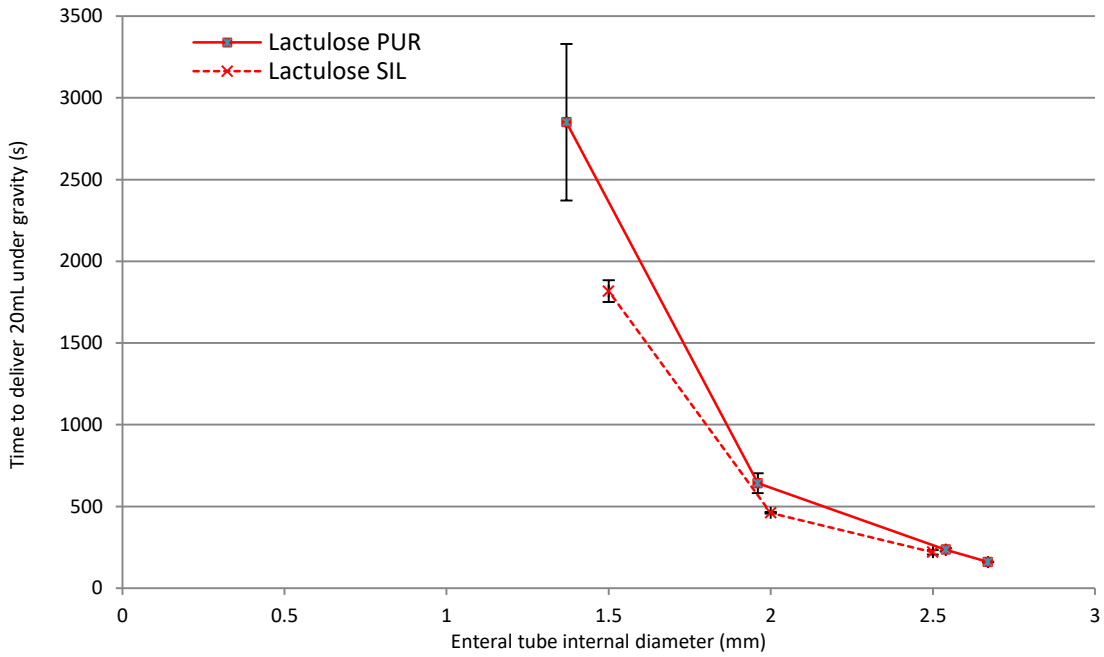



**Figure 3.5.4b Effect of tube material on speed of flow (Lactulose)**

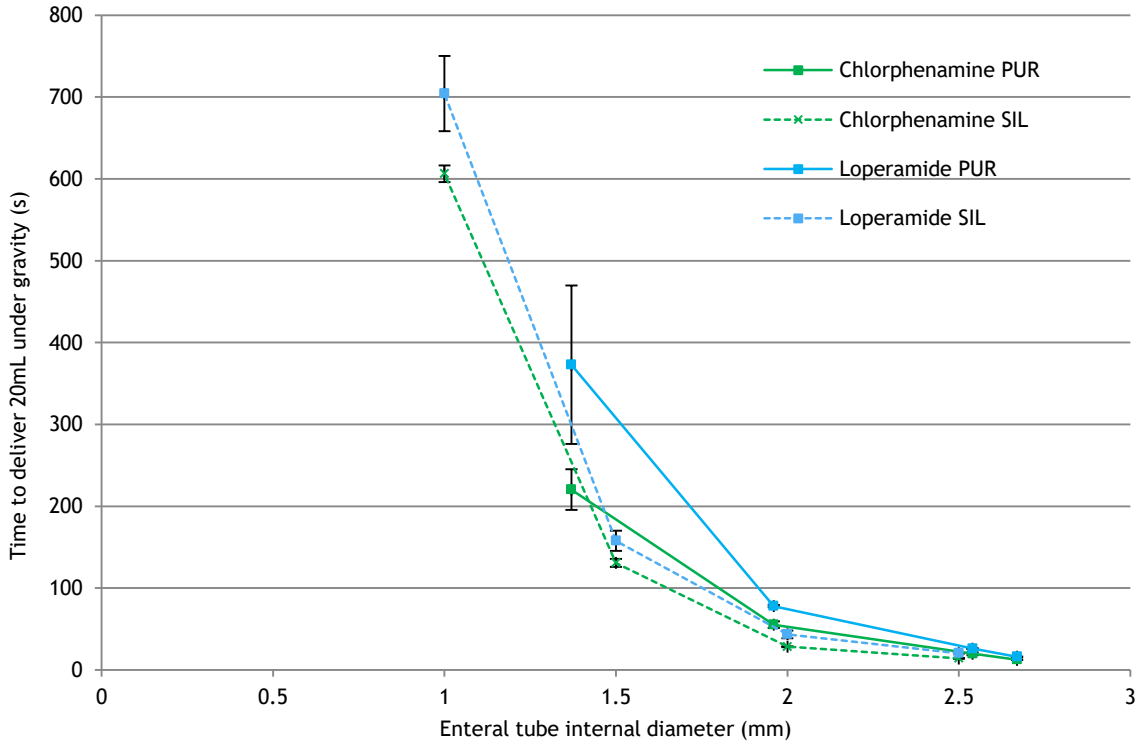



**Figure 3.5.4c Effect of tube material on speed of flow (chlorphenamine, loperamide)**

This data demonstrates that at small tube sizes the interaction between the liquid and the tube surface impacts the flow rate and the width of the boundary layer is important, this

becoming less influential as the tube size increases when the viscosity of the liquid is the main influence on flow rate.

## 3.6 Discussion

This research is the first to explore the relationship between the rheological properties of liquid medicines and their flow behaviour through an enteral tube, focussed on those liquid formulations associated with administration problems by the professional and patient communities.

By using a simple model of enteral tube administration under gravity based on the clinical approach, the flow properties of liquid medication both 'problem' and 'non-problem' can be easily assessed and contextualised against the flow properties of enteral feeds.

### 3.6.1 Limitations of this research

The rheological evaluation of fluids is very complex. This model, although providing a very simple concept, does not provide comprehensive data on all the aspects of fluid flow properties that may impact the delivery of medication via a feeding tube.

All methods were conducted under gravity, a further data set is required looking at the flow properties from a syringe under pressure, such as could be achieved with the human hand. This would require evaluation of the range of pressures that could be generated by the pincer grip strength of healthcare professionals and patients.

Other liquid medication attributes such as density and tackiness potentially providing insights into the properties affecting the dynamic at the interface.

This would be a significant project in its own right.

### 3.6.2 Characteristics associated with problem liquid medicines

The simulated nasogastric flow model was simple to set up and use and the inclusion of enteral feeds in the testing provides a reference point for comparison.

It is immediately evident from the enteral tube flow rates detailed in table 3.5.1 that all the problem liquid medicines, identified by the professionals and patients surveyed in the previous chapter, flow slowly through an enteral tube at a rate more than twice that of even the most viscous enteral feed studied.

There were also a number of medications identified that did not flow at all due to their highly thixotropic or granular nature.

Comparison of the flow times with the maximum and minimum viscosities determined by rheometry revealed that several of the 'problem' formulations were shear thinning (thixotropic) with a rapid drop in viscosity as pressure was applied. This was particularly evident with paracetamol, ibuprofen, warfarin and sulphasalazine liquids. However this low viscosity under pressure is not evident when administering via gravity.

Specific data relating to the shear pressure applied within an enteral syringe are not available, therefore it is not possible to determine the likely apparent viscosity of these liquids when administered using a syringe. However, these liquids were identified as 'problem' despite likely administration from a syringe under pressure and therefore we can conclude that other shear thinning liquids, particularly those based on xanthan gum are likely to be associated with problems.

### 3.6.3 Relationship between flow rate and viscosity

When comparing the flow behaviour of medicines with very similar viscosity profiles, as with lactulose and codeine, there were differences in the run time; this indicates that there are other factors involved other than viscosity alone. The very small difference in density would not account for this difference; therefore there must be either a difference in the width of the boundary layer or in the interaction happening at the liquid/tube interface. This effect could be influenced by the width of tube used and may become less influential as the tube diameter increases.

This was not demonstrated statistically in the administration through different diameter tubes, however it could be considered clinically relevant.

Research has been published focussing on the flow of feed through enteral tubes (Skidmore, 1980, Elia et al., 1984) and independently on the electrostatic surface interaction between proteins and material surfaces (Xu and Yeung, 1998, Lima et al., 2011), this interaction is hypothesised to be one of the factors in obstruction of feeding tubes with enteral feed residue. Surface coating has been evaluated as a strategy to reduce the adherence of proteins to reduce the incidence of occlusion.

Gaither et al. studied (Gaither et al., 2009), in vitro, the effect of coating polyurethane feeding tubes with PVA (polyvinyl alcohol), demonstrating a reduced adherence of gastric acid coagulated feed. There was no difference with native casein protein only the acid denatured protein, leading the investigators to conclude that the hydrophobic regions exposed on the denatured protein were adhering to the hydrophobic polyurethane, PVA is hydrophilic accounting for the apparent resistance to adsorption.

This research into the surface properties of polyurethane may provide an insight into the different flow rates of liquids with identical viscosities. Both lactulose and codeine syrup are essentially saturated sugar solutions, lactulose is galactose-fructose disaccharide and codeine syrup is in a base of sucrose (glucose-fructose disaccharide) with alcohol as an excipient. It is plausible that the difference in hydrophobicity of these sugars affects the adherence at the fluid/tube interface however the complexity of liquid pharmaceutical formulations and the range of excipients included could also be a contributing factor. Although scientifically intriguing it is unlikely to be clinically applicable research due to the unique nature of each formulation.

### 3.6.4 Dilution of liquid medication to facilitate administration

Dilution of liquid medication prior to administration has been shown to reduce potential loss of dose through interaction with the tubing for carbamazepine, phenytoin and warfarin (Clark-Schmidt et al., 1990, Seifert et al., 1993, Klang et al., 2010). A dilution step is recommended in most consensus guidelines although the volume of water recommended varies from dilute as necessary, to a specific volume based on dosing volume (Bankhead et al., 2009, Wohlt et al., 2009).

This requirement for dilution of a liquid medication before administration has been evaluated within studies of medication errors. In an observational study in ICU, 55% of errors occurred in the administration step, 18% of these were described as inadequate dilution of a liquid preparation (Al Rakaf and Lababidi, 2009). Within a residential care facility, 46% of liquid medicines were not diluted prior to administration (Joos et al., 2015a).

As demonstrated in this study, dilution of viscous medication can achieve flow rates under gravity similar to those of enteral feeds. In light of the new data described here a dilution step may not be necessary for all liquid medicines and this step could be removed from the guidelines for low viscosity liquid medicines.

If an administration time twice that of enteral feed is considered acceptable then for the majority of the more viscous medicines studied dilution with an equal volume of water, as recommended in the guidance, would be sufficient. For baclofen and phenytoin the total volume is likely to exceed 50mL per dose, increasing the number of syringe manipulations required to administer a single dose. This should be considered in the context of the patient's fluid requirements, particularly if on a fluid restriction as this additional fluid load may become clinically relevant. The impact of the additional time and effort taken to administer the medication should be borne in mind as this may influence adherence.

Paracetamol was one of the most frequently administered medication by the patients and professionals in chapter two, in the context of this data the choice of formulation should be balanced against the fluid necessary to administer the liquid and the potential sodium load from the dispersible tablets.

In the case of baclofen a licensed dispersible preparation is not available however the tablets have been shown to disperse in water and this may be considered an appropriate alternative to dilution of the liquid preparation if fluid restriction is necessary.

### 3.6.5 Impact of tube material on medication flow properties

This limited study of three medications through enteral tubes of two materials demonstrated that both tube material and internal diameter can influence the rate of flow of medication through an enteral tube. The finding that the wider internal diameter of a polyurethane tube

permitted a more rapid flow than the smaller internal diameter of the silicone tube was not surprising. This finding that medication viscosity had less of an impact on medication flow rates as tube size increased was expected, although there is no previously published data on medication it is consistent with the literature with enteral feed.

Skidmore was one of the first researchers to investigate the flow of nutrient solutions through nasogastric tubes and evaluate the effects of nutrient viscosity and internal tube diameter (Skidmore, 1980). The 13 feeds evaluated are no longer available however the conclusions are still valid. The researchers demonstrated that the viscosity of the feed had a significant impact on flow rates for fine bore feeding tubes but as the internal diameter of the tube increased the viscosity had less of an influence.

This was also demonstrated by Elia et al. (Elia et al., 1984) additionally finding that the speed of enteral feed flow through an enteral tube, under gravity, was minimally affected by tube length.

Research by Hearne et al. (Hearne et al., 1984), studying the flow of enteral feeds, demonstrated that flow of enteral feed was slower through silicone tubes compared to polyurethane tubes of the same French size. The flow rates were 78-107% slower for the feeds delivered through 8fr silicone tubes, the flow rates through the 8fr polyurethane tube were not statistically significant from that of the 10Fr silicone tube. These authors had earlier proposed tube sizes for outpatient use based on their flow rates of the intended feed to facilitate gravity feeding at appropriate rates (Hearne et al., 1982). This was followed by research by Metheny et al. (Metheny et al., 1988) confirming that flow through silicone tubes is slower than flow through polyurethane tubes of the same external diameter, and that tube material has a greater effect on feed flow than the internal diameter.

The data presented in this chapter is the first to compare the flow rates through the two materials analysed by internal diameter not external diameter, and indicates that flow through silicone is faster than polyurethane, the impact of this diminishing as internal diameter increases. The reason for this difference is not known, it may be a difference in electrostatic forces as the surface level, or it could simply be that at a microscopic level silicone is smoother (Lima et al., 2011). This data, although interesting, is unlikely to be clinically important enough to warrant further investigation.

## 3.7 Conclusion

This research highlights that the study of the rheological properties of liquid medication using scientific principles is complicated. It is unlikely that there is a direct relationship between any one parameter and the perceived difficulty in administration of that liquid. This rudimentary simulated clinical model provides a simple method by which liquids can be assessed and the flow described in the context of feed flow. Further data are required on the properties of liquid medication when administered under pressure from a syringe rather than under gravity.

The range of data from this study indicates that many liquids may not require dilution to aid administration and that guidance on such should be determined at a formulation level. Making data widely available may limit patients diluting medication unnecessarily, thus simplifying their administration process.

The relationship between tube material, internal diameter and fluid viscosity requires a clinical perspective to determine if there is a tube size at which administration of a 'problem' drug is no longer a problem. A practical exploration of this with both professionals and patients would provide useful insights into both liquid formulation development and tube design.

Further research following on from this initial study should evaluate the effect of pressure rather than gravity on flow rate, identify other rheological properties which may better predict suitability for enteral tube administration and then develop and evaluate the utility of a model that incorporates these aspects to be able to proactively assess formulation suitability for enteral tube administration.

The key data that can be taken forward into clinical guidelines are the following:

- Liquid formulations with a maximum viscosity of less than 100cP are likely to be able to be administered via an enteral tube without dilution or problem.
- Shear thinning liquid formulations, particularly those based on xanthan gum are likely to be associated with problems and should be diluted with an equal amount of water prior to administration.

- Syrup based liquid formulations (sucrose or sorbitol) are likely to be associated with problems and should be diluted prior to administration, an equal volume of water should suffice with the exception of baclofen which may require up to 3 times the volume of water.

The data presented in this chapter indicates that liquid formulations may not always be the most appropriate choice for enteral tube administration. There are potentially some situations where the manipulation of a solid dosage form may be considered, however this aspect also requires further study and is the focus for the next chapter.

# 4 Dose recovery following tablet manipulation for enteral tube administration

## 4.1 Introduction

The introduction to this thesis described the circumstances where a solid dosage form may be the only licensed formulation commercially available to manage a particular clinical condition, the use of solid dosage forms for administration to patients with enteral tubes was evidence from the research described in chapter two of this thesis. This lack of a suitable licensed preparation poses a challenge for safe medication administration via an enteral feeding tube where a liquid formulation is required. The use of specials manufacturers to compound liquid formulations where none is available commercially is possible (RPS, 2010), however due to the cost associated with liquid medicines and a potential lack of understanding of the associated risks, tablet crushing for enteral tube administration is common (Mota et al., 2010, Wright, 2002).

This component of research was undertaken between September 2011 and December 2012. At this time there were limited data in the literature exploring the consequences of tablet crushing on dose delivered via enteral feeding tubes. The existing data indicated that crushing a tablet for enteral tube administration may result in a potential reduction in dose delivered (Powers and Cascella, 1990) or alter pharmacokinetics (Zafar et al., 2009). However despite this evidence there was no specific mention in guidance as to why tablet crushing should be considered a last resort(BAPEN, 2003a). The loss of dose of the proportions described in the literature could have an impact on therapeutic effectiveness of some medicines with a narrow therapeutic margin.

The survey derived data at the start of this research revealed several methods that were used in clinical practice to facilitate solid dosage form administration to patients with enteral feeding tubes. The primary aim of this in-vitro research was to evaluate the effect of tablet manipulation for enteral tube administration on dose delivery, using the these tablet preparation methods and also from the literature (Paradiso et al., 2002, Phillips and Endacott, 2011, Mota et al., 2010, Naysmith and Nicholson, 1998).

## 4.2 Background

### 4.2.1 Tablet crushing and the potential impact on dose delivery

Powers and Cascella (Powers and Cascella, 1990) published the first study to demonstrate that dose recovery may be affected by the method of tablet manipulation in 1990. Despite demonstrating a significant reduction in dose delivery of 25% when using a pestle and mortar there was little subsequent interest and the use of crushing devices, include pestle and mortar have become accepted as normal practice. It has only been in very recent years that an interest in the impact of tablet manipulation on pharmacokinetics has resurfaced. Powers and Cascella, using aspirin as their model drug, compared three methods; dispersion in a syringe, crushing in a pestle and mortar, and crushing between two medicine pots.

Although the study was conceived with nasogastric administration in mind it did not actually administer the dose via a tube, so although providing some insight into potential causes of loss of active drug during administration the actual interaction with the tube was not studied.

### 4.2.2 Tablet crushing and methodological inconsistency

Literature descriptions of tablet manipulation for enteral tube administration vary widely with respect to equipment, technique, fluid and fluid volume (Paradiso et al., 2002, Wohlt et al., 2009, Williams, 2008), however there are fundamentally two methods for breaking up the solid dosage form; crushing or dispersing.

Dispersal methods can be carried out in closed systems, for example using a syringe. These are advocated for high-risk medication, such as cytotoxic and teratogenic drugs, when occupational exposure may be an issue (White, 2015b, NIOSH, 2004, RPS, 2011). Open systems, such as a medicine pot or beaker, appear more commonly in the literature (Naysmith and Nicholson, 1998) but in addition to exposure risk also raise concerns regarding spillage and incomplete dosing (Paradiso et al., 2002).

Crushing methods can either involve crushing the tablet and transferring the dry powder into another container for suspension and administration, or suspended directly in the crushing device. The only closed system crushing device referred to in the literature is the crushing

syringe (Figure 4.2.2a), all other devices require the powder to be transferred or suspended prior to transfer (Figure 4.2.2b-d). These devices vary significantly in the material and device surface area to which the drug is exposed and also in crushing effectiveness; some being more dependent on the operator than others. Many of these devices are available for patients to purchase directly without advice from an appropriate healthcare professional.

**Figure 4.2.2a Crushing Syringe**

(www.caregiverproducts.com)

**Figure 4.2.2b Pestle and Mortar**

(www.scilabware.com)

**Figure 4.2.2c Screw down pill crusher**

(www.livingmadeeasy.org.uk)


**Figure 4.2.2d Lever tablet crusher with pill bag**

(www.pharmasystems.com)

Pre, post and between medication flush volumes vary widely in the literature and in clinical practice, as seen in chapter two. Likewise the volume of fluid used to suspend crushed tablets also varies as does the volume of water used for rinsing equipment; the most common recurring fluid volume recommended for crushed tablet suspension is between 10mL to 30mL.

### 4.2.3 Surface interactions as a cause of drug loss

Plastics used in medical devices have distinct surface-active properties (McKeen, 2014). Studies demonstrating loss of drugs onto plastics have primarily focussed on medication administered by infusion, the long contact times usually intending to replicate the conditions experienced in continuous infusion of injectables through an infusion device. Adsorption is a surface-based process where in molecule being studied accumulates on the material surface; absorption is the assimilation of molecules throughout the bulk of the material.

Kowaluk et al. (Kowaluk et al., 1982) studied 45 drugs from intravenous solutions, through PVC, polyethylene and silicone tubing. There were a limited range of drugs that appeared to bind to the plastic, for those drugs there was a higher proportion of drug binding to silicone, a lower proportion with PVC and almost negligible with polyethylene. They concluded that sorption of particular drugs was reduced through the use of inert plastics, although did not draw any conclusions in relation to the drug characteristics or the type of sorption occurring.

There have been very few studies evaluating the loss of drug through adsorption onto feeding tubes. A study in 1990 by Clarke-Schmidt et al. (Clark-Schmidt et al., 1990) revealed that the dilution of carbamazepine liquid prior to administration via a PVC enteral tube could reduce the loss of drug that was seen with undiluted liquid. They concluded that carbamazepine adsorbing onto the surface of the tubing was to blame for reduction in effectiveness when administered via a feeding tube, although there was no subsequent evaluation to determine if this was a saturable phenomenon.

More recently, Manessis and co-workers (Manessis et al., 2008) noted that patients who changed from oral levothyroxine to enteral via a PEG tube became hypothyroid. They hypothesised that levothyroxine adsorbed onto silicone gastrostomy tubes during administration, using radiolabelled levothyroxine they demonstrated a small amount of adsorption onto the tubing with a contact time of 10 seconds, however they concluded it was less than 5% and that clinical effects seen in their patients may be attributable to drug lost during crushing and transfer.

Klang et al. (Klang et al., 2010) demonstrated a loss of 35% of a warfarin dose when crushed and administered through a polyurethane feeding tube using an in vitro model which

simulated gastric administration. They hypothesized that the loss was due to adsorption onto the tubing and tested this through immersion of tubing material in the gastric acid and drug solution, demonstrating loss of drug onto the tubing.

These limited examples indicate that there is a possible risk of drug loss on the tubing of the administration device and that this should be considered when administering medication via and enteral tube and contact times should be minimised (Klang et al., 2010) although there are no data to indicate that this would reduce the extent of surface binding.

What is also clear from the data presented is that there is a risk of drug loss during transfer from one container to the other, either by partial retention in the original container or due to spillage on transfer.

### 4.2.4 Methodological approach to drug quantification

Drug stability of small molecules can be affected by exposure to light and extremes of temperature, humidity, pH, and physical forces. It is recommended that stability indicating analytical methods should be validated to identify and quantify degradation products in addition to active content in pharmaceutical products, including unlicensed specials (NHS, 2014). There is no guidance on the scope of stability testing required for extemporaneous preparations intended for immediate use, as in the case of crushed and dispersed tablets, however there is considered to be minimal concern in relation to stability (RPS, 2011). Crushing a tablet by hand will exert pressures far lower than those used to compress the tablet during manufacture. Mixing a crushed tablet in water at room temperature would not be considered a 'high stress' situation and therefore the rapid degradation of active compound leading to a reduction in dose delivered is highly unlikely.

High performance liquid chromatography (HPLC) is considered the gold standard for the analytical quantification of small molecule medication from dosage forms (Kazakevich and LoBrutto, 2007). The higher levels of excipients in solid dosage forms when compared to injectable formulations can impact the design of the assay method due to the risk of co-eluting peaks with the active compound; this should be considered in assay design and elution parameters adjusted to minimise any overlapping peaks, if this cannot be achieved, then HPLC-MS can be considered (Kassel, 2007).

## 4.3 Aim and Objectives

The aim of this chapter was to evaluate the suitability and accuracy of methods used to manipulate tablets for enteral tube administrationin order to determine a preferred method for tablet manipulation for enteral tube administration.

The objectives were to determine if dose:

1. recovery varied depending on the method used
2. received would be reduced due to drug loss on the tube material

This was to be achieved through an in vitro evaluation of dose recovery of a small range of commonly used medication, administered through a feeding tube following the methods identified from the literature.

## 4.4 Materials and Methods

### 4.4.1 Reagents, drug standards, and consumables

Standard reagents and chemical substances were used for manufacture of the mobile phase: Acetonitrile, Sodium phosphate monobasic monohydrate, phosphoric acid, methanol and milliQ water. Pharmaceutical grade drug standards were used for manufacture of standards for calibration: ramipril, naproxen and amlodipine besylate. Full details are in table 4.4.1.

*In all studies HPLC analysis was carried out in reverse phase with a series 200 Perkin Elmer high performance liquid chromatography having a Perkin Elmer series 200 isocratic pump, equipped with a Perkin Elmer 600 series link interface and a Perkin Elmer series 200 UV-VIS detector. Perkin Elmer TotalChrom software was used to collect, integrate and analyse the chromatographic data.*

A HyperClone 5µm $C_{18}$-BDS 130Å 250x4.6mm column (Phenomenex, UK) was used for all assays. The mobile phase consisted of 0.01M phosphate buffer (pH 2.6) and acetonitrile, the proportions varied (A:B) for each drug analysed to achieve a suitable elution time and peak resolution. Full details are included in Table 4.5.1.

**Table 4.4.1 Materials and consumables**

| Product details | Grade/Details | Source/Supplier |
|---|---|---|
| **Ramipril 10mg Tablet** | Licensed medicine | Sanofi |
| **Amlodipine Besilate 10mg** | Licensed medicine | Accord |
| **Naproxen 250mg Tablet** | Licensed medicine | Accord |
| **Ramipril** | EP Reference standard | Sigma-Aldrich |
| **Amlodipine Besylate** | EP Reference standard | Sigma-Aldrich |
| **Naproxen** | EP Reference standard | Sigma-Aldrich |
| **Acetonitrile** | HPLC grade | Sigma |
| **Methanol** | HPLC grade | Sigma |
| **Sodium phosphate monobasic monohydrate** | | Sigma |
| **Phosphoric acid** | | Sigma |
| **Enteral syringe** | 50mL | Medicina |
| **Polyurethane Enteral Feeding Tube** | Corflo®, 8 French (1.8mm ID), 92cm | Corpak Medsystems |
| **Personal tablet crusher (7335)** | | Health Care Logistics Inc, OH |
| **Crushing Syringe (7334-01)** | 60mL | Health Care Logistics Inc, OH |

### 4.4.2 Medication and tube selection

Ramipril, naproxen and amlodipine were chosen for evaluation. Ramipril and amlodipine were both identified as common medication in the nursing home survey in chapter two, naproxen had recently been put forward locally as NSAID of choice (East and South East England Specialist Pharmacy Services, 2011). They all featured in the top 100 drugs prescribed in England (taken from 2010 prescribing data, ranked by number of prescriptions per year)(Health & Social Care Information Centre, 2010) and at the time of research were not available in a liquid formulation and therefore were likely to be crushed or dispersed in practice. They were chosen to represent a range of solubility and excipient to active weight ratio (see table 4.4.2a)

**Table 4.4.2a Tablet formulation details**

| Drug name and strength (manufacturer) | Nominal excipient to active ratio (w/w) | Aqueous solubility | Clinical usage data(Health & Social Care Information Centre, 2010) |
|---|---|---|---|
| Amlodipine besilate 10mg (Accord Healthcare Ltd) | 24:1 (Accord, 2014) | Slightly Soluble (1 part in 100-1000)(Moffat et al., 2011) | 4th most commonly prescribed drug, top CCB, 21M prescriptions p.a. |
| Naproxen 250mg (Accord Healthcare Ltd) | 0.52:1 | Practically Insoluble (1 part in less than 10,000)(Moffat et al., 2011) | 61st most commonly prescribed drug, 3rd NSAID, 3M prescriptions p.a. |
| Ramipril 10mg (Aventis Pharma Ltd – trading as Sanofi) | 9:1 (Sanofi, 2014) | Sparingly Soluble (1 part in 30-100) (Moffat et al., 2011) | 9th most commonly prescribed drug, top ACEI, 18M prescriptions p.a. |

CCB=Calcium channel blocker, NSAID=Non-steroidal anti-inflammatory drug, ACEI=Angiotensin converting enzyme inhibitor

The brand and dose of tablet were chosen based on their excipient content, the intention being to minimise the risk of excipients interfering with the drug HPLC assay. Formulations with pigment dyes were purposely excluded (see table 4.4.2b for full excipient listing).

**Table 4.4.2b Excipient details (as described in summary of product characteristics)**

| Ramipril 10mg (Aventis Pharma, 2015) | Naproxen 250mg (Accord Healthcare, 2016) | Amlodipine Besilate 10mg (Accord Healthcare, 2015) |
|---|---|---|
| Hypromellose | Lactose monohydrate | Microcrystalline cellulose |
| Pregelatinised starch | Maize starch | Sodium starch glycollate |
| Microcrystalline cellulose | Polyvinylpyrollidone | Sodium acid citrate |
| Sodium stearyl fumarate | Magnesium stearate | Magnesium stearate |
| | | Croscarmellose sodium |
| | | Crospovidone |

The enteral tube type most commonly used in clinical practice is the nasogastric tube. A single eyelet exit port has been shown to minimise the risk of blockage(Probst, 2006), this tube was chosen to reduce variables that may influence loss of drug such as tube blockage. An 8Fr (1.8mm internal diameter) polyurethane enteral feeding tube and Oral/Enteral 50mL syringes were used for all experiments.

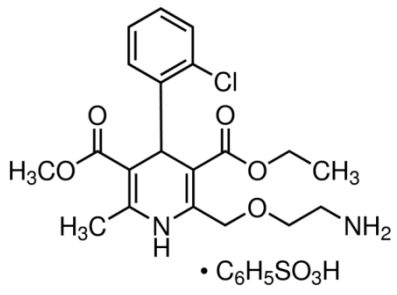
### 4.4.3 Drug quantification method development

A literature search was undertaken to identify HPLC analytical methods utilised to quantify the selected drugs in solid dosage forms. Assay procedures were optimised for reduced run time, optimal UV absorbance wavelength and peak resolution.

In this study the procedures were consistent with ward based preparation of the tablet dispersions, with no prolonged storage prior to administration. For this reason, forced degradation and analysis of degradation products and impurities was not undertaken.

#### 4.4.3.1 Amlodipine methodological development

Amlodipine, a 1,4-dihydropyridine, is a calcium channel blocker widely used in the management of hypertension and angina. Two salt forms are used in tablet formulations, the maleate and besylate. The besylate has a more favourable stability profile (Murakami et al., 2008) and the tablet form has been shown to be a suitable base for extemporaneous preparation of a liquid formulation with an extended shelf life (Nahata et al., 1999).



Amlodipine Besilate

Many HPLC methods for analysis of amlodipine tablets exist in the literature, however the majority are for the simultaneous quantification of a combination of ingredients and therefore analytical parameters may not be optimal for single drug determination due to their need to use a wavelength common to the combination (Patil et al., 2011) and to separate peaks for multiple components (Dongre et al., 2008).

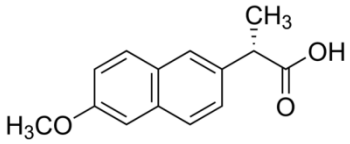
The pKa of amlodipine is 9.48 in acetonitrile (Narasimham and Barhate, 2011), UV $\lambda_{max}$ is 240nm. Most published HPLC methods use a binary mobile phase mix of acetonitrile or methanol (Kumudhavalli et al., 2011) with acetate (Nahata et al., 1999) or phosphate buffer

(pH range 2.6-7.0) either with or without trimethylamine, to reduce peak tailing (Kumudhavalli et al., 2011, Dongre et al., 2008).

Three methods described the use of a simple mobile phase of phosphate buffer and acetonitrile (ACN) (Mohammadi et al., 2007, Murakami et al., 2008, Prajapati et al., 2011). The pH in these methods varied between 4.5 and 2.6. A pH of 2.6 was selected, as buffer is most effective when within one pH unit of its pKa (phosphoric acid pKa = 2.15). In the method by Prajapati (Prajapati et al., 2011), a ratio of 60 (phosphate buffer):40 (ACN) was used for the mobile phase due to their requirement to separate amlodipine from perindopril; there was no need for peak separation for our analysis so this ratio was reversed to give a shorter retention time.

#### 4.4.3.2 Naproxen methodological development

Naproxen is a non-steroidal anti-inflammatory drug commonly used in the management of pain resulting from inflammatory conditions.

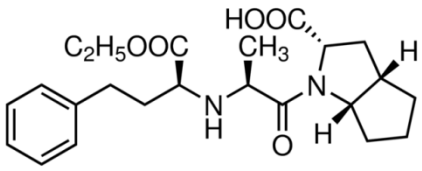



The available literature relating to analytical methods for naproxen determination in tablet formulations was very limited. All obtainable references related to simultaneous analysis of naproxen with another drug in combined products (Zakeri-Milani et al., 2005, Kumar et al., 2011, Haque et al., 2010, Wahbi et al., 2009, Jain et al., 2011). Mobile phase composition varied from binary to ternary (Zakeri-Milani et al., 2005), buffered (pH range 3.2 to 8.2) with a detection range from 240 to 300nm, and elution times ranging from 2.6 to 12.4 minutes.

The pKa of naproxen is 4.15 and and UV $\lambda_{max}$ was selected at 247nm. A decision was made to use the same mobile phase components as the method for amlodipine, at a pH of 2.6 the binary mobile phase ratio was adjusted to give an elution time of 5.6 minutes.

#### 4.4.3.3 Ramipril methodological development

Ramipril is an angiotensin II receptor antagonist used for the treatment of hypertension.




The British Pharmacopeia chromatographic procedure for the quantification of Ramipril is complicated by the inclusion of peak separation of ramipril from its degradation products, requiring a gradient liquid chromatographic process. Degradation products of Ramipril are structurally similar, posing challenges for separating the response peaks in RP-HPLC (Hanysova et al., 2005). Degradation products do not appear immediately on exposure to light, heat or water (Hanysova et al., 2005) and so identification and quantification of degradation products were not required for the purposes of this study and a simplified method could be adopted.

The available literature relating to analytical methods for ramipril determination in tablet formulations is extensive and varied. Most methods to quantify ramipril were for tablet formulations in combination with one or more other active component. Mobile phase composition was mainly binary, buffered (pH range 2.5 to 5) with a detection range from 208 to 230nm, and elution times ranging from 3 to 5.6 minutes. (Yilmaz, 2010, Bonazzi et al., 1997, Joseph et al., 2008, Patole et al., 2010, Chandra Bose et al., 2011, Damle et al., 2010, Naveen.B, 2013, Yadav, 2012)

The method by Yilmaz(Yilmaz, 2010) was very similar to the method already determined for amlodipine and naproxen, with a pH of 2.5 and a binary mobile phase of acetonitrile and phosphate buffer, and was used as the basis of our adapted method.

#### 4.4.3.4 Method accuracy

In order to be assured of the analytical method accuracy, for the first drug tested, stock standard solutions of varying concentrations were tested in triplicate for each data point on both the calibration curve determination and all method test samples as recommended by ICH guidance (ICH, 2005). This was reduced to duplicate testing for each sample for subsequent drugs tested.

### 4.4.4 Tablet crushing method development

The six methods identified for evaluation were: Dispersal in a syringe, dispersal in a small pot/container, crushing using a crushing syringe, crushing device, pestle and mortar or two stainless steel teaspoons. Pragmatic instructions were developed for each method, with minimal steps reflecting clinical practice, full details in table 4.4.4a.

The dispersal volume was taken from the crushing syringe instructions which specified 30mL (Health Care Logistics, 2011), this is consistent with the guidance in the literature (Wohlt et al., 2009, Williams, 2008) and in line with current practice as indicated in the data obtained in the survey in chapter two.

In order for tablet dispersion to be a practically applicable method for clinical practice an acceptable maximum time is required. A maximum of 2 minutes was considered acceptable for utilisation of this method; this is in line with the practice in the observational study by van den Bemt (van den Bemt et al., 2006). If dispersion took longer than 2 minutes this method would have been discounted as a pragmatic option.

Dry powder transfer from pestle and mortar was used in the study by Powers and Cascella, therefore dry powder transfer was used for the pestle and mortar and crushing device methods in this study. This method is not consistent with guidance for trituration of powder and dispersion as recommended in pharmaceutical practice for the preparation of suspensions (Jackson and Lowey, 2010), but there are no reports of this level of methodological attention in ward based clinical practice.

The flush volume of 10mL was the most common between medication flush volume as determined by the survey results in chapter one, and is consistent with the Powers(Powers and Cascella, 1990) study therefore this volume was used across all methods.

The control samples were prepared by dispersing a whole tablet directly in the volumetric flask; this was assumed to achieve 100% dissolution and recovery.

**Table 4.4.4a Tablet preparation methods**

| | | |
|---|---|---|
| A. Control | 1.1a | Place whole tablet in 40ml of water in a 100mL volumetric flask |
| | 1.2a | Agitate to disperse |
| B. Crushing in pestle and mortar | 1.1b | Crush tablet in pestle and mortar |
| | 1.2b | Tip dry powder into plastic cup |
| | 1.3b | Add 30ml of water and swirl to mix |
| | 1.4b | Draw dispersion into 50ml enteral syringe |
| | 1.5b | Flush dose down tube into 100ml volumetric flask. |
| | 1.6b | Draw 10ml water into syringe and also flush this into tube. |
| | 1.7b | Continue with sample preparation as detailed below. |
| Crushing in a crushing device | 1.1c | Put tablet into pill crusher and screw down to crush tablet |
| | 1.2c | Tip dry powder into plastic cup |
| | 1.3c | Add 30ml of water and swirl to mix |
| | 1.4c | Draw dispersion into 50ml syringe |
| | 1.5c | Flush dose down tube into 100ml volumetric flask. |
| | 1.6c | Draw 10ml water into syringe and also flush this into tube. |
| | 1.7c | Continue with sample preparation as detailed below. |
| D. Crushing between 2 spoons | 1.1d | Crush tablet between 2 spoons over plastic cup and tip powder into cup |
| | 1.2d | Add 30ml of water and swirl to mix |
| | 1.3d | Draw dispersion into 50ml syringe |
| | 1.4d | Flush dose down tube into 100ml volumetric flask. |
| | 1.5d | Draw 10ml water into syringe and also flush this into tube. |
| | 1.6d | Continue with sample preparation as detailed below. |
| E. Dispersion in medicine pot | 1.1e | Put tablet into plastic cup |
| | 1.2e | Add 30ml of water and swirl until dispersed |
| | 1.3e | Draw dispersion into 50ml syringe and record volume |
| | 1.4e | Flush dose down tube into 100ml volumetric flask. |
| | 1.5e | Draw 10ml water into syringe and also flush this into tube. |
| | 1.6e | Continue with sample preparation as detailed below. |
| F. Dispersion in barrel of syringe | 1.1f | Remove plunger from syringe, place tablet into barrel |
| | 1.2f | Draw up 30ml of water and shake syringe until tablet disintegrates |
| | 1.3f | Flush dose down tube into 100ml volumetric flask. |
| | 1.4f | Draw 10ml water into syringe and also flush this into tube. |
| | 1.5f | Continue with sample preparation as detailed below. |
| G. Dispersion in crushing syringe | 1.1g | Remove plunger from crushing syringe, place tablet in barrel. |
| | 1.2g | Replace plunger and safety cap and twist plunger to crush tablet. |
| | 1.3g | Remove safety cap and draw up 30ml of water. |
| | 1.4g | Replace safety cap and shake well to disperse. |
| | 1.5g | Remove safety cap and flush contents down tube into 100ml volumetric flask. |
| | 1.6g | Draw 10ml of water into syringe and also flush this via tube into flask. |
| | 1.7g | Continue with Sample preparation as detailed below. |

Following tablet preparation detailed above, a further 40mL of acetonitrile was added to the 100mL volumetric flask. This was sonicated for 15 minutes (equipment name, manufacturer) and allowed to return to room temperature, before making to volume with acetonitrile.

Samples from these solutions were further serially diluted using the appropriate mobile phase to achieve a final drug concentration within the linear range for the assay. Samples were filtered as a final step. Details of serial dilution contained in table 4.4.4b.

**Table 4.4.4b Final target concentration for HPLC analysis**

| Drug | Initial nominal sample concentration | Final target concentration |
|---|---|---|
| **Amlodipine** | 100µg/mL | 20µg/mL |
| **Naproxen** | 2.5mg/mL | 25µg/mL |
| **Ramipril** | 100µg/mL | 50µg/mL |

In all studies HPLC analysis was carried out in reverse phase with a series 200 Perkin Elmer high performance liquid chromatography having a Perkin Elmer series 200 isocratic pump, equipped with a Perkin Elmer 600 series link interface and a Perkin Elmer series 200 UV-VIS detector. Perkin Elmer TotalChrom software was used to collect, integrate and analyse the chromatographic data.

A HyperClone 5µm $C_{18}$-BDS 130Å 250x4.6mm column (Phenomenex, UK) was used for all assays. The mobile phase consisted of 0.01M phosphate buffer (pH 2.6) and acetonitrile, the proportions varied (A:B) slightly. Details of HPLC parameters are detailed in table 3.

**Table 4.5.1 HPLC parameters**

| Medication | Mobile Phase A | Mobile Phase B | UV absorbance Peak (nm) | Injection volume (µL) | Elution time (min) | Run time (min) | Linear range (µg/mL) | Number of test articles |
|---|---|---|---|---|---|---|---|---|
| Amlodipine | 40 | 60 | 240 | 10 | 3.3 | 5 | 1-95 | 4 |
| Naproxen | 45 | 55 | 247 | 25 | 5.6 | 7 | 1-100 | 6 |
| Ramipril | 40 | 60 | 210 | 10 | 3.3 | 5 | 1-100 | 4 |

### 4.4.5 Test article preparation

Six test articles were prepared for each method for naproxen. Three samples were taken from each test article. Following analysis of the naproxen results the number of test articles was reduced to 4 for amlodipine and ramipril.

### 4.4.6 Statistical analysis

Data were analysed using Microsoft Excel 2010 Data Analysis Tools package statistical software and GraphPad software (www.graphpad.com). The method used controlled for drug, diluent, volume, enteral tube material, size and analytical method, however as the method of preparation differed and the tablets tested, although from the same batch, were destroyed during testing and therefore multiple tests could not be completed on a single tablet. For that reason an unpaired (2 sample) t-test was used to compare the dose recovered for each method to the control sample. Dose recovered was correlated with tablet composition and drug solubility using standard regression analysis.

## 4.5 Results

### 4.5.1 Validation of analytical methods

Under the experimental conditions described using pharmaceutical grade active ingredients, linear calibration curves were obtained for amlodipine, naproxen and ramipril with five concentration levels. Regression equation and correlation coefficients were determined by linear regression analysis of the peak area and concentration of each drug using Microsoft Excel 2010. The linearity ranges are detailed in table 4.5.1, R values are shown in figures 4.5.1.1a, 4.5.1.2a and 4.5.1.3a.

Accuracy of the analytical method was determined through triplicate measurement of stock standard solutions of varied concentrations (ICH, 2005). The mean dose recovery from the non-manipulated tablet was considered to be indicative of the completeness of recovery if above the accepted pharmacopeial limits for licensed medication.

Limit of detection and limit of quantification were not determined as the dose recovery values, based on data from the literature, were predicted to be between 75% and 100% and therefore in the mid-section of the linear range.

Robustness was not determined however in order to control for minor variances in temperature and mobile phase, the five standard concentrations were analysed in the same run as the test articles and a new regression equation calculated for each run.

#### 4.5.1.1 Amlodipine

The calibration curve was determined using a standard stock solution of purchased amlodipine. Linearity was demonstrated across the range from 1 microgram/mL to 95 microgram/mL. This is consistent with the linear range in similar methods in the literature (Prajapati et al., 2011).

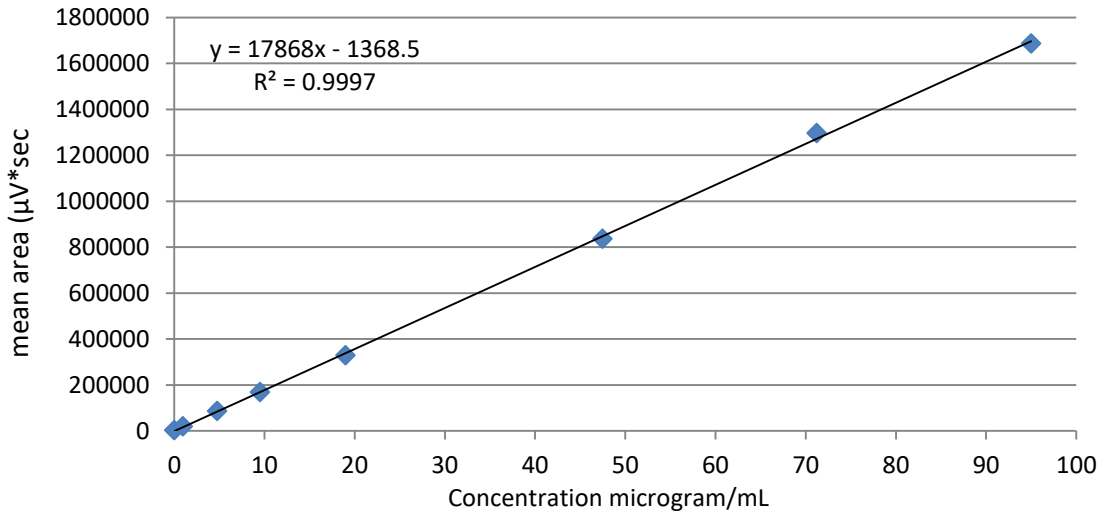
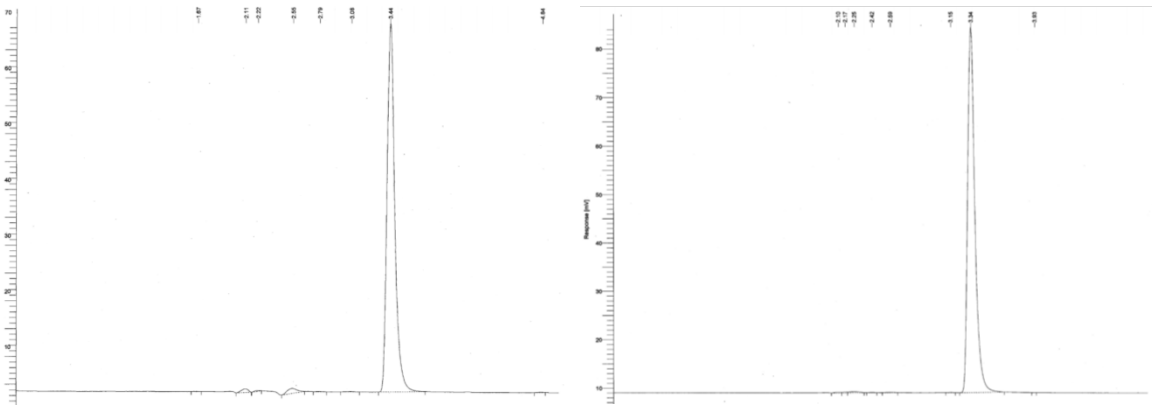



**Figure 4.5.1.1a Calibration curve for amlodipine**

The chromatograms for amlodipine besilate standard and the tablet formulation were almost identical indicating that there was no interference from the excipients within the tablet formulation (See figure 4.5.1.1b). Sample peak eluted at 3.3 minutes, no other significant peaks were identified.



Amlodipine stock solution 20microgram/mL Amlodipine tablet control 20microgram/mL

**Figure 4.5.1.1b Amlodipine chromatograms**

#### 4.5.1.2 Ramipril

The calibration curve was determined using a standard stock solution of purchased ramipril. Linearity was demonstrated across the range from 1microgram/mL to 100 microgram/mL. Linearity for ramipril assays has been demonstrated across a wide range of concentrations in the literature, from 0.25 to 650microgram/mL. (Yilmaz, 2010, Yadav, 2012)

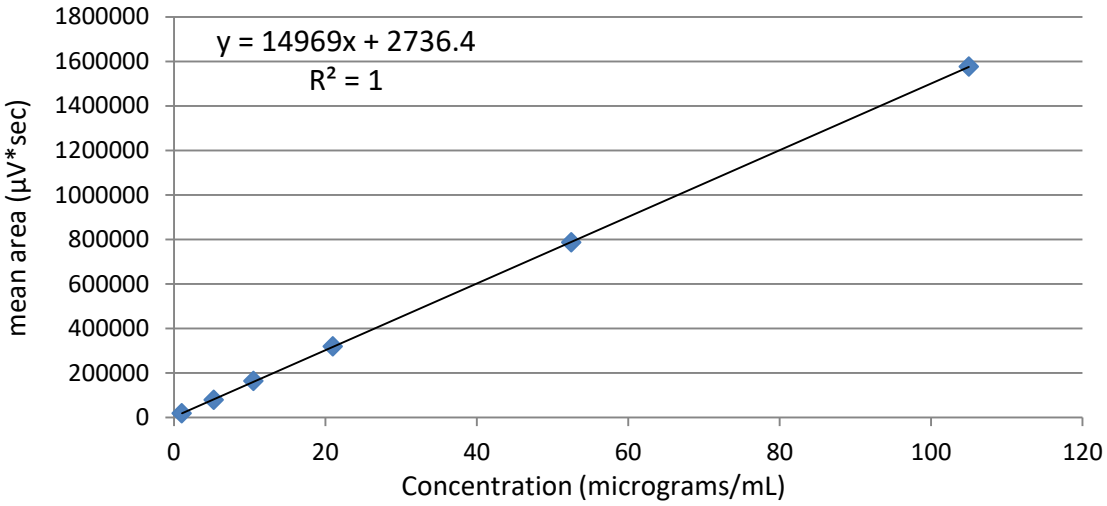
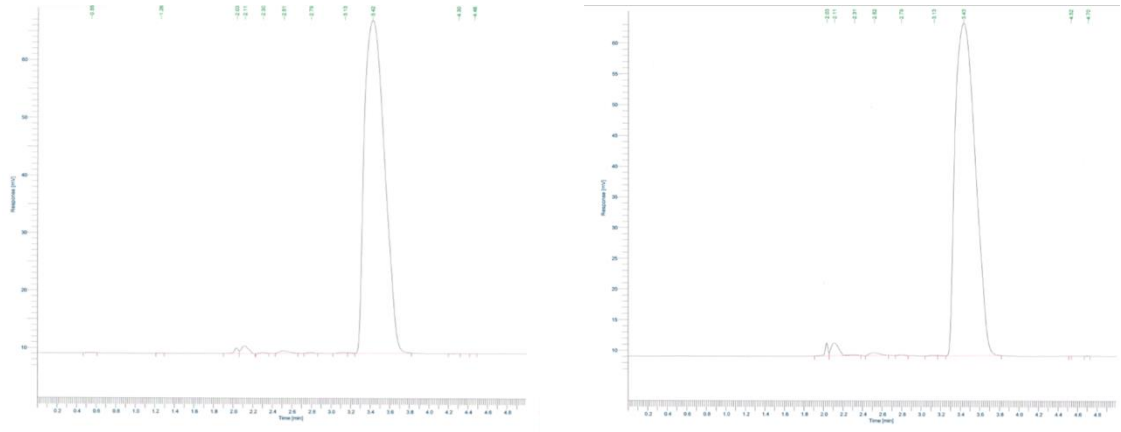



**Figure 4.5.1.2a Calibration curve for ramipril**

The chromatograms for ramipril standard and the tablet formulation were almost identical indicating that there was no interference from the excipients within the tablet formulation (See figure 4.5.1.2b). Sample peak eluted at 3.4 minutes, no other significant peaks were identified.



Ramipril stock solution 50microgram/mL Ramipril tablet control 50microgram/mL

**Figure 5.4.1.2b Ramipril Chromatograms**

#### 4.5.1.3 Naproxen

The calibration curve was determined using a standard stock solution of purchased naproxen. Linearity was demonstrated across the range from 1microgram/mL to 100 microgram/mL. Linearity for naproxen assays has been demonstrated across a wide range of concentrations in the literature, from 1.5 to 250microgram/mL. (Wahbi et al., 2009, Jain et al., 2011)

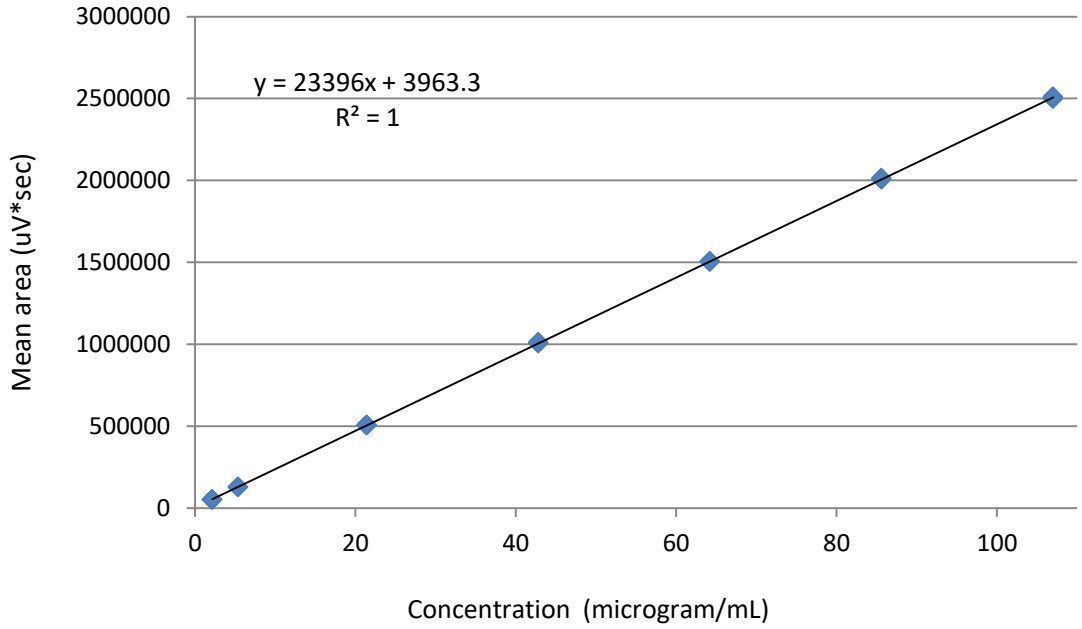
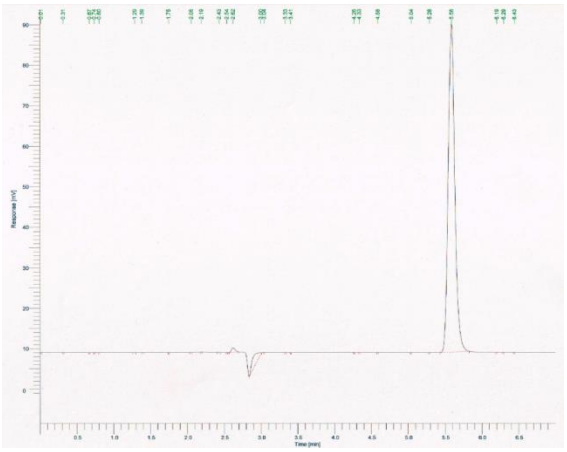


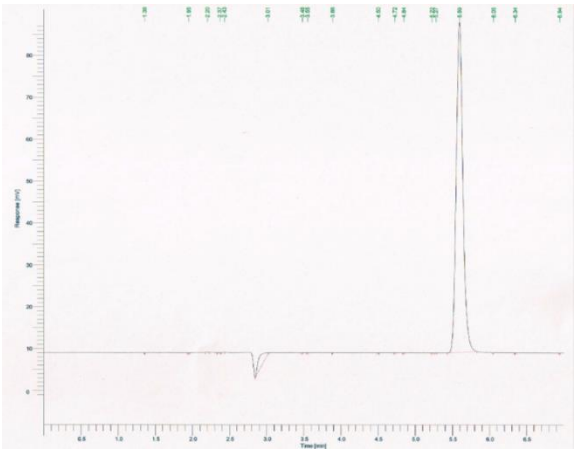

**Figure 4.5.1.3a Naproxen Calibration Curve**

The chromatograms for naproxen standard and the tablet formulation were almost identical indicating that there was no interference from the excipients within the tablet formulation (See figure 4.5.1.3b). Sample peak eluted at 5.6 minutes, no other significant peaks were identified.

There was negligible tailing of the response peak and no determinable interference from excipients.



Naproxen stock solution 25micrograms/mL



Naproxen tablet control 25microgram/mL

**Figure 4.5.1.3a Naproxen chromatograms**

### 4.5.2 Determination of dose recovery

The dose recovered from the control sample was 10.74±0.24mg for amlodipine (label claim 10mg), 244.25± 4.62mg (label claim 250mg) for naproxen and 10.32±0.15mg (label claim 10mg) for ramipril. For the purposes of dose recovery calculations the dose recovered from the control samples was considered to be 100% of recoverable dose for the purposes of comparison.

All tablets dispersed within 2 minutes. No tube blockage occurred for any tablet prepared by any method.

For Naproxen six tablets were prepared using each method (test article), triplicate samples were taken from each test article. The dose recovered for each method is shown in table 4.5.2a. There was no statistically significant difference in the dose recovered from the use of the syringe dispersal method when compared to control. All other methods yielded a lower dose that was both statistically significant and also a mean value below the pharmaceutically acceptable level of 95%.

**Table 4.5.2a Naproxen dose recovery from tablet manipulation** (n=6)

| Method | % dose recovered | SEM | p |
|---|---|---|---|
| **Control** | 100% | 0.9 | |
| **Dispersal in syringe** | 98% | 0.5 | 0.0807 NS |
| **Crushing syringe** | 94.5% | 1.2 | 0.0043 |
| **Dispersal in medicine pot** | 90.5% | 3.4 | 0.0223 |
| **Pestle and mortar** | 90.1% | 1.5 | 0.0002 |
| **Crushing device** | 90.1% | 2.7 | 0.0059 |
| **Crushing between 2 spoons** | 88.8% | 1.1 | 0.0001 |

For amlodipine, four tablets were prepared using each method; duplicate samples were taken from each test article. The dose recovered for each method is shown in table 4.5.2b. There was no statistically significant difference in the dose recovered from the use of the syringe dispersal method or the crushing syringe when compared to control. All other methods yielded a lower dose that was both statistically significant and also a mean value below the pharmaceutically acceptable level of 95%.

**Table 4.5.2b Amlodipine dose recovery from tablet manipulation** (n=4)

| Method | % dose recovered | SEM | p |
|---|---|---|---|
| **Control** | 100 | 1.13 | |
| **Dispersal in syringe** | 97.31 | 0.49 | 0.717NS |
| **Crushing syringe** | 94.89 | 1.92 | 0.0616NS |
| **Crushing between 2 spoons** | 94.80 | 0.54 | 0.0060 |
| **Dispersal in medicine pot** | 93.03 | 2.57 | 0.0476 |
| **Crushing device** | 84.18 | 1.55 | 0.0002 |
| **Pestle and mortar** | 79.99 | 0.91 | <0.0001 |

For ramipril four tablets were prepared using each method, duplicate samples were taken from each test article. The dose recovered for each method is shown in table 4.5.2c. There was no statistically significant difference in the dose recovered from the use of the syringe dispersal method, medicine pot dispersal or crushing syringe when compared to control. All other methods yielded a lower dose that was both statistically significant and also a mean value below the pharmaceutically acceptable level of 95%.

**Table 4.5.2c Ramipril dose recovery from tablet manipulation** (n=4)

| Method | % dose recovered | SEM | p |
|---|---|---|---|
| **Control** | 100 | 1.00 | |
| **Dispersal in syringe** | 99.07 | 0.71 | 0.4770NS |
| **Dispersal in medicine pot** | 98.35 | 0.78 | 0.2410 NS |
| **Crushing syringe** | 97.57 | 1.64 | 0.2528 NS |
| **Crushing between 2 spoons** | 92.81 | 2.17 | 0.237 |
| **Crushing device** | 84.50 | 1.54 | 0.0002 |
| **Pestle and mortar** | 81.43 | 3.88 | 0.0036 |

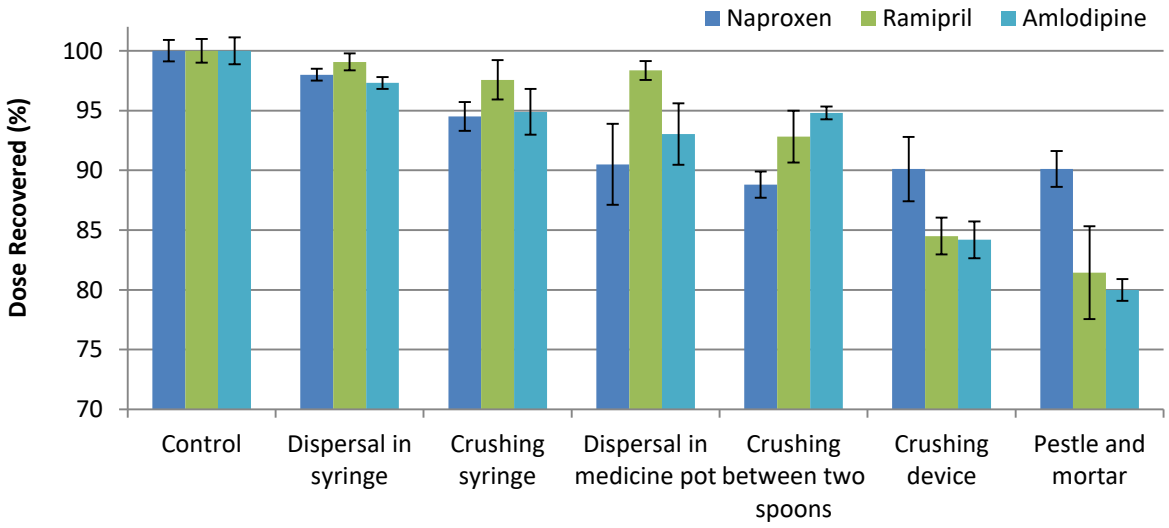



**Figure 4.5.2a Dose recovery for naproxen, amlodipine and ramipril following tablet crushing methods (including SEM)**

There appeared to be no relationship between dose recovery and solubility by method, however with only three data points there are limited conclusions that can be drawn. There was an potential relationship between dose recovery and tablet composition for the pestle and mortar and crushing device methods, as shown in table 4.5.2d and figure 4.5.2b, this may be of interest but requires further investigation with tablet formulations representing a wider range of active to bulk ratios before any firm conclusions can be drawn.

**Table 4.5.2d Relationship between manipulation method and tablet composition**

| Method | $R^2$ (Note limited statistical value due to small number of data points) |
|---|---|
| Dispersal in syringe | 0.0013 |
| Crushing syringe | 0.2753 |
| Dispersal in medicine pot | 0.4713 |
| Crushing between two spoons | 0.9419 |
| Crushing device | 0.9984 |
| Pestle and mortar | 0.9981 |

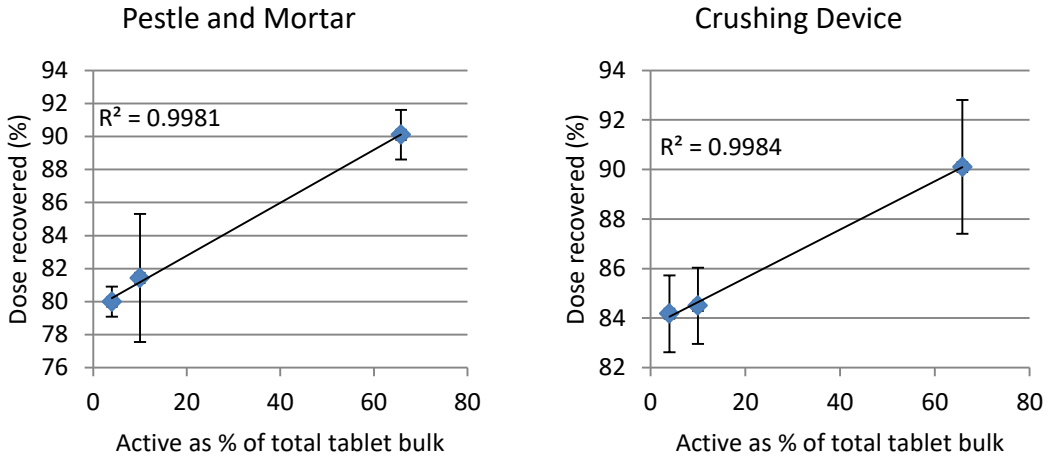



**Figure 4.5.2b Relationship between manipulation method and tablet composition**

## 4.6 Discussion

This research is the first to determine the impact on dose recovery of a full range of methods used for tablet manipulation specifically for enteral tube administration, including both dispersion and crushing techniques. Although only undertaken with a limited number of drugs, it provides useful insights into the effect of tube administration on dose recovery, the impact of the preparation technique and equipment choice. These can be used as a basis for further research.

### 4.6.1 Effect of tube administration on dose recovery

The administration method using dispersal in the administration syringe represented the minimum number of steps, transfers and surface area contact and therefore is most likely to demonstrate a chemical interaction with the syringe or tube rather than a physical loss of drug

during the transfer process. There was no significant difference between control and dose recovered following dispersal in the syringe for any of the three drugs studied. This indicates that any drug binding to the syringe barrel, plunger or polyurethane enteral tube is negligible.

The dispersed medication in this study was only in contact with the enteral tube for 10-20 seconds as the administration step was rapidly followed by the flush step, this would limit any loss of drug to surface binding only. In the studies by Kowaluk et al. (Kowaluk et al., 1982), the administration syringe was also the storage device and the dwell time was much longer (up to 8 hours) allowing a potentially rate dependent sorption process to occur although the authors conclude that there was no relationship between the partition co-efficient and degree of binding.

### 4.6.2 Impact of manipulation method on dose recovery

There was a significant loss of dose as both the number of transfers and the potential contact surface area increased. In all cases dispersal in the syringe achieved a dose slightly below 100% but statistically insignificant. The accepted pharmacopoeial limit for drug content is 95%, the crushing syringe also delivered a dose above this for ramipril and only slightly below this for naproxen and amlodipine. This is in contrast to the open crushing methods, two spoons, crushing device and pestle and mortar, which all delivered a significantly lower dose.

All the medicines studies are considered to have a wide therapeutic index, and in the use of ramipril and amlodipine for hypertension the clinical effect is easily monitored and dose adjusted as required. There are no data relating to the clinical acceptability of under dosing due to tablet crushing in clinical practice, however dosing accuracy of equipment used for liquid medication (Beckett et al., 2012) and tablet dispersion in the paediatric community have been evaluated (Broadhurst et al., 2008).

Powers et al. (Powers and Cascella, 1990) were the first to document that dose recovery may be affected by tablet manipulation. Our study, like theirs, demonstrated that dispersion in the barrel of the syringe delivers a complete dose. Their method describing the use of one medicine pot inside another to crush the tablets achieved an 86% dose recovery; this method is most similar to our crushing device, which yielded between 84 and 90% depending on drug studied in our research. The lowest yield was achieved using a pestle and mortar to crush the

tablets, achieving 74% in Powers' study; this is also largely consistent with the findings of our study.

In comparison to our study, the magnitude of dose lost and variability of dose delivery are greater in the Powers' study this may be due to a number of reasons. It may be due to the techniques, surface area of the equipment or the suspension and flushing volume. Our study used 40mLs of water in total to suspend and administer the dose in comparison to 20mL in their study.

Throughout the literature the pestle and mortar has been consistently the most commonly used piece of equipment to crush tablets (Phillips and Endacott, 2011, Paradiso et al., 2002, Mota et al., 2010). The original research by Powers and this study indicate that this method results in the lowest dose delivery with potentially the highest variability under laboratory conditions.

Salmon (Salmon et al., 2013) et al. compared three methods of tablet preparation for enteral tube administration on three different drugs using analysis of physical properties. The methods investigated were open crushing and dispersion using a pestle and mortar; closed crushing and open dispersion; and closed crushing and dispersion. The method did not involve the passage of the tablet dispersion through a feeding tube or determination of dose recovery. Crushing efficacy was measured using sedimentation rate, as determined by change in turbidity, and suspension stability. Dispersion particle size was determined as was aerial contamination. All three methods produced dispersions of a similar nature, with an average particle size in the range of 2-6µm. The open crushing methods produced aerial contamination with particles greater than 5µm of more than $10^6$ particles/$m^3$. This raises concerns over using open crushing methods due to the significant risks of operator exposure, particles less than 10µm are considered inhalable and subject to occupational exposure limits (HSE, 2011).

Recently several investigators have evaluated the effect of tablet crushing on in vivo pharmacokinetics. Zafar et al. (Zafar et al., 2009) evaluated the pharmacokinetic consequences of crushing clopidogrel tablets for NG administration. Nine healthy volunteers participated in a crossover design study. The clopidogrel tablets were crushed in a pestle and mortar, mixed with 10mL of water and administered through a nasogastric tube, which was then flushed with another 20mL of water. The time to peak plasma concentration was earlier in the crushed

tablet group than the whole tablet group, 44 and 70 minutes respectively and the peak plasma concentration was 88% higher in the crushed tablet group, indicating a more rapid absorption profile. Despite this change in pharmacokinetics, the area under the curve over 24 hours was similar for both groups leading the investigators to conclude that this method of administration did not cause any loss of dose.

McNeely et al. (McNeely et al., 2013) examined the pharmacokinetic consequences of nasogastric administration of crushed tolvaptan tablets. This group determined that crushing tolvaptan and administration via the nasogastric tube resulted in a lower $C_{max}$ and earlier $t_{max}$, reducing the $t_{½}$ and resulting in a 25% decrease in AUC. Although the study was not designed to determine clinical consequence there was no evidence of difference in aquaresis. This group concluded that the tolvaptan had been sequestered onto the materials used to administer the dose; due to the method used this could have been at several points in the administration process. A silent knight pill crusher was used which utilises a polyethylene pouch to contain the tablet during crushing (ref:personal com Manex), the material of the pot or syringe used to reconstitute the resulting powder and administer via the tube were not documented, the enteral tube material was PVC (ref: www.kendalhealthcare.com). A total volume of 240ml was used to administer the dose, comprised of one 60ml reconstitution step and three 60mL flush steps. A follow-up in-vitro study was undertaken by this research group which confirmed a 12% decrease in dose administered. This method of administration was not evaluated by our project as it is not a common technique or piece of equipment in the UK, the loss of dose is similar to the loss of dose exhibited when using the crushing device in our study, however there are a number of potentially influencing factors which are different. The volume used is much larger than that used in UK practice, this may have increased the amount of drug flushed through, the tube material was PVC in this study which would have difference surface active properties to the polyurethane used in our study, the tube size was much larger which would have affected the volume to surface area ratio.

Best et al. (Best et al., 2011) evaluated the effect of crushing Keletra ® tablets on the pharmacokinetic profile. The tablets were crushed using the same type of pill crusher used in my study; however the crushed tablets were mixed with pudding for oral administration. The time to peak concentration was shortened by crushing, 2hrs for the crushed tablets and 4 hours for the whole tablets. The AUC 0-12hrs for the two constituent components was 45% lower for lopinavir and 47% lower for ritonavir. The researchers conclude that there may have

been a number of factors affecting the dose and pharmacokinetics such as loss of drug and impact on the delivery matrix of the tablet, however they did not comment on the sampling profile which due to the shorter time to peak concentration in the crushed tablet group may not have had sufficient sample points in the first four hours to determine the magnitude of the early peak in this group and therefore may have overestimated the consequence of crushing. It is unfortunate that none of the pharmacokinetic studies evaluated any possible loss of drug as a result of the tablet preparation step.

However despite the concerns about inaccurate dosing there is clinical evidence to suggest that the impact may be minimal for some drugs. Crushed voriconazole tablets, suspended in 50ml of water, were successfully administered via a jejunostomy tube yielding plasma levels comparable to oral administration (Martinez et al., 2003).

### 4.6.3 Potential factors affecting dose recovery

#### 4.6.3.1 Loss of drug on device or spillage

The potential for loss of drug powder during transfer from a crushing device, through the suspension process to the administration syringe may be dependent on the volume and number of rinse steps, the flush volume and also the meticulous nature with which the procedures are performed. This study did not evaluate the impact of varying the rinsing and flushing volume or frequency.

Within a laboratory environment with a skilled operator the loss through spillage is likely to be low; however in a clinical environment this has been demonstrated to be a potentially important issue. In an observational study in a residential care facility medication was spilled during the process of crushing in 70% of cases (Paradiso et al., 2002). In an observational study in ICU, the preparation step accounted for 32% of the errors (Al Rakaf and Lababidi, 2009). Within the preparation step not washing the pestle and mortar either before or after occurred in 20% of the preparation errors and incomplete administration of the powder was observed in 9% of the administration errors.

Complete tablet does were evaluated in this study and care was taken to ensure the sample was well mixed prior to withdrawal of the test sample, however sedimentation rate of

dispersions is of importance if a complete dose is not being administered. Tablet dispersion and proportional administration is utilised in clinical practice in order to deliver doses less than a single tablet. Broadhurst et al. (Broadhurst et al., 2008) evaluated proportional dosing of dispersible aspirin and determined that dissolution time and point of sample withdrawal affected dose recovered, with doses as low as 24% obtained using this method. The authors call into question the safety of continuing with this method in clinical practice.

This study did not evaluate the impact of co-administration with feed on dose recovery, as this practice is not recommended, however it is common in some areas of practice and has been evaluated by others, these studies also provide some insight into the effect of crushing tablets on dose recovery. Carrier et al. (Carrier et al., 2004) extensively studies tegaserod, used for constipation predominant IBS, crushed and mixed with various liquids and food stuffs. Tablets were crushed within an aluminium foil pouch to minimise dose loss on the crushing device. They determined that crushed tegaserod formed a homogenous suspension and was stable in tap water for 3 days, with mean dose recovery being 95.4%, potentially indicating minimal impact of this crushing method on dose recovery.

In a study (Burkhardt et al., 2005) investigating the effect of enteral feeding on moxifloxacin absorption three methods of administration were compared: whole tablets, crushed tablets with water; and crushed tablets administered at the same time as continuous enteral feeding. The group demonstrated that in both crushed tablet arms the total bioavailability was reduced to 91%. A pestle and mortar was used to crush the tablets in both arms of the study, a large flush volume of 200ml was used, however this reduction in dose is consistent with crushing using a pestle and mortar rather than an effect of tube administration or interaction with enteral feed. This group also demonstrated an earlier peak plasma level in the crushed tablet groups highlighting the impact of tablet crushing on pharmacokinetic profile.

### 4.6.3 Development and validation of analytical methods

The development of the analytical methods used in this study, although not the main focus of the research, do serve to reinforce the simplified approach that can be used for non-stability indicating studies of solid dosage forms.

The RP-HPLC analytical methods developed for use in this chapter were a simplified approach based on the available literature at that time. Shortly after undertaking this work a paper describing a remarkably similar method was described for the analysis of Ramipril.(Yadav, 2012) The researcher for this paper used a phosphate buffer (pH3): acetonitrile (30:70) mobile phase, with a flow rate of 2ml/min at a temperature of 30$^{o}$C but with an identical column and detection wavelength. Elution time was 3 minutes, compared to the 3.4 minutes in our study, the lower pH in our study would decrease elution time, however the higher temperature, faster flow rate and higher acetonitrile concentration in the mobile phase used in their method would account for the shorter elution time.

When comparing the assay for amlodipine with those from the literature, a study using the same mobile phase proportions and ambient temperature gave a similar elution time despite the use of a shorter column (Naveen.B, 2013), however the flow rate was lower and the pH higher, indicating the impact that these variables have on elution time. A method developed after our work was undertaken also used a similar proportion of buffer and acetonitrile, but at pH3, resulting in a longer retention time(Mahajan et al., 2012).

### 4.6.5 Limitations of this research

The scope of this study was limited to an in vitro evaluation of a single aqueous tablet suspension and flush volume. Expansion of the scope of this research to other medication not available in a liquid formulation and with a narrow therapeutic range could have provided more insight into the impact of varying the flush volume, flush technique, number of rinses and flushes.

Although this research does provide further evidence around the health and safety risks of crushing medication and provides some insights into the potential impact on dosing accuracy it does not provide data on the clinical impact on pharmacokinetics and physiological outcomes. This can only be achieved through an in vivo pharmacokinetic and response study. This would have required significantly resource which was not available within the scope of this study.

## 4.7 Conclusion and further research

This confirms the findings of previous similar work undertaken with other drug molecules and crushing devices and adds to the breadth of devices studied. It also serves to offer insight into the potential reasons for reduction in apparent bioavailability when crushed medications are administered via enteral tube. This data clearly calls into question the continued use of crushing devices such as pestle and mortar in routine clinical practice, and provides evidence to support the assertion that tablet crushing for enteral tube administration should only be considered when all other options have been excluded.

This study also provides new data that, in the drugs studied, adsorption to the tubing, if it does occur, is minimal and the dose delivered remains within pharmaceutically acceptable limits.

It is clear that crushing tablets for enteral tube administration can result in loss of drug during the preparation phase and that there may be a relationship between the composition of the tablet and the extent of loss on transfer. With a loss of up to 20% of the dose, use of open crushing devices and pestle and mortar is sufficiently inaccurate to warrant an impact assessment of their routine use in clinical practice. The drugs studied had potentially wide therapeutic margins, however a loss of dose of 20% may be considered clinically important for medication where peak levels are required for efficacy such as anti-infective agents.

Also the wide variation between methods are of concern as inter-operator choice of method may directly impact on dose delivered from one dose to the next, this may be of concern where dose titration is important, warfarin for example.

Further extensive laboratory investigation would be required to fully investigate the impact on dose recovery of all the variables, not limited to; i) crushing method, ii) rinsing method and volume, iii) flush volume and method and iv) tube material.

No data were identified in the literature evaluating what is considered an acceptable accuracy for drug delivery via this route. Medication manipulation is prevalent through all areas of healthcare and has a potential impact on dose accuracy in a number of high risk clinical areas. Further evaluation of the perception and actual clinical consequence is warranted.

The data generated within this chapter and the preceding chapter studying liquid medicines are sufficient to warrant a review of the existing consensus guidance and an update considered clarifying the value of diluting liquid medication prior to administration and the risks associated with tablet crushing. However from the original survey research it is evident that the existing guidance is not reported to be consistently applied in clinical practice. In order to move forward with the design of an intervention to improve practice in these areas it was necessary undertake a systematic review to determine which intervention design has been shown to be effective in this field.

# 5 A Systematic Review: Evaluation of the evidence base in medicine focussed interventions to improve related outcome measures in patients with dysphagia or an enteral feeding tube

## 5.1 Introduction

The literature review undertaken at the introduction to this thesis revealed a lack of evidence and inconsistent guidance in the administration of medication to patients with enteral feeding tubes or dysphagia. This lack of consistent guidance, and non-adherence to standards where they do exist, adversely impacts the outcomes of patients receiving their medication via this route resulting in medication errors, a risk of inadequate dosing, increased toxicity and the occlusion of feeding tubes.

The inconsistent practice identified from the literature with regards to formulation manipulation and flushing practice was also evident in the studied populations in chapter two. The high degree of variability in flushing practice, both frequency and volume, formulation choice and tablet crushing method was revealed both across and between professional groups. This inconsistent approach was reflected in the clinical practice of the patient population studied, potentially resulting in episodes of tube blockage. This research provided insight that interventions to improve clinical outcomes related to medication administration in this group of patients may be influenced by the staff interacting with the patient and the subsequent materials that the patient accesses.

New evidence in this field would provide potential benefit to patient outcomes if imbedded into clinical practice. As seen in chapter two, in the professional survey responses, pharmacists were reported to be influential in determining the medication formulation choice for inpatients with enteral feeding tubes, however this was not reported in the patient population in the community where the GP and hospital doctor are seen as more influential. This would indicate that the target professional audience of an intervention intended to positively influence medication administration in patients with enteral feeding tubes will differ depending on the care location.

Chapter three clearly showed a limited association between liquid medication viscosity and administration issues. It served to clarify that not all liquid medicines require dilution prior to

administration via an enteral feeding tube, this is contrary to some consensus guidance and therefore a change in practice may be warranted.

Chapter four adds weight to the concern expressed in the literature about inconsistent dose delivery through administration method variation. The data generated indicated that tablet manipulation using a pestle and mortar and other open crushing devices can result in significant loss of dose. This method of manipulation is frequently used in all care settings. Changing habitual practice and de-implementing outdated practice is a challenging and complex area of health research (Potthoff et al., 2017), with an estimated ten to twenty years for original research to be translated into routine practice (Sussman et al., 2006).

Knowledge translation and subsequent behaviour change are currently areas of increased research focus in healthcare. The time lag between evidence generation and practice change is being challenged (Morris et al., 2011) and questions being raised about which interventions effectively drive behaviour change and how can these be better utilised.

When determining how to imbed new evidence into clinical practice it is essential to understand which intervention methods have been evaluated as effective at delivering sustained quality improvements and practice change in this area of clinical practice, and put into context the data presented thus far on which professionals may be in a position to positively influence this group of patients care.

In order to develop a strategic approach to embedding the evidence into clinical practice, a systematic review of the literature was undertaken with a clear focus on pharmaceutical service or medication based interventions specifically evaluated in patients with dysphagia or enteral feeding tubes. This determination of interventions already evaluated could then be used to inform future intervention design.

## Part A The Systematic Review

## 5A.2 Background

### 5A.2.1 Intervention potential

Patients with dysphagia, and dependent on an enteral feeding device as their route of access for medication, have complex pharmaceutical requirements. They represent a diverse patient group with extremes of age, multiple co-morbidities and clinical conditions, from children with complex disabilities to adults with Parkinson's disease or cancer (Smith et al., 2011).

Medication administration to patients with dysphagia or enteral feeding tubes renders the patient three times more likely to be involved in a drug administration error (Kelly et al., 2011). The problems associated with medication administration via an enteral feeding device include device obstruction, reduced medication effectiveness or increased toxicity, and errors (van den Bemt et al., 2007, Bankhead et al., 2009); all have a potential negative impact on patient outcomes, even resulting in fatalities (Schier et al., 2003).

From the literature review in chapter one it appears that improving medication related outcomes and minimising complications and medication errors in this patient group is complicated by safety concerns relating to formulation manipulation and a lack of published evidence. The assessment, prescription, formulation and administration processed are complicated in this group as they sit largely outside licensed medication use and therefore are unsupported by standard information provided by the pharmaceutical company holding the marketing authorisation.

Many of the publications in the area of medicines management in dysphagia or enterally fed patients relate to the development of evidence based guidelines or administration practice protocols, and yet without an effective implementation strategy the full potential of these interventions may not be achieved.

Over recent years there has been a drive towards improving the quality and sustainability of care improvement initiatives across the breadth of healthcare, supported by the activities of the NHS Sustainable Improvement Team (previously NHS QI). Historically major interventions,

such as the 'productive ward', were rolled out with significant financial support and little robust evaluation of the benefits (White, 2015a), however there is now closer scrutiny on Quality Improvement (QI) initiatives.

## 5A.3 Aim and Objectives

The aim of the systematic review was to identify barriers and enablers to quality improvement initiatives in the medicines management of dysphagic patients, in order to determine the structure of an intervention that would be appropriate for further development and testing.

The objectives of this review were to assimilate the current research evaluating the effectiveness of medicines focussed interventions on improving related outcome measures in patients with dysphagia or an enteral feeding device.

- identify which medicines focussed interventions have been evaluated in this group of patients
- determine which intervention components were effective in which care setting
- propose an intervention or guidance to improve medicines administration in patients with enteral feeding tubes

## 5A.4 Method

### 5A.4.1 Protocol registration

Prior to undertaking the systematic review a search of the literature and PROSPERO, an open register of systematic reviews completed or planned, was undertaken to ensure that this topic had not already been evaluated (Booth et al., 2013). Subsequently the protocol details were registered with PROSPERO in August 2016 (Ref:42016043969) to provide a public record of the proposed method as laid out in this chapter.

### 5A.4.2 Search Strategy

The search strategy was designed prospectively, with refinement through an iterative process of search term testing. The search strategy was designed to identify original research identifying and describing intervention methods evaluated in the target patient population.

Initial Medline and CINAHL searches were undertaken in November 2015 using the search terms identified in Table 5.4.2, column A.

The search terms were derived using the PICOS notation (Moher et al., 2009):

**Population :** All patients, including children, where the route of administration or type of medication formulation is influenced by the presence of dysphagia or an enteral tube. As the pool of literature was likely to be small, there was no care area or geographical limits placed on the search. It was considered possible that dysphagia may not be specifically mentioned in the title or abstract for some patient groups where it is an accepted symptom and therefore the 'all text' field was used to extend the search beyond the 'title/abstract' fields.

**Intervention:** Any pharmaceutical care intervention that is undertaken in a patient group where the patient is dysphagic or has an enteral feeding tube. Interventions undertaken by any healthcare professional were included.

**Control:** No specific search terms were included, as all studies both controlled and pre-post within group studies would be considered for analysis

**Outcome:** Any measure which can define an outcome change impacted by the intervention.

**Study design:** All study designs were considered that included a pre- and post- intervention evaluation.

Additional search terms were added following test searches to accommodate variances in descriptors used within studies (See column B in Table 5.4.2)

**Table 5A.4.2 Systematic review search terms and fields**

| | Initial test search terms | Revised search terms following test search | Location |
|---|---|---|---|
| **Population** | Dysphagia | Dysphagia | All text |
| | Dysphagic | Dysphagic | All text |
| | Nasogastric | Nasogastric | All text |
| | Enteral tube* | Enteral tube* | All text |
| | Gastrostomy | Gastrostomy | All text |
| | | PEG | All text |
| | | Jejunostomy | All text |
| | | JEJ | All text |
| | | Feeding tube* | All text |
| | | Swallowing difficulties | All text |
| **Intervention** | Medication* | Medication* | Title/abstract |
| | Pharmaceutical | Pharmaceutical | Title/abstract |
| | Tablet* | Tablet* | Title/abstract |
| | Drug* | Drug* | Title/abstract |
| | | Medicine* | Title/abstract |
| | Intervention | Intervention | Title/abstract |
| | Protocol* | Protocol* | Title/abstract |
| | Guideline* | Guideline* | Title/abstract |
| | Education | Education | Title/abstract |
| | Guidance | Guidance | Title/abstract |
| | Tool* | Tool* | Title/abstract |
| | Review | Review | Title/abstract |
| | | Toolkit | Title/abstract |
| | Training | Training | Title/abstract |
| | Lecture* | Lecture* | Title/abstract |
| | Poster | Poster | Title/abstract |
| **Control** | No search terms included as no control required for analysis | | |
| **Outcome** | Error* | Error* | Title/abstract |
| | Safety | Safety | Title/abstract |
| | Knowledge | Knowledge | Title/abstract |
| | Quality | Quality | Title/abstract |
| | Blockage | Blockage | Title/abstract |
| **Study design** | No specific search terms included as all study designs considered | | |

### 5A.4.3 Search methods for identification of studies

#### 5A.4.3.1 Electronic searches

The databases listed below were used to search the literature, no language or date restrictions were applied.

- MEDLINE, 1950-, in-process and other non-indexed citations, OvidSP
- EMBASE, 1947-, OvidSP
- CINAHL, OvidSP
- Applied Social Sciences Index and Abstracts (ASSIA)
- Psycinfo

#### 5A.4.3.2 Other search strategies

The bibliography of included studies was reviewed to identify further studies not identified in the search strategy above (snowballing).

A grey literature search was conducted by using the same search terms used in the above databases using the website: www.opengrey.eu. All full studies and thesis were included. Short abstracts were excluded from analysis unless additional information could be obtained from the author.

Results from each search were exported into the reference manager Endnote X7.2.1 (Thompson Reuters, 2014). Any duplicates were removed.

### 5A.4.4 Process for study selection

Citations from the search strategy were reviewed independently by RW and DW. As the number of citations was likely to be limited a three phase approach to screening was planned:

1. Initial screening of titles against the inclusion criteria to identify papers for abstract retrieval. Reasons for exclusion at this stage will be documented on a specific form.
2. Screening of abstracts against the inclusion criteria to identify papers for full text retrieval. Reasons for exclusion at this stage will be documented on a specific form.

3. Assessment of full papers for inclusion in the review. Reasons for exclusion at this stage will be documented.

Each stage was conducted by two researchers independently to create duplicate results, any discrepancies were resolved by discussion or if needed, by the inclusion of a third researcher. The citations were screened in a 3 step process; title screen, abstract screen and then full text review.

Citations with more than one of the following criteria were excluded:

- General review of the subject/ background information only
- Not involving medicines management
- No intervention
- Not involving dysphagic or enterally fed patients
- No assessment of impact of intervention

In the case of conference abstracts reasonable attempts to contact the primary author to gain further information were undertaken; if sufficient information could be obtained from the author then this was taken through to full evaluation within the systematic review. If no further information was available or none of the authors were traceable or responded then the corresponding abstracts were not taken forward.

Due to the significant global interest in this subject area, foreign language was not an exclusion criteria, all reasonable attempts were taken to locate and translate foreign language papers.

#### 5A.4.5 Data extraction

A data extraction tool was developed for use exclusively for this systematic review, based on the Cochrane (EPOC) data collection checklist. (EPOC, 2002) Data were extracted from the full text of the included citations using an iteratively developed thematic tool based on an extension of the PICOS elements with additional fields to capture research techniques, intervention elements, assessment of bias, and mapped to TDF elements.

The tool was structured to assimilate the following data:

- Citation details: Author, year, country,

- Study details: Study setting
- Intervention detail: Type of intervention, profession (NB: in multi-intervention studies, each intervention and its effectiveness considered individually if possible)
- Outcome measures: Metrics, nature of desired change
- Outcome of intervention: Effective and Ineffective aspects will be evaluated
- Methodological evaluation in line with EPOC checklist
- Risk of bias assessment
- Alignment with the Theoretical domains framework: Using TDF (2012) (Cane et al., 2012)

The tool was piloted with a representative sample of studies to determine inter-rater reliability for data capture and quality assessment.

All fields from the data extraction tool are included in Appendix 5.1

### 5A.4.6 Risk of bias (quality) assessment

An assessment of publication bias was undertaken in line with the PRISMA statement(Moher et al., 2009), based on the Cochrane Collaboration risk of bias tool (Higgins.J.P.T. and Green.S, 2011) modified to include assessment criteria relevant to non-randomised and uncontrolled studies. This assessment was included to provide a perspective on the bias and quality of the studies evaluated. Assessment tool in included in Appendix 5.2

### 5A.4.7 Data Synthesis

The data was collated and reviewed within an iteratively conceptual framework to provide a description of the effectiveness of modes of intervention to improve medication use in this patient population. Data extracted into the framework was validated by a second reviewer.

## 5A.5 Results

### 5A.5.1 Search results

The final literature search was undertaken using the revised search terms in December 2015. Review of the returned citations was undertaken during January and February of 2016.
Results from each search were exported and managed using the reference software Endnote X7.2.1 (Thompson Reuters, 2014).

Initial search results yielded 1494 citations, 306 were removed using deduplication feature in Endnote, a further 85 duplicates were identified manually and removed, leaving a final total of 1104 citations for screening. Specific database results are detailed in Table 5A.5.1

**Table 5A.5.1 Number of citations returned from each database**

| Database | Number of citations |
|---|---|
| **CINAHL** | 104 |
| **Medline and EMBASE** | 1211 |
| **ASSIA** | 29 |
| **Opengrey** | 6 |
| **Psycinfo** | 108 |

### 5A.5.2 Study selection results

Citations from the search strategy were independently reviewed by RW and DW.
Initial screening of titles against the inclusion criteria to identify papers for abstract retrieval identified 96 citations for abstract review. Each stage was conducted by the two researchers independently to create duplicate results, there were 34 discrepancies at the title screening stage these were resolved by mutual agreement. A large number of titles were excluded at this stage due to the use of the search term PEG, which was associated with papers relating to pegylated drug molecules. There was moderate agreement at this stage (Table 5A.5.2a).

**Table 5A.5.2a Title screen result**

| | Number |
|---|---|
| Exclusion Full Agreement: Both reviewers agreed the citation should be excluded | 1008 |
| No Agreement: Either one of the reviewers included but the other excluded the citation – in all cases the citation went forward to the next phase of review | 34 |
| Inclusion Full Agreement: Both reviewers agreed the citation should be included | 62 |
| **Cohen's Kappa(McHugh, 2012)** | **0.776** Moderate Agreement |

Ninety six abstracts were taken forward to the abstract screening stage. Screening against the inclusion criteria to identify papers for full text retrieval identified 30 citations independently identified, there were 5 discrepancies at the abstract review stage these were resolved by mutual agreement taking 35 citations through to the full text review phase; see Table 5A.5.2b for agreement and Cohen's Kappa. Reasons for exclusion at this stage are detailed in Table 5A.5.2c

**Table 5A.5.2b Abstract screen result**

| | Number |
|---|---|
| Exclusion Full Agreement: Both reviewers agreed the citation should be excluded | 61 |
| No Agreement: Either one of the reviewers included but the other excluded the citation – in all cases the citation went forward to the next phase of review | 5 |
| Inclusion Full Agreement: Both reviewers agreed the citation should be included | 30 |
| **Cohen's Kappa** | **0.888** Strong Agreement |

**Table 5A.5.2c Primary reasons for exclusion at abstract review stage**

| Primary reasons for exclusion at abstract review stage | n |
|---|---|
| **No intervention** | 28 |
| **Not medicines management** | 12 |
| **General/systematic review of the subject** | 11 |
| **Not involving dysphagic or enterally fed patients** | 4 |
| **Abstract of subsequently published paper** | 3 |
| **Undetected duplicate from previous review** | 1 |
| **Local language publication of a prior English language publication** | 1 |
| **Conference abstract only with insufficient detail for evaluation** | 1 |

35 papers were taken forward for further full text review or follow up, this included 12 conference abstracts. Five of the 23 full articles were not in English, one article was published in a Chinese journal with only the abstract available in English, it was not possible to obtain a full copy of the article for translation within a reasonable timeframe so this article was excluded from further analysis but the bibliography was reviewed, the remaining 4 foreign language articles were translated and included in the assessment.

All full papers for inclusion in the review were assessed and bibliographic review undertaken; no further studies were identified for inclusion at this stage. Three papers did not include an evaluation of the intervention; two papers described an intervention in dysphagic patients but not related to medication and two papers were review articles indicating possible intervention strategies.

12 conference abstracts were identified, 5 were excluded on further review of the content, authors were untraceable for 1, no responses were received for 2, responses were received from 2 authors (relating to 3 abstracts) unable to provide sufficiently detailed information to proceed further, 1 author responded with a full article recently approved for publication, this was included for full analysis and replaced the corresponding abstract. See figure 5A.5.2a.

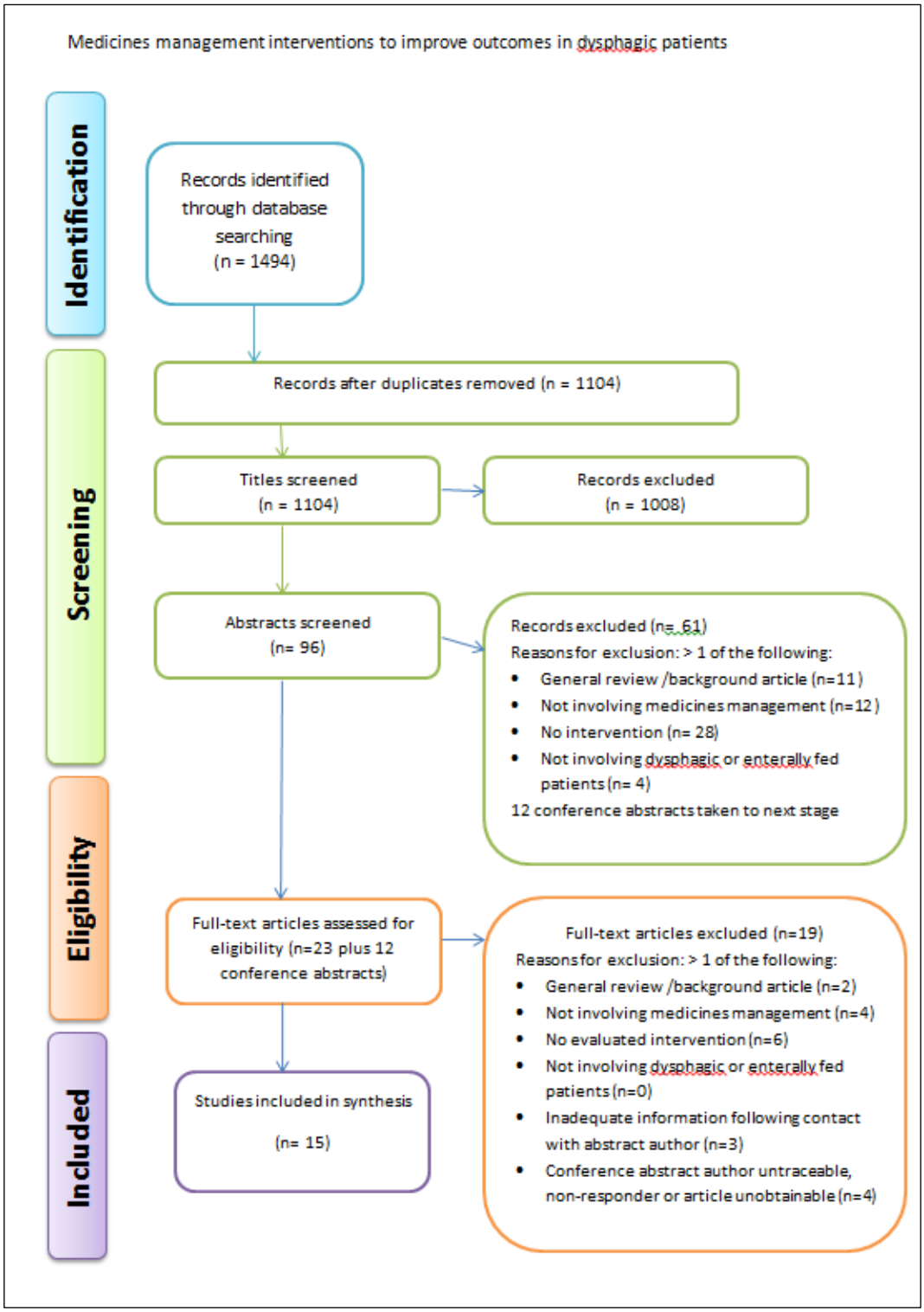



**Figure 5A.5.2a PRISMA flow diagram**

### 5A.5.3 Analysis

#### 5A.5.3.1 Study design and population details

Fifteen full text publications were reviewed and data extracted using the specifically designed framework.

The publications originated from around the globe. Four publications were from the Netherlands, three of them originating from the same research group. Kelly (Kelly, 2012) and Santos (Santos et al., 2012) evaluated the same intervention using different methodologies and outcome measures so both are included in analysis for completeness. The countries of origin of all publications are detailed in table 5A.5.3a.

All studies identified, with the exception of one service evaluation (Santos), used a before and after design, only two had a control group. Thirteen of the publications described prospective evaluation of the intervention, one was retrospective, another appeared to be retrospective but was not clearly described enough to be certain.

The patient populations studied represent the spectrum of patient groups that may present with dysphagia or require an enteral tube for nutrition support due to neurological impairment, encompassing acute and community managed care.

No studies were identified which evaluated interventions targeted at patients being cared for in their own home or independently living patients.

**Table 5A.5.3a Publication setting and broad study design**

| First Author | Country | Healthcare Setting | Patient population | Perspective | Controlled |
|---|---|---|---|---|---|
| **Bennett (Bennett et al., 2013)** | UK | Acute Hospital | Post stroke | Prospective | Uncontrolled |
| **Bertsche (Bertsche et al., 2010)** | Germany | Acute Hospital | Paediatric neurology | Prospective | Uncontrolled |
| **Dashti-Khavidaki (Dashti-Khavidaki et al., 2012)** | Iran | Acute Hospital | Critical Care | Prospective | Controlled |
| **Garcia Aparicio (Garcia Aparicio et al., 2011)** | Spain | Acute Hospital | Medicine | Prospective | Uncontrolled |
| **Hanssens (Hanssens et al., 2006)** | Qatar | Acute Hospital | Critical Care | Prospective | Uncontrolled |
| **Idzinga (Idzinga et al., 2009)** | Netherlands | Residential Facility | Neurodisability | Prospective | Uncontrolled |
| **Jackson (Jackson et al., 2008)** | Canada | Continuing Care facility | Dysphagic | Prospective | Uncontrolled |
| **Kelly (Kelly, 2012)** | UK | Acute Hospital | Medical and stroke | Prospective | Controlled |
| **Kenny (Kenny and Goodman, 2010b)** | USA | Military Hospital | All patients with nasogastric tube | Unclear | Uncontrolled |
| **Lohmann (Lohmann et al., 2015)** | Germany | Acute Hospital | Gastroenterology critical care and head and neck surgical | Prospective | Uncontrolled |
| **Santos (Santos et al., 2012)** | UK | Acute Hospital | Medical | Prospective | Uncontrolled |
| **Stuijt (Stuijt et al., 2013)** | Netherlands | Nursing Home | Psychogeriatric | Prospective | Uncontrolled |
| **Van Welie (van Welis.S, 2016)** | Netherlands | Nursing Home | All patients | Prospective | Uncontrolled |
| **Van den Bemt (van den Bemt et al., 2006)** | Netherlands | Acute Hospital | Neurology and general medicine | Prospective | Uncontrolled |
| **Zhu (Zhu et al., 2012)** | China | Acute Hospital | All patients with nasogastric tube | Retrospective | Uncontrolled |

#### 5A.5.3.2 Risk of bias assessment and data quality

The Cochrane review recommends against the use of assessment tools that provide a summary score or assessment (Higgins.J.P.T. and Green.S, 2011), therefore a full bias risk assessment was undertaken using the framework in Appendix 5.2. As the majority of studies were uncontrolled by design there is an inherent risk of bias due to the lack of randomisation. Kelly (Kelly, 2012) and Santos (Santos et al., 2012) evaluated the same intervention but using different methodologies and therefore the bias assessment was included for both in the analysis. The full details of bias assessment against each of the criteria are detailed in figure 5A.5.5b.

This analysis indicates that most researchers used strategies to minimise bias through use of standardised intervention delivery and assessment, with over half determining the appropriate sample size to infer statistical significance from the results. There were 5 studies where the manuscript quality and lack of detail made a full assessment of bias impossible; these are evident from the 'unclear' indicators.

**Table 5A.5.3b Risk of bias assessment** (✓ Low risk ✘ High risk ? Unclear )

| | Design bias | Selection bias - sample | Selection bias - randomisation | Selection bias – allocation concealment | Performance bias - delivery | Performance bias-outcome measurement | Detection bias | Incomplete outcome data | Adequacy of study power |
|---|---|---|---|---|---|---|---|---|---|
| **Bennett (Bennett et al., 2013)** | ✘ | ✓ | ✘ | ✘ | ? | ✘ | ✘ | ? | ✘ |
| **Bertsche (Bertsche et al., 2010)** | ✓ | ✓ | ✘ | ✘ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **Dashti-Khavidaki (Dashti-Khavidaki et al., 2012)** | ✓ | ✓ | ✘ | ✘ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **Garcia Aparicio (Garcia Aparicio et al., 2011)** | ✓ | ✓ | ✘ | ✘ | ? | ? | ✘ | ✓ | ✘ |
| **Hanssens (Hanssens et al., 2006)** | ✓ | ✘ | ✘ | ✘ | ✓ | ✓ | ✘ | ✘ | ✘ |
| **Idzinga (Idzinga et al., 2009)** | ✓ | ✓ | ✘ | ✘ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **Jackson (Jackson et al., 2008)** | ✓ | ✓ | ✘ | ✘ | ✓ | ✓ | ✓ | ✘ | ✘ |
| **Kelly (Kelly, 2012)** | ✓ | ✓ | ✘ | ✘ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **Kenny (Kenny and Goodman, 2010b)** | ✘ | ✓ | ✘ | ✘ | ? | ? | ✘ | ? | ✘ |
| **Lohmann (Lohmann et al., 2015)** | ✓ | ✓ | ✘ | ✘ | ✓ | ? | ✘ | ✓ | ✓ |
| **Santos (Santos et al., 2012)** | ✘ | ✓ | ✘ | ✘ | ✓ | ✓ | ✘ | ✓ | ✘ |
| **Stuijt (Stuijt et al., 2013)** | ✓ | ✓ | ✘ | ✘ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **Van Welie (van Welis.S, 2016)** | ✓ | ✓ | ✘ | ✘ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **Van den Bemt (van den Bemt et al., 2006)** | ✓ | ✓ | ✘ | ✘ | ✓ | ✓ | ✘ | ✓ | ✘ |
| **Zhu (Zhu et al., 2012)** | ? | ✓ | ✘ | ✘ | ? | ✓ | ✓ | ? | ? |

### 5A.5.3.3 Intervention strategies and target groups

Education is the predominant intervention in all studies, with the development of supporting documentation in most cases; IT system modification was the least frequently employed

intervention. Kelly (Kelly, 2012) and Santos (Santos et al., 2012) evaluated the same intervention using different methodologies and outcome measures therefore to minimise duplication for this analysis they are considered as a single publication with Kelly (2012) being the most complete description.

With the exception of Bennet (Bennett et al., 2013) and Hanssens (Hanssens et al., 2006) all studies evaluated multicomponent interventions, six studies evaluated 2-component interventions, three evaluated 3-component interventions and four studies evaluated 4-component interventions. The details are included in table 5A.5.3c

**Table 5A.5.3c Intervention component themes**

| | Education | Documentation | IT system | Care communication Pathway |
|---|---|---|---|---|
| **Bennett (Bennett et al., 2013)** | Y | N | N | N |
| **Bertsche (Bertsche et al., 2010)** | Y | Y | N | N |
| **Dashti-Khavidaki (Dashti-Khavidaki et al., 2012)** | Y | Y | N | N |
| **Garcia Aparicio (Garcia Aparicio et al., 2011)** | N | Y | N | Y |
| **Hanssens (Hanssens et al., 2006)** | Y | N | N | N |
| **Idzinga (Idzinga et al., 2009)** | Y | Y | Y | Y |
| **Jackson (Jackson et al., 2008)** | Y | Y | Y | Y |
| **Kelly (Kelly, 2012)** | Y | Y | N | Y |
| **Kenny (Kenny and Goodman, 2010b)** | Y | Y | N | N |
| **Lohmann (Lohmann et al., 2015)** | Y | Y | Y | Y |
| **Stuijt (Stuijt et al., 2013)** | Y | Y | Y | N |
| **Van Welie (van Welis.S, 2016)** | Y | Y | N | N |
| **Van den Bemt (van den Bemt et al., 2006)** | Y | Y | Y | Y |
| **Zhu 2012(Zhu et al., 2012)** | Y | Y | Y | N |

Thirteen of the fourteen evaluated studies included an education component in the intervention.

All interventions with an educational component were targeted at the nursing staff directly caring for the patient group, with two also including physicians and one including pharmacists. The study in children additionally targeted parents as they were directly involved in the care of their children. No study evaluated an intervention targeted at self-caring patients.

The preferred method of delivery was face to face, however very little detail was provided in the study reports on the content and teaching styles used; only three specified that a practical element was included. Seven studies confirmed the learning, predominantly through questionnaire, however only two specified a check of practical competence. Two studies utilised eLearning platforms for educational material delivery. Full details are contained in Table 5A.5.3d.

**Table 5A.5.3d Education component detail**

| | Education component delivered to: | Method of delivery: | Knowledge check method | Practical competence check method |
|---|---|---|---|---|
| **Bennett (Bennett et al., 2013)** | Nurses<br>HCAs | eLearning<br>Practical session | Done but not specified | Done but not specified |
| **Bertsche (Bertsche et al., 2010)** | Nurses<br>Physicians<br>Parents | Lecture<br>Practical session | None | None |
| **Dashti-Khavidaki (Dashti-Khavidaki et al., 2012)** | Nurses | Lecture | Questionnaire | None |
| **Hanssens (Hanssens et al., 2006)** | Nurses | Pre-work<br>Lecture<br>Practical session | Questionnaire | |
| **Idzinga (Idzinga et al., 2009)** | Nurses | Lecture | None | None |
| **Jackson (Jackson et al., 2008)** | Nurses | Lecture | Questionnaire | None |
| **Kelly (Kelly, 2012)** | Nurses | Lecture | None | Questionnaire |
| **Kenny (Kenny and Goodman, 2010b)** | Nurses | Lecture | Questionnaire | None |
| **Lohmann (Lohmann et al., 2015)** | Nurses | Lecture<br>eLearning | Questionnaire as part of eLearning programme | None |
| **Stuijt (Stuijt et al., 2013)** | Nurses | Lecture | None | None |
| **Van Welie (van Welis.S, 2016)** | Nurses<br>HCAs | Lecture<br>Newsletter | None | None |
| **Van den Bemt (van den Bemt et al., 2006)** | Nurses | Training sessions | None | None |
| **Zhu (Zhu et al., 2012)** | Nurses<br>Physicians<br>Pharmacists | Not specified | Questionnaire | None |

Twelve of the fourteen studies contained development of written resources as part of the intervention. This ranged from general guidelines or protocol, through drug specific administration guidelines to patient level information. This is the intervention component where the baseline was not comparable, a number of studies did not include guideline or protocol development because it was already in existence although the studies do not evaluate the extent to which staff were aware of the existing resources or if they were utilised. Full details of the documentation component can be found in table 5A.5.3e.

**Table 5A.5.3e Documentation component detail**

| | Guideline | General Protocol | Drug specific protocol | Patient level information | Location of documentation |
|---|---|---|---|---|---|
| **Bertsche (Bertsche et al., 2010)** | Y | Y | Y | N | Not specified |
| **Dashti-Khavidaki (Dashti-Khavidaki et al., 2012)** | Y | Y | Y | N | Not specified |
| **Garcia Aparicio (Garcia Aparicio et al., 2011)** | N | N | N | Y | With medication chart |
| **Idzinga (Idzinga et al., 2009)** | N | N | N | Y | Documented on MAR |
| **Jackson (Jackson et al., 2008)** | Y | N | N | Y | Patient specific advice on MAR, all other resources on units and hospital intranet |
| **Kelly (Kelly, 2012)** | N | N | N | Y | With medication chart |
| **Kenny (Kenny and Goodman, 2010b)** | Y | Y | N | N | Ward poster<br>Newsletter sent to all staff |
| **Lohmann (Lohmann et al., 2015)** | N | Y | Y | N | Drug preparation areas |
| **Stuijt (Stuijt et al., 2013)** | Y | N | Y | N | Not specified for guideline, pocket guide of drug specific protocols given to each nurse |
| **Van Welie (van Welis.S, 2016)** | Y | N | N | Y | Do not crush symbol on patients medication<br>Awareness poster on ward |
| **Van den Bemt (van den Bemt et al., 2006)** | Y | Y | Y | Y | Instructions on medication cart<br>Do not crush symbol on medication labels<br>Site or access to database not specified |
| **Zhu (Zhu et al., 2012)** | N | Y | N | N | Not specified |

Six studies utilised IT modifications as part of the intervention. Three modifications were to the pharmacy dispensing and labelling system, one was to the electronic patient record, one was to the prescribing system and one developed a database to be available at ward level. With the exception of the database, all system modifications were to add a flag or prompt that the

patient was dysphagic or had a feeding tube and therefore had altered medication formulation requirements.

Five studies formalised an aspect of the care communication pathway as part of the intervention. Two of these introduced a documentation contact between the speech and language therapist (SLT)and the pharmacy service, two used the medication order sheet for nurses to identify patients with dysphagia to pharmacy, and two used the medication administration record as a means of documented advice from pharmacy. One study also clarified the role of pharmacy in physician liaison regarding changes in therapy.

#### 5A.5.3.4 Intervention Outcomes

The interval between intervention and follow up varied with only two studies undertaking two periods of follow up. Nine studies assessed impact of intervention immediately after implementation and three within 1 month.

Only one study indicated a non-significant impact of the studied intervention, all other studies reported a positive impact from the intervention. There was a spectrum of outcomes evaluated; medication errors being the most common with eight studies evaluating various aspects specific to enteral tube or dysphagic medication administration.

One study objectively measured tube blockage as an outcome, and two studies anecdotally reported on tube blockage and aspiration. All other studies used medication errors, adherence to protocol or staff knowledge as proxy markers for improved patient care and outcome. A summary of the primary outcomes of the studies are detailed in table 5A.5.5f.

Outcome measures related to medication errors or patient tolerance were collected using observational techniques in nine studies. Outcomes of knowledge were evaluated by questionnaire in eight studies. In addition two studies used documentation audit to determine adherence to policy.

It is interesting that proxy markers were chosen rather than the patient outcomes, this is most likely due to the difference in incidence of the proxy marker and the adverse patient outcome, with the incidence of the latter being much lower. A study of adverse patient outcomes would

have required much larger sample sizes, additional resource and potentially different detection methods.

**Table 5.5.3f Systematic review citations – primary outcomes**

| Author (year) | Follow up period | Primary outcome as described in method | Key Results |
|---|---|---|---|
| **Bennett (Bennett et al., 2013)** | 1 month | Promote evidence based practice | Greater confidence in the nurses ability to manage dysphagia including the administration of medicines |
| **Bertsche (Bertsche et al., 2010)** | 3 weeks | Administration errors | Medication errors by nurses before 42.8%, after 7.8% ($p<0.001$), medication errors by parents 96.6 to 5.6% proportion of doses administered by parents increased after intervention 4.3% to 7.4% |
| **Dashti-Khavidaki (Dashti-Khavidaki et al., 2012)** | 3 months | Improving nursing knowledge and practice regarding medication administration via enteral feeding tubes | Significant improvement in knowledge of medication prep, tube flushing and interaction recognition in intervention group, also improvement in self-reported practice. Observed errors reduced from 43% to 27% (37% reduction) |
| **Garcia Aparicio (Garcia Aparicio et al., 2011)** | Immediate | improvement in patient taking medication | 59% of doses required medication to be mixed with thickener to improve tolerance, 41% medication mixed with water alone. No episode of significant aspiration during the study period. |
| **Hanssens (Hanssens et al., 2006)** | Immediate | improvement in knowledge and practice | Improvement in knowledge 0 to 40% or questions about CR meds, 51 to 91% for the other knowledge questions. Quality and value of course by participants scored 96% |
| **Idzinga (Idzinga et al., 2009)** | Immediate | reduce medication errors | Administration errors and tube blockage. Admin errors reduced from 64.5% to 30.1%, only medication dispensed in automated dispensing system contributed to multivariate model |
| **Jackson (Jackson et al., 2008)** | Immediate knowledge 2 years – adherence to process | adherence to new communication processes | Average knowledge score improved from 60% to 80%. Over 90% Adherence to policy at 2 years |
| **Kelly (Kelly, 2012)** | Immediate | Effect of iMAgs on nurse practice | Slight improvement in medication errors if timing included, if timing excluded there was no difference Significant decrease on control ward (but high baseline may confound), Non-significant improvement in questionnaire score 62% to 66%. |

| Author (year) | Follow up period | Primary outcome as described in method | Key Results |
|---|---|---|---|
| **Kenny (Kenny and Goodman, 2010b)** | Immediate | evaluate impact - no further detail | Staff knowledge improved 57% to 62% (p 0.05), quality of documentation of tube care, flushing documentation improved from 25% to 40%, anecdotal reports of reduction in tube blockage |
| **Lohmann (Lohmann et al., 2015)** | Immediate | rate of inappropriately crushed or suspended drugs | Incorrect crushing and/or suspending reduced from 9.8% to 4.2% (P<0.01) on ICU and 5.7 to 1.4% (P<0.01) on the surgical ward.<br>Of incorrectly prepared medication - Incorrect prescription was origin - ICU 94.9% to 93.8%, surgical ward 77.4% to 66.7%<br>Increased compliance with use of safety equipment, 1.4 fold on ICU, 2 fold on surgical ward.<br>Decreased use of incorrect solvent on surgical ward 93% to 11.9%. No change on ICU – low baseline 10.4%. |
| **Santos (Santos et al., 2012)** | 2 months | acceptability and relevance of iMAGs | Staff views - improved confidence of staff, potentially saved time (more time to administer but less time looking up information), improved safety and patient care, timely administration (not quantified) |
| **Stuijt (Stuijt et al., 2013)** | Immediate And 9 month | reduce medication errors | First observation period MAEs decreased by 23.9% and crushing errors by 63.2%, inappropriate technique and food-drug interactions were not reduced. Only reduction in crushing avoidance was sustained to second period, but became non-significant after adjusting for confounding factors. |
| **Van Welie (van Welis.S, 2016)** | 1 month | relative risk reduction in crushing errors | General crushing error rate decreased from 3.1% to 0.5% (RR=0.15 CI 0.05-0.51), in patients with swallowing difficulties rate dropped from 87.5% to 30.0% (RR 0.34 CI 0.13-0.89) |
| **Van den Bemt (van den Bemt et al., 2006)** | Immediate | reduction in tube blockage and medication errors | The integrated program in hospital 1 resulted in a decrease in the number of tube obstructions (OR 0.22, 95% CI 0.047-1.05). There was a significant decrease in the number of administration errors per nurse in hospital 2 (OR 0.003, 95% CI 0.0005 to 0.02). |
| **Zhu (Zhu et al., 2012)** | Not specified | Not stated | Irrational medication orders were abolished, nursing knowledge about the crushing of MR/SR drugs increased to 100%. |

This systematic review permitted a description of the intervention components that have been evaluated within this are and the positive immediate impact on relevant indices of patient experience and outcomes. However, only three studies evaluated outcomes beyond 3 months (Dashti-Khavidaki et al., 2012, Stuijt et al., 2013, Jackson et al., 2008), with only two studies undertaking two time separated evaluations. The work by Jackson et al. demonstrated adherence to protocol 2 years after the original intervention, whereas Stuijt at al. failed to demonstrate a sustained response at 9 months.

This difference in the sustainability of the interventions was of particular interest, in order to better understand if there were particular attributes or approaches that may have influenced this an additional analysis was undertaken using a conceptual framework.

## Part B Use of a conceptual framework to provide insights into the potential sustainability of evaluated interventions

### 5B.1 Introduction to Implementation Science

There are many healthcare interventions that fail to translate into improvement in patient outcomes outside of the academic environment in which they were evaluated. Barriers to the effective implementation of any intervention can exist on multiple levels; patient, provider, organisational or policy (Ferlie and Shortell, 2001).

The effectiveness and sustainability of an intervention is not only determined by the details of the intervention but by the mechanisms by which it is implemented. In recent years many approaches have been adopted to support healthcare intervention design and knowledge translation through better understanding of the drivers and barriers to effective change. Process improvement tools such as Six Sigma and Lean were adopted from the manufacturing industry and applied to process redesign in healthcare with varying degrees of success (de Koning et al., 2006).

More recently tools and approaches that utilise a better understanding of the broader aspects of designing and evaluating complex healthcare interventions have been developed, the medicines research council published their initial guidance in 2000, updating it in 2006 (Craig et al., 2008). Much has been published in this area since then; a preference for use of the Theoretical Domains Framework (TDF) has emerged supported by positive evidence of its use and utility (Phillips et al., 2015).

The theoretical domains framework has demonstrated utility when used prospectively, recently demonstrated to support the design of patient safety interventions associated with placement of nasogastric tubes (Taylor et al., 2013), and in the identification of barriers to the reporting of adverse drug events in hospitalised patients (Mirbaha et al., 2015). Additionally

the TDF had been applied retrospectively to undertake a theory-based evaluation of a healthcare intervention (Curran et al., 2013).

## 5B.2 Background

First described in 2005 (Michie et al., 2005), the TDF is a conceptual framework to support the design and implementation of strategies to increase the uptake and effectiveness of evidence based practice.

The originators of the TDF used an iterative process of consensus and testing to construct the TDF from psychological theories relating to behaviour change, the contributors were health psychology theorists, health service researchers and health psychologists. Their goal was to clarify and simplify psychological theory to maximise the accessibility to non-psychologists, to facilitate the study, development or selection of evidence based practice interventions. The original framework had 12 domains, each with multiple associated component constructs (Michie et al., 2005).

Each theoretical domain groups together a number of component constructs ; the construct descriptions facilitate shared meaning supporting understanding of the behaviours associated with that domain. For example, within the skills domain the constructs include skills, competence, ability, skill assessment, practice, skills development, interpersonal skills and coping strategies.

In 2011 the same research group devised a 'behaviour system' involving three essential conditions, capability, opportunity and motivation. This system (COM-B) is illustrated as a behaviour change wheel, shown in figure 5B.2 (Michie et al., 2011). In 2012 a group led by the originator of the 2005 TDF framework validated it for use in behaviour change and implementation research, and modified it to include a further two domains (Cane et al., 2012). The 14 current domains were mapped against the behaviour change wheel's COM-B system and are detailed in table 5B.2 This approach increases the accessibility of the framework and provides further context for its use in healthcare.

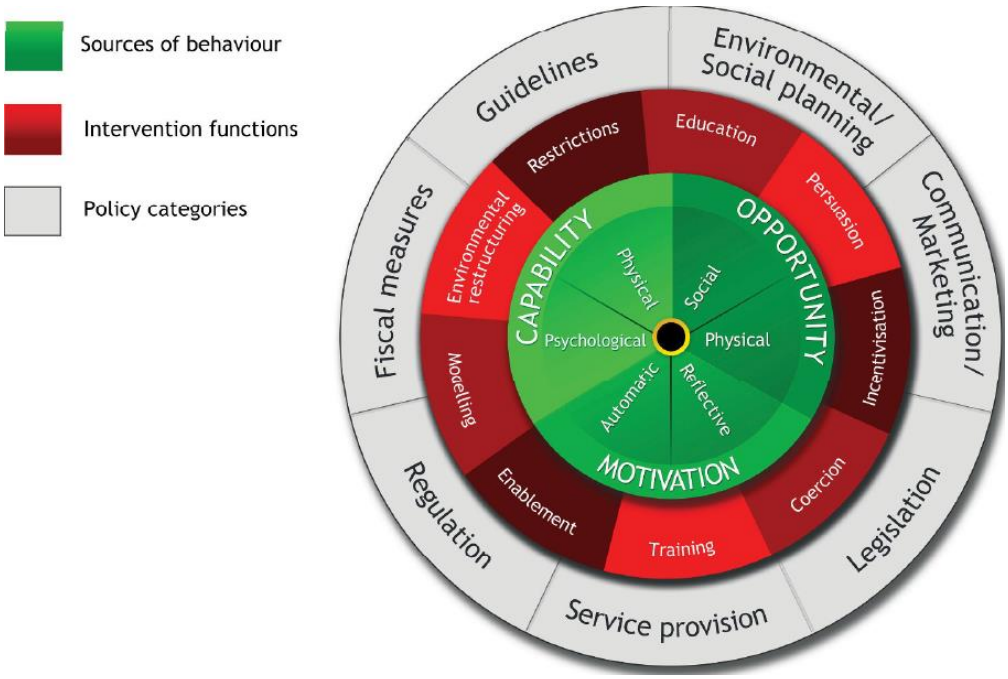



**Figure 5B.2** **Behaviour change wheel** (reproduced with permission)(Michie et al., 2011)

**Table 5B.2** **Mapping of the Behaviour Change Wheel's COM-B system to the TDF Domains**

| COM-B Component | | TDF Domain |
|---|---|---|
| Capability | Psychological | Knowledge<br>Skills<br>Memory, attention and decision process<br>Behavioural regulation |
| | Physical | Skills |
| Opportunity | Social | Social influences |
| | Physical | Environmental context and resources |
| Motivation | Reflective | Social/Professional role and Identity<br>Beliefs about capabilities<br>Optimism<br>Beliefs about consequences<br>Intentions<br>Goals |
| | Automatic | Social/Professional role and identity<br>Optimism<br>Reinforcement<br>Emotion |

The application of these theoretical frameworks in healthcare research ensures that the design and implementation of interventions and change strategies are appropriate for the context and desired outcomes. Evaluation of existing strategies and development of future interventions has been based on these principles, utilising the TDF (Curran et al., 2013, Taylor et al., 2013).

Mapping evaluated interventions against these frameworks assists in identifying behaviour change enablers and drivers that have been utilised and also those that have been overlooked. This may provide insights into which domains effectively contribute to or sustain intervention objectives.

## 5B.3 Aims and objective

The aim of this addition to the systematic review was to determine if use of the TDF could provide insights into the successful implementation and sustainability of an intervention targeted at reducing adverse outcomes associated with medicines administration in dysphagia.

The objective was to map the evaluated interventions components against the TDF framework domains.

## 5B.4 Method

The data extraction tool that was developed for use exclusively for this systematic review was extended to include additional fields to map the intervention elements to the descriptions in the TDF framework as laid out in appendix 5.3. The examples of evidence for each domain in relation to the components of the interventions were adapted from the literature relating to the application of the TDF.

## 5B.5 Results

The intervention components and assessment activities were reviewed and mapped against the TDF framework domains as laid out in Appendix 5.3. Examples of intervention components and strategies were included as prompts for consistent mappings.

Knowledge and environmental context and resources were the main domains that the interventions mapped against, as indicated in table 5B.5

An educational component was present in all but one of the interventions, these all mapped clearly to the ‘knowledge’ domain. Four interventions also included practical skills training and positively mapped to this domain, in addition there were four instances where the study

report contained inadequate detail about the educational component to be certain that practical skills were not covered in the educational component, but as there was no competence check as part of the assessment it could not be discounted so has been annotated on the table as unclear.

**Table 5B.5 Intervention components or outcomes mapped to TDF domains**

| | Bennett (Bennett et al., 2013) | Bertsche(Bertsche et al., 2010) | Dashti-Khavidaki (Dashti-Khavidaki et al., 2012) | Garcia Aparicio (Garcia Aparicio et al., 2011) | Hanssens (Hanssens et al., 2006) | Idzinga (Idzinga et al., 2009) | Jackson (Jackson et al., 2008) | Kelly (Kelly, 2012) | Kenny (Kenny and Goodman, 2010b) | Lohmann (Lohmann et al., 2015) | Santos (Santos et al., 2012) | Stuijt (Stuijt et al., 2013) | Van Welie (van Welis.S, 2016) | Van den Bemt (van den Bemt et al., 2006) | Zhu (Zhu et al., 2012) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Knowledge** | Y | Y | Y | | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| **Skills** | Y | Y | | | Y | U | U | | U | U | | Y | | | |
| **Social/professional role and identity** | | Y | | | Y | Y | Y | U | | | | Y | | Y | |
| **Beliefs about capabilities** | Y | Y | | | | | Y | | | | Y | | | | |
| **Optimism** | | | | | | | | | | | Y | | | | |
| **Beliefs about consequences** | | | | | Y | U | U | U | | Y | | | | | Y |
| **Reinforcement** | | | | Y | | Y | Y | Y | Y | Y | Y | | Y | Y | Y |
| **Intentions** | | | | | | | | | | | | | | | |
| **Goals** | | | | | | | | | | | | | | | |
| **Memory, attention and decision process** | | | Y | | | | Y | Y | Y | Y | Y | Y | Y | Y | |
| **Environmental context and resources** | PI | Y | Y | Y | | Y | Y | Y | Y | Y | Y | Y | Y | Y | U |
| **Social influences** | | | | | | | | | | | | | | | |
| **Emotion** | | | | | | | | | | | | | | | |
| **Behavioural regulation** | | | | | | | | | | | | | | Y | Y |

Y = component of intervention, U = unclear from description but not explicitly stated, PI = in existence prior to intervention

Six interventions aimed to redefine or change roles and responsibilities of members of the care team, these involved pharmacists, pharmacy technicians, SLTs, nurses and parents. The baseline of service provision specifically pharmacist and pharmacy technician input was unclear in most study reports, with only the studies by Bennett et al. (Bennett et al., 2013) and Kelly (Kelly, 2012) giving a clear description of relevant pre-intervention service and resource levels.

Four of the interventions included pro-active feedback on performance mapping positively to the 'belief about capabilities' domain, however only the study by Santos et al. confirmed the nurses felt more confident in their knowledge after the intervention thereby positively mapping to 'optimism'.

Three of the interventions clearly stated that they used incidents and examples of drug errors as part of the educational materials, an additional three interventions implied this but did not state explicitly in the report. This component maps to 'belief about consequences' domain.

Interventions such as posters, newsletters and other visual prompts were used to reinforce the action required as part of the intervention, near patient cues such as medication label modifications, MAR chart annotations or near patient instructions served to remove the need for the individual to recall the information. All these aspects mapped to the 'reinforcement', 'memory, attention and decision process' and 'resources' domains on the framework. However, the production of a protocol or guidelines with no point of use reminder was mapped to 'resources' and 'memory, attention and decision process' only and not reinforcement.

None of the interventions contained aspects that mapped clearly to either 'intentions' or 'goals', or provided an assessment of such.

## 5.6 Discussion

### 5.6.1 The body of literature

In general the report quality of the selected studies was highly variable, with inconsistent levels of detail both within and between reports. Although there were a few very high quality reports of well-designed and conducted studies, the overall variability of reporting may reduce the validity of any conclusions drawn from this systematic review.

Preliminary searching prior to finalisation of the protocol enabled a better understanding of the breadth of keywords and free text words that are used in this therapeutic area. As was expected the majority of citations were retrieved from Medline and Embase. A large number of articles were found within CINAHL highlighting the direct interest of this to the nursing community, ten of which were included in the final analysis. Despite the large number of citations found within the psychiatry literature only one was selected for final analysis mainly due to the lack of focus on medicines management specifically within this subgroup of publications.

It was disappointing that several of the abstracts identified had not been published; however when the authors responded to email contact sufficient detail could not be provided to include into the full analysis, calling into question the robustness of the research.

Despite reports of medication errors and issues with enteral drug administration and administration in dysphagia in the literature since the mid 1990's it is interesting that all studies taken through to final analysis were published in the last 10 years. This may be influenced by a number of factors. The population is ageing and therefore incidence of dysphagia will also be increasing this is directly impacting the prevalence of enteral feeding in developed healthcare systems (Ojo, 2015). The publication focus may also be influenced by the global healthcare imperative to demonstrate the value of healthcare interventions prior to wider implementation.

### 5.6.2 Research design and bias

Twelve of the fourteen studies evaluated a complex intervention consisting of two or more component parts; the preferred design for the majority of the evaluated studies was a prospective before and after approach. Guidance on the development and evaluation of complex interventions has been published by the Medical Research Council (MRC), recommending quasi-experimental or observational studies only where an experimental design is not feasible (Craig et al., 2008) the use of the prospective before and after design is therefore an appropriate design to evaluate complex multicomponent care interventions. Randomised controlled trials are challenging to design for multicomponent complex interventions, particularly those delivered at a service level rather than patient level. The need for restrictive inclusion and exclusion criteria can dramatically limit the generalisability of research output and does not remove the risk of 'sample contamination' (Black, 1996).

Observational techniques were used, both disguised and non-disguised, and applied robustly, decreasing the risk of bias in the reported results. Knowledge was predominantly assessed by questionnaire, this objective measure also reducing bias from the assessor.

In most studies the interventions were applied to the healthcare staff rather than individual patients, with the impact on staff knowledge and confidence and practice (error rates) used as a proxy measure for improved patient outcomes.

The use of a control group can be used to reduce bias in non-randomised studies. Only two of the 15 studies included a control group. Kelly(Kelly, 2012) used two separate wards with a similar cohort of patients as a control. Dashti-Khavidaki (Dashti-Khavidaki et al., 2012) used an alternative hospital ICU as the control site, comparison of demographic data indicated higher years qualified in the control group. In the study by Kelly, the practice in the control group improved significantly. The researcher indicated that there were a number of factors which may have contributed to this finding including control group contamination through working shifts on the intervention wards, increased vigilance by the ward pharmacist and an increase in staffing on the control ward in response to practice being observed as part of a trial. In the Dashti-Khaviadaki study the researchers indicate that the difference in years qualified may have influenced the baseline data in the control group. Both of these examples demonstrate the challenges of the use of a control group.

An alternate method would be the use of interrupted time series design; this enables the impact of an intervention to be assessed against a potentially variable baseline, and also provides some insight into the rate of adoption and sustainability of the intervention (Soumerai et al., 2015). This method is recommended when randomisation is not feasible (Bernal et al., 2016). No studies in this review adopted this approach.

A study must be adequately powered to be certain that the results seen did not occur by chance. Seven of the fifteen studies included a sample size calculation and achieved that number, thereby providing statistical confidence in the results.

Of particular interest was the predominant focus on measurable proxy outcomes such as medication errors rather than patient specific outcomes such as adverse events or complications, the relative incidence of these favours the use of proxy measures to minimise sample size and resource impact to complete the study.

### 5.6.3 Intervention strategies

All but two of the studies used multicomponent strategies to achieve their aims. Complex interventions are used extensively in healthcare (Craig et al., 2008) necessitated by the multiple stakeholders and communication pathways and methods that exist in most areas of care delivery. The use of multicomponent interventions makes it challenging to interpret the value or contribution of each aspect individually. The core themes of the evaluated intervention components were education, documentation, IT development and care communication pathway redesign. Each aspect of the interventions is considered in more detail in the subsections below.

The study by Garcia Aparacio et al. was the only one with a patient focussed intervention, implementing an assessment of swallow function as part of the medicines management strategy. All other studies focussed on the nursing and care staff as the target group for the intervention, with only two including other members of the multidisciplinary team. This may reflect inadequate care pathway and stakeholder mapping prior to intervention development.

Understanding the context of the intervention is crucial. Ten of the fifteen publications provided no description of pre-existing resource; the five that did, provide an insight into the variation that does exist. Van den Bemt (van den Bemt et al., 2007), based in the Netherlands, describe a baseline of no ward based pharmacy input and no formal training, this contrasts with the environment studied by Kelly(Kelly, 2012), based in the UK, where a pharmacist and SLT were already embedded into the ward team prior to the intervention. This difference in baseline characteristics may have affected the impact size of the intervention studied, the former study reporting both a significant decrease in tube blockage and medication errors whereas the latter study reported a non-significant increase in knowledge and only a slight improvement in medication error rate. Globally medical services are structured in a variety of ways with very different roles and responsibilities of healthcare professionals; this affects ability to predict the outcome of transferring a complex intervention to another healthcare environment. This data does appear to confirm that a higher baseline of service provision reduces the potential impact of an intervention in this setting.

#### 5.6.3.1 Knowledge and skills development

The majority of the interventions focussed on the improvement of nursing knowledge and skills, this approach being justified in a limited number of studies during the intervention design process. All studies proposed that improving nursing knowledge would improve practice, reduce medication errors and thereby improve care, only two studies implemented a single component education strategy unfortunately neither evaluated the impact on medication errors, both reported an improvement in knowledge or confidence. Four studies contained a two-component intervention combining education with a documentation strategy (protocol/guidelines), three of these observed a significant reduction in medication errors as a result of the intervention, although the scale of impact varied potentially influenced by the baseline error rate.

Educational material can vary enormously in content, scope and delivery method, however in its simplest form of a face to face lecture it is labour intensive and requires a skilled teacher or facilitator to effectively deliver, but is relatively easy to develop, documentation likewise. A face to face lecture requires only preparation by the person delivering the material, and represents the most passive way of delivering educational material, insufficient detail about the training content was provided in the majority of study reports to draw any conclusions about the most effective method to improve knowledge.

Information and skills can be transferred in a number of ways; however each individual has their own preferred learning style. Auditory learners enjoy the spoken language, visual learners learn best by watching first and kinaesthetic learners learn best by doing, moving, experiencing and experimenting. The preferred learning style is varied across nursing staff but tends towards interactive or kinaesthetic styles (Crannell.B.A and Witte.M.M, 2012, Frankel, 2009), this may have impacted the potential effectiveness of the training delivered by more didactic methods within the interventions studied.

It is interesting that although an educational component was a key feature in all but one study, only seven included a check of the understanding of the participants and therefore there is no certainty that the nurses understood, retained or had applied the information that they had been given.

The variability with which educational material is delivered may affect the fidelity of the intervention. Two groups, Lohman and Bennett, developed and utilised e-learning tools, indicating a significant organisational investment in the intervention development, however neither group formally evaluated the impact of this on the nurses' knowledge. The use of a standardised delivery method such as e-learning tools increases the fidelity of that aspect of the intervention, but does not allow for flexible approach to learning. As knowledge impact was not assessed in the two studies, no conclusions can be drawn about the potential education benefits of this approach other than the theoretical benefits, both studies reported positive outcomes. Bennett reported an improvement on staff confidence but no impact assessment on patient outcomes, Lohman reported a decrease in medication error rate, however as this latter intervention contained all four elements it is unclear the contribution the e-learning made to the overall outcome.

Translation from knowledge into practice does not necessarily follow, and a full evaluation against the principles of knowledge translation is outside the scope of this review but should be considered in the design of education based interventions. Medication errors are the result of the nurses' actions, not their knowledge. Assessment of practice and competence were only assessed in three studies. Without a comprehensive description of education, evaluation and feedback, there is insufficient evidence to determine the impact on confidence or belief about capabilities. The TDF mapping provided some potential insights into the lack of specific

elements in the interventions designed to motivate application of the knowledge gained or adherence to guidance. No studies made reference to the use of targets or key performance indicators to monitor adherence.

Although there is insufficient scrutiny of the impact of the education component alone to be able to draw any firm conclusions on the direct contribution to reducing error rates, based on the presence of an education component in all the multi-component interventions with a positive impact it is reasonable to recommend that any strategy should include an educational component. In addition steps should be taken to regularly reassess knowledge and application.

#### 5.6.3.2 Information resources

Documentation development and its location were part of most of the interventions; however the accessibility of this information varied widely. Strategies included endorsements on medication record cards, symbols on drug labels, posters, information sheets, protocols, policies and databases. The target audience were nurses, pharmacy staff, SLT and physicians, and the information provided was general guidance, drug specific protocols and patient specific information. With the exception of the study by Kelly, all others demonstrated a positive impact on outcomes when the multi-component intervention included the provision of documentation.

The site of placement of the information or cue to act (presence of specific equipment) should be at the point of use. This removes the need for staff to remember complex information or to take the time to look for information. This was demonstrated in the evaluation of near patient medication administration guides by Santos (Santos et al., 2012); the nursing staff indicated that the presence of the information at point of need saved them time seeking out the information. the intervention by Lohmann (Lohmann et al., 2015) the drug specific preparation and administration protocols were located in the drug preparation area; the resulting reduction in preparation errors was significant.

Even the presence of the information or equipment is itself a cue that a particular course of action is warranted. Nine of the interventions studies provided information in such a way as to provide reinforcement of the correct course of action; seven of these reported a reduction in medication error rates.

Within the TDF framework, the proximity of the information affects the domains that the intervention component maps to. Near patient information maps to 'reinforcement', 'memory, attention and decision process' and 'environmental context and resources', thus potentially increasing the impact and sustainability of this aspect of the intervention.

Consistent guidance at a patient and staff level is essential to support familiarity. The papers from the Netherlands and one from the UK referred to specialist handbooks recognised nationally as the source of recommendations. Several studies referred to undertaking a literature review in order to develop the guidance being disseminated, this in itself is time-consuming and adds to the set up cost of the intervention, the resource required to maintain this should also be considered.

The source of information generation within an intervention can contribute to its fidelity, resilience and sustainability. System generated information such as dispensing label modifications and dysphagia flags on the electronic patient record ensure that the intervention does not rely on an individual to remember to annotate or endorse instructions. Wherever possible the knowledge of a specialist should be built into a system so that it is not lost to organisation when there is a change in staffing, thereby improving resilience.

The nature of the multicomponent intervention makes it impossible to determine the direct contribution of the documentary aspect, there is sufficient evidence to indicate that information availability at the point of use, either prescription , preparation or administration has a role in reducing medication errors and should be incorporated into future intervention design.

#### 5.6.3.3 Care Pathway Redesign

No studies identified significantly modified the overall care pathway, however intervention components related to communication pathways and methods, and patient assessment were utilised in several studies.

The study by Jackson et al. (Jackson et al., 2008) is a good example of the use of a quality improvement framework during the design phase to study existing communication pathways

and identify the most effective method of communicating information between members of the healthcare team. They observed that nursing practice was consistent with the information on the Medication Administration Record (MAR). The simple concept of using the MAR as the agreed place for the nurse, SLT and pharmacist to consistently document information relating to the dysphagia status of the patient and associated medication specific requirements was rapidly embedded into routine practice and effect sustained at 2 years. This particular intervention mapped to eight of the fourteen domains in the TDF, the highest number of all the studies mapped.

In contrast, the study by Kelly (Kelly, 2012) which also utilised patient level information, failed to demonstrate a significant benefit on medication errors when compared to the control group, however this document was not used as a two way communication tool and had a low baseline due to pre-existing specialist resources. It did not evaluate intervention impact over time where a positive impact may have been seen.

The scale and scope of communication pathway modification can be viewed as an indicator of organisational commitment to the initiative, the wide range of stakeholders at all levels of the organisation engaged in the intervention by Jackson et al. may also have contributed to its success.

Information technology (IT) changes represent a permanent change in communicating a specific piece of information between parts of the care pathway, rather than between two individuals as would occur with verbal communication. Five studies utilised either modifications to the pharmacy system to add an alert or developed and provided access to a database.

The utilisation of IT and communications within healthcare is driven by system usefulness and ease of use (Gagnon et al., 2012) , none of the publications made reference to the impact of the IT change on the ease of use of the system.

The study by Zhu at al. (Zhu et al., 2012) was the only one to add automatic warnings onto the prescribing system, however the evaluation of the intervention was lacking in detail and context, so although ‘irrational medication orders were abolished’ the scope and scale of impact is not clear.

The development or modification of any IT infrastructure can be time-consuming and costly. No information was provided on the resource necessary to develop or implement any of the IT based changes.

Overall the impact of changing the method of communicating information was positive, however the sustainability of the impact was only evaluated in one study, this aspect warrants further investigation particularly in relation to the aspects of the intervention as a whole and the breadth of domains mapped to within the TDF.

#### 5.6.3.4 Appropriateness of outcome measures

Outcomes in the reviewed papers were evaluated at three levels; organisational through adherence to policy, nurse level through assessment of knowledge, practice, confidence and medication error rates, and patient level through evaluation of rates of tube blockage and medication tolerance.

Medication errors as an outcome measure were assessed in eight of the publications. Six studies used locally derived definitions of medication errors specifically relating to enteral tube administration; however the description of the breadth and scope of definitions was limited but, from the results presented, appeared to be focussed around inappropriate crushing and/or dispersing.

The definitions of medication errors utilised by Idzinga et al. had been used previously by the group in other similar studies, the criteria were modified to account for errors relating to technique such as flushing or crushing. The definitions applied by Kelly were adapted from a previously modified 8 point proforma based on the ASHP classification; she extended this to 11 points to incorporate preparation errors unique to enteral tube administration. This approach allowed for a broader evaluation of medication error types in these patient groups. Both these studies highlight the need to have an agreed definition for medication error types in this area of healthcare to enable comparison between future intervention evaluations.

Lohmann et al. (Lohmann et al., 2015) determined that over 90% of wrongly prepared medication on the ICU were inappropriate at the prescription stage, and several of the other

studies indicated in their discussion that administration errors in patients with dysphagia or feeding tubes was linked to the appropriateness of the original prescription. Despite this knowledge of the origin of the preparation and administration errors in these patients, only two studies targeted physicians with the educational aspect of the intervention. The study by Bertsche (Bertsche et al., 2010) provided face to face training for both nursing and medical staff but did not evaluate impact on physician knowledge or change in prescribing practice. The study by Zhu (Zhu et al., 2012) refers to physician education but gives no further details of the scope of extent of training.

None of the studies appeared to undertake a full root cause analysis of error types prior to designing the intervention; this may explain why the impact of inappropriate prescribing on subsequent preparation and administration errors was not incorporated into the intervention design.

The study by Van den Bemt was the only one to evaluate intervention impact on a patient level outcome, tube blockage. All other researchers preferred medication errors as a proxy measure, primarily based on the assumption that a reduction in errors will result in patient benefit. The magnitude of any benefit from a reduction in errors will be entirely dependent on the magnitude and expected consequence of that error.

The outcome measures were directly relevant to the area of study, however only three studies objectively evaluated more than one outcome. One study evaluated both medication error rates and tube blockage rates, demonstrating a decrease in both, thereby providing some assurance that error rates can be used as a proxy measure for patient experience outcomes such as tube blockage.

#### 5.6.3.5 Sustainability

Sustainability is a core aim of any intervention. There are many factors that can affect sustainability of healthcare interventions; the TDF can be used to facilitate the identification of such (Curran et al., 2013).

Resource availability, including staff resource can impact the sustainability of an intervention. Nurses were the target group for the majority of evaluated interventions; if nurse education

was a sole component of the intervention staff turnover could adversely impact sustainability. Most studies evaluated impact of intervention immediately after delivery of the intervention. Only two studies evaluated both immediately and after a period of time. Jackson (Jackson et al., 2008) demonstrated adherence to the policy 2 years after the intervention, whereas Stuijt (Stuijt et al., 2013) demonstrated only a marginal effect at 9 months, the researchers in the latter group attributed this to a decrease in medical staffing, and a different distribution of nursing staff members. This supports the hypothesis that staffing changes may negatively impact sustainability of intervention effect.

However when the two studies are mapped to the TDF framework a difference is seen.
Jackson et al. redesigned the care communication pathway embedding patient identification into the process and providing information at patient level this maps to 'motivation' on the TDF framework, whereas Stuijt et al. did not alter the communication pathway and provided information at nurse level therefore not embedding any patient level association with the guidance rolled out in the intervention. This lack of reinforcement may reduce the prompt to act, and provides a valuable insight into how to improve the sustainability of an intervention in this area.

The evaluated interventions did not map well to the TDF domains that relate to attitude or motivation. There were no references to care goals and only minimal reference to beliefs about consequences of non-adherence to the action recommended in the intervention. It was not possible to determine if the interventions impacted on optimism or intentions due to the lack of information contained within the study reports.

Almost all interventions were targeted at the nursing staff and procedures, with little focus on the working environment, other than to ensure equipment and information was available. There appeared to be no focus on financial constraints and there was no baseline evaluation of the prescribing culture as part of the process mapping for the design phase of the intervention. These aspects would have mapped to the intentions, goals and social influence domains of the TDF framework. These aspects should be considered in the context of future intervention design to improve the sustainability of the intervention.

### 5.6.4 Strengths and weaknesses of this systematic review

It is an accepted fact that publication bias and the failure of researchers to publish their results in full following abstract publication has a direct impact on the quantity and quality of the literature available for any systematic review, resulting in the over-estimation of treatment results. All studies taken through to the final analysis were non-randomised and observational in nature, this would tend towards over predicting a positive effect of the intervention, and this is borne out in the data with only one study demonstrating a neutral impact.

Overall the quality of the reporting was highly variable, with inconsistent detail of the intervention or the evaluation. The lack of detail influenced the granularity of data that could be included in the data extraction tool. The addition of relevant fields such as fidelity, flexibility and detailed context were of no value due to the lack of detail included in the original publications. The highly complex nature of the some of the interventions described would have benefitted from better articulation, the poor or absent descriptions of the functional components of the intervention. Inconsistent terminology may also have adversely influenced the ability to directly compare similar functional components of different interventions.

The publication screening process was robust with good agreement between reviewers, demonstrated by the high kappa values.

The data was only mapped to one conceptual framework, it is possible that mapping to other frameworks, as recommended in the MRC guidance (Craig et al., 2006), may have provided different insights.

## 5.7 Conclusions

A systematic review of the identified publications indicated that multi-component interventions, within single site models, targeting medicines management in dysphagia are associated with an improvement in proxy measures for patient outcomes such as medication errors and staff knowledge.

The exact scale and scope of the impact of each individual component within these interventions could not be clarified due to the heterogeneity of the study conditions and

variability in outcome measures within the evaluated publications. However, the use of a multicomponent intervention is justified by the evidence presented, and there is confidence that use of medication error rates can be related to patient outcomes in this patient group. Each aspect of the interventions reviewed; education, documentation, pathway redesign and IT adaption, warrant inclusion in any future intervention.

With the exception of one study, the lack of substantive evidence of sustainability of the intervention effect is a major limitation to recommending a specific intervention based on the approaches described in the studies, as any improvement could be attributed to a well-motivated team and high level of awareness during the intervention period.

The direction of future intervention design should be in line with the reviewed studies but with the addition of the insights gained from mapping to the TDF framework in relation to improving aspects that relate to motivation and organisational culture

The design process for any new intervention in this area should be considered in three steps: Problem definition, Intervention and evaluation process.

The problem definition is clear from the background literature; inappropriate medication administration in patients with dysphagia or an enteral tube can result in adverse outcomes. The implications of inaccurate medication dosing and delayed or omitted doses are common to both subsets of this patient group. However, patients with dysphagia may be susceptible to aspiration if the incorrect formulation type is used, whereas patients with an enteral feeding tube may experience tube blockage. Despite this, clear articulation of the problem definition and full evaluation of the pre-intervention processes, drivers and barriers was absent in the reports of the publications considered in the systematic review.

The primary aim is common for all medication error prevention projects, the difference being that the baseline level is likely to be higher due to the contribution of the higher proportion of preparation errors. Simply put, the aim is to reduce medication errors. Patient level aims should be to reduce the incidence of aspiration or tube blockage.

The use of the TDF both prospectively during the design phase and retrospectively at the evaluation phase can be justified by the existing body of work using this framework, and the higher degree of positive domain mapping in the sustained intervention in this review.

The strategic approach must be underpinned with a clear understanding of the existing care pathways and resources available. All opportunities to improve communication and embed information into existing resources should be identified. A clear care pathway map must be the initial step for any improvement process in order to identify all the key stakeholders and possible handoffs in the communications process. This allows for the identification of appropriate patient level prompts such as medication cards, prescription or patient medical record; these were used to good effect within the evaluated interventions.

Patient identification and assessment was shown to be associated with a positive intervention outcome and therefore should be embedded into routine care pathways, if this is not feasible across an organisation these efforts should be targeted at higher risk populations such as critical care, older populations, cerebrovascular and neurological specialties and GI tract specialties (ENT, head and neck and upper and lower gastroenterology). Once identified and assessed this record should be visible to all stakeholder members of the healthcare team such as the prescriber, pharmacist, SLT and primary carer.

Education was a key component of all interventions evaluated, and although not necessary for the practical delivery of a therapy, general training on condition awareness and consequences of errors in this population should be imbedded into induction training materials; evaluation should include evidence of increasing confidence, motivation and awareness of consequences of non-compliance. The use of technology such as e-learning with interactive element, therefore not dependent on resource being available to teach, may be a cost effective and auditable method of delivering this training.

Technical administration skills should be taught and supported at ward level through standardised training materials; with effective feedback and opportunities to reflect this will increase confidence and familiarity.

The positive impact of documentation and guidance components of the studied interventions supports the recommendation that specific guidance for this route of administration must be

consistent throughout the organisation to foster a culture of evidence based practice. In view of the wide range of professional and domiciliary staff interacting with these patients, it is reasonable to recommend that the guidance must be easy to access and use and appropriate to the intended audience. Resources and equipment should be readily available to minimise any barriers to following the protocols.

Motivation and attitude were shown to be under-represented constructs in the interventions evaluated. Understanding consequences through shared learning from errors and adverse events in a non-blame environment is a method that has been used to reinforce positive behaviour. Motivation can be achieved through support, feedback and encouragement. The use of role models such as link nurses or champions has been effective in other areas although not included in the interventions included in this review. Opportunities to share learning should be encouraged, with supportive environments for root cause analysis discussions, to continue the quality improvement process.

There is a requirement for medication error reduction strategy for this patient group to focus on all stages of the prescription to patient pathway. The quality of the original prescription was the root cause of over 90% of medication errors in the study by Lohmann (Lohmann et al., 2015). Influencing prescribing quality requires appropriate information and prompts at the point of prescription, mechanisms to achieve this will be dependent on the resources available either IT or paper based. As there were no evaluated interventions that focussed on this area, further research is required on this topic.

In order to effectively evaluate the intervention appropriate outcome measures should be clearly related to medication administration in dysphagic or tube fed patients. This should include measures of medication errors at all stages in line with accepted categorisation frameworks, although an additional focus on preparation and administration will be necessary as demonstrated by Kelly (Kelly, 2012). An assessment of these leading indicators, such as near misses and medication errors in addition to the lag indicators of tubes requiring replacement or removal due to blockage, will allow for the development of a clearer relationship between these two measures. This would have a subsequent impact on sample size necessary for research as the low rates of tube blockage seen currently necessitate a large sample size to enable identification of a statistically significant difference in rates.

The assessment of the effectiveness of knowledge and skill transfer with an assessment of practical competence and a periodic retention check should be considered in order to demonstrate the sustainability of the intervention. An assessment of motivation and attitude could also be included in the assessment to provide the organisation an insight into the safety culture in this area over time.

Further clarity is required to determine the effect of baseline service levels on the scale of impact that any one intervention can achieve. Any further research should take into account the impact of staff turnover on these subjective and objective measures and evaluate the intervention sustainability using an appropriate method such as an interrupted time series study.

Design and evaluation of such a complex intervention would require significant initial resource however if effective may prove cost effective both in improved outcomes and also in patient experience.

# 6 Final Discussion and Conclusions

Research into aspects of medication administration to patients with an enteral feeding device is not a new endeavour. Early reports of success with naso-enteric feeding in the 1970's using fine bore tubes (Metz et al., 1978) were shortly followed by studies in the early 1980's on how to maintain patency and unblock them (Cataldi-Betcher et al., 1983). The enteral tube was acknowledged as a drug delivery system by the mid 1980's (Wright and Robinson, 1986, Campbell, 1987), with an increasing interest in the potential benefits and challenges.

Despite over four decades of clinical practice there remains very little robust evidence on which to build a foundation of good clinical practice, as a result a series of consensus guidelines have emerged (Bankhead et al., 2009, BAPEN, 2003a, Dougherty and Lister, 2008). The diverse patient group that can be affected by dysphagia and require medication delivered by an enteral tube spans from critical care to community care, affecting patients of all ages, and requiring support from all healthcare disciplines. Publications are predominantly in the nursing domain focussing on administration practicalities and pharmaceutical domain focussed on drug nutrient interactions and formulation options.

Recently the focus on translational research, or bench to bedside, has led to renewed focus on how scientific knowledge gained can be embedded into clinical practice more effectively acknowledging the significant delays that occur in this process (Morris et al., 2011). However, to create data of clinical relevance the research journey is one of 'bedside to bench and back again'.

The design of this research was based on that principle. A surveyed review of bedside practice, not limited to a single site but drawn from the clinical advice given by a broad UK wide distribution of specialist healthcare professionals and mirrored by the responses of patients in the community, gave an updated perspective on this route of medication administration. A localised view of declared practice in care homes with nursing was also undertaken to represent the dependent care of patients in the community.

The key pharmaceutical questions from this initial phase were then explored in a laboratory environment in an attempt to define some of the underpinning scientific principles behind formulation recommendations and administration practice.

The final phase of this research was to systematically review the interventions evaluated for outcome improvement in this field with the intention of defining how best to effectively integrate new knowledge gained rapidly and sustainably into clinical practice.

## 6.1 Limitations

This journey, like many, has been somewhat convoluted and protracted. The temporal span of this entire project, having been undertaken over a period of seven years, will have reduced the generalisability of some of the initial survey findings and latterly published research would have influenced study design and focus if it had been conducted more recently.

The initial study design was based on the perspective from the literature and therefore was focussed on the preparation and administration issues, in hindsight the survey could have provided more valuable insights if questions around formulation choice, supply, prescriber engagement and perceived barriers to good practice had been included in the survey design.

An observational technique would have given a more 'honest' representation of practice; however the logistics of completing this on a single patient/single location basis rendered this option resource intense and un-fundable.

As described in chapters three and four the resource available for these areas of study limited the scope of evaluation and the range of medication and scientific methods employed. That is not to devalue the outputs of those activities merely highlighting that with additional resource more is possible.

The major limitation of the systematic review was the availability and quality of published data in this area. The literature and systematic review both revealed a lack of robust data. Anecdotally the topic of medication administration via enteral tubes is a frequently audited area in pharmacy practice and yet the number of full publications identified in the literature was few, indicating a low rate of publication. This is a common issue with clinical practice research with numerous studies demonstrating a low transition rate from research to conference proceeding and onto full publication (Scherer et al., 2007, O'Dell and Shah, 2012, Hung and Duffett, 2013, Prohaska et al., 2013), particularly for pharmacy practice research (Irwin et al., 2013).

Despite the challenging nature of the evidence base, mapping the available intervention studies to the TDF framework did reveal new insights that can be used to support the design of a structured intervention.

## 6.2 Effective intervention by design

This thesis has identified a number of opportunities, generated new data and insights, and evaluated the impact of interventions. A strategy is required to ensure that existing guidelines are updated in line with the new data, and that specific information is included in relevant resources where appropriate.

The primary aim of all this research was to improve medicines management in dysphagic patients and those with an enteral feeding tube. In order to achieve this, care pathway redesign needs to be undertaken and a full evaluation of a complex intervention is required.

The insights from this research as a whole provide new data requiring inclusion and a framework on which to build that complex intervention. The process steps are identified below.

### 6.2.1 Patient identification

In order for any intervention to be successful it must be clear which patients will benefit from that intervention. The identification of patients with an enteral feeding tube is relatively straight forward in acute care as in most cases it will be a visible nasogastric or nasojejunal tube. Where percutaneous devices are used in the hospital and in community these are less visible and therefore a mechanism for identifying these patients to their healthcare team is essential.

Dysphagia has a higher prevalence in certain patient groups (Ney et al., 2009) and questions should be routinely asked regarding the patients ability to eat, drink and swallow without adverse symptoms. The responses should be recorded as part of the health record.

It is important that this requirement for consideration of an alternative formulation is clearly identified in the health care record, in much the same way as allergy status is recorded, so that any healthcare professional prescribing or advising on therapy for that patient can take this into account when considering therapy options.

A cue or prompt is only effective at eliciting the desired response if the recipient has been pre-conditioned or if additional relevant information is provided at the time it is needed. This is the first opportunity for intervention.

The sustainability of education based interventions is likely to be poor unless frequently repeated, tested and reinforced. An IT based, and therefore process driven, solution would be preferable. Prompts within electronic medication record systems have been shown to effectively alert users to potential safety hazards (Ojeleye et al., 2013), and were demonstrated to positively impact medication errors within the systematic review.

### 6.2.2 The prescription – getting it right first time

The survey data presented indicated that the prescription and supply of an appropriate formulation for use via an enteral tube was high amongst the patient group studied, but that there was still potential to improve this further. It was inferred that cost pressures may impact formulation choice but unfortunately there was not opportunity to explore this aspect further within this research project.

A number of the interventional studies within the systematic review indicated that inappropriate formulation choice of the initial prescription lead to subsequent issues during the preparation and administration steps. However, this aspect was not explored further within those interventional studies and therefore no specific data are available on the preferred approach for information provision to prescribers for this group of patients. This is an area that warrants further research both in secondary and primary care.

Based on the information available thus far, early consideration of non-enteral options such as trans-dermal patches should be encouraged. Liquid medicines remain a suitable option in the majority of cases however the additional information gained in chapter three should be published to allow it to be incorporated into drug specific prescribing guidance to highlight

'problem' medication and make recommendations regarding alternatives, and the limited need for dilution to facilitate administration. The data in chapter three, relating viscosity to ease of administration, should be shared with relevant sections of the pharmaceutical industry to encourage appropriate formulation development for this patient group.

The range of transdermal, dispersible and liquid dosage forms available is limited and therefore a directory of appropriate therapy options for common conditions should be produced and be freely available to prescribers. Again the utilisation of IT solutions should be encouraged, with formulation options provided at the point of prescription.

### 6.2.3 Safe preparation and administration

The focus of a complex intervention aimed at reducing error rates in preparation and administration should focus on simple, consistent guidance and skills based training. Information availability at the point of preparation or administration was shown to reduce error rates in the interventional studies evaluated, the most effective method of providing this would need to be localised.

Staff administering medication should be aware of what constitutes a preferred and appropriate formulation choice, and should be empowered to challenge the prescription rather than continue with unsafe practice. This confidence comes from knowledge and skills but is also a reflection of the organisational culture. Education, training and skills assessment should be included in routine skills training and can be delivered in several ways but due to the practical nature of the issues a kinaesthetic approach is required. Consideration should be given on how to foster the right culture within an organisation to sustain the impact of the intervention.

The data generated in this thesis can be used directly to simplify medication administration for patients with an enteral tube. Liquids remain first choice, but a dilution step is only required for a limited number of medicines. If a tablet is the only formulation available, then dispersion in the barrel of the syringe as a closed system should be considered the preferred option. Tablet crushing should not be routinely recommended and considered a last resort only to be undertaken within an appropriate environment by suitably qualified staff due to the high risk of reduced dose delivery and occupational exposure.

Mixing medication to facilitate administration was a common theme in the surveys and literature; however without evidence of safety the practice should be strongly discouraged. An understanding of the potential consequences should be included in any training.

The final focus, but possibly the most important, for administration is the importance of tube flushing. This was identified as the main area where reported practice was not aligned with guidelines. Raising the awareness of the risk of tube blockage with medication and the positive impact that regular appropriate flushing can have will support good practice. The before medication and between medication flush should be reinforced as this was demonstrated to be the area of lowest compliance.

Specific data regarding flush volumes and frequency is still lacking although consensus guidelines have settled on 30-50ml for before and after medication flush. The area where research is required is the between medicine flush as it is not known how much volume is required to deliver a full dose. The data from chapter four provides a signal that a 10mL flush may be sufficient for tube clearance following administration of dispersed tablet, but data is still required for liquid medications.

### 6.2.4 Transfer of information

The transfer, retention and availability of information are important aspects of a complex intervention. The signal from the systematic review was that providing information at the point of use was beneficial and removes the need for recall of learnt information.

The availability of patient specific information was shown to be beneficial, although currently labour intensive. IT development, although initially resource heavy, may be a means to provide patient specific information at point of use with minimal ongoing resource.

Effective transfer of information between healthcare settings is important to consistent care and advice. The patient survey hinted at a lack of confidence in some healthcare professionals to be able to provide advice. No intervention studies outside of a managed care environment were identified, and therefore there is no specific evidence to guide intervention design. However it would be reasonable to assume that through shared information a degree of

upskilling could be achieved, however to optimise the community pharmacists role in this aspect of medicines management targeted education is required.

### 6.2.5 Patient Centricity

The ultimate aim for any healthcare intervention is to improve outcomes. More research is required into which aspects and issues are important to patients and how patients can be better engaged in their care and medicines management.

The expert patient is a term used to describe a patient who is knowledgeable about their condition and its treatment. Several of the patients who responded to the survey, by the nature of their responses, are expert patients. Engagement with patient groups should be actively encouraged to develop and shape the content of resources aimed at patients.

## 6.4 Recommendations for future research

Drawing together the literature and insights from the survey, advice from UK practitioners is reported to be broadly in line with consensus guidance with a small degree of variability. There remain some concerns about how this is translated into practice by community carers and patients.

Further research is required on the awareness, knowledge and motivations for prescribers and advisors (community pharmacists and practice nurses) in the community; this could be undertaken during the mapping process for the design of any community based intervention.

A different approach to assessment of behavioural change and habit formation would be a longitudinal study of practice and therapy following patient from tube placement through discharge, potentially evaluating changes in healthcare professional influence on practice over time. This study type would provide more insights into the factors that affect the sustainability of interventions targeted at patients.

A major contribution to the evidence base from this research is within the increased understanding of dose recovery from tablet manipulation; this new data adds to existing knowledge, long forgotten, and raises new questions about the ongoing use of crushing

devises for tablet manipulation for tube administration. The significant loss of dose through the use of equipment such as pestle and mortar is a particular concern for medication with a narrow therapeutic range. New guidance should strongly discourage these methods of tablet manipulation.

From the data generated within this research tablet dispersal appears more accurate and a safer alternative to tablet crushing and should be encouraged; however an evaluation of the barriers to that change in practice will need to be undertaken, both in the healthcare and home environment.

The scope of the laboratory work was limited by both time and resource; an increased scope of testing to include further generation of tablet dispersion dose delivery data, particle size distribution and risk of tube blockage assessment would be of value to inform therapy options.

The limited data relating to liquid medicines provides information to guide dilution practice for the viscous medication tested and offer clarity for those where dilution is not necessary. However at present, there is limited information to guide future formulation development for enteral tube administration. Viscosity is clearly associated with problems but other factors, as yet unknown, also play a part in flow properties. As recommended in chapter three an extension of the scientific methods used to evaluate the properties of the liquid medicines should be undertaken.

The initial survey phase of this research did not specifically examine cost as an influencing factor in prescribing practice or clinical advice, although it was raised in free text responses. The cost-effectiveness of the intervention studies in the systematic review could not be evaluated due to a lack of information contained in the publications around resource consumption. The cost effectiveness of use of an appropriate formulation via this route is unknown; a health economic evaluation of this would be of value to healthcare providers looking to invest in service development.

The systematic review, through mapping to behaviour change enablers, demonstrated that existing evaluated interventions have focussed on preparation and administration tasks and not on the root causes of prescribing, resource, culture and communication. These prescription influencing factors need to be explored and better understood to develop

motivational and habit forming practices, in addition to the identification of IT related solutions to develop process change in preference to knowledge transfer.

## 6.3 Conclusions

This multifaceted research has made a number of contributions to existing knowledge. It has highlighted the potential gap between professional guidance and clinical practice and offered insights into specific areas for focus. It has produced new data on liquid formulation properties for enteral tube administration and consolidated and broadened the existing knowledge base in relation to tablet crushing. Finally offering a view of an intervention programme focussed on quality and outcome improvement in this field.

Specific findings which should influence future guidance and focus of interventions are:

- Adherence to administration guidance, particularly in relation to enteral tube flushing and mixing medication is lower in community care organisations and independent patients and carers.
- High viscosity liquid medication are associated with administration problems and may require dilution to facilitate administration via a feeding tube.
- Liquid medication with a viscosity of less than 100cP are suitable for administration via an enteral feeding tube without dilution.
- Dispersion in the barrel of the administration syringe is the most accurate method for suspension and delivery of tablets.
- Tablet crushing in a pestle and mortar may reduce dose delivery by 10-20% and therefore should be avoided where possible.
- Multi-component interventions have been shown to improve medication related outcomes in patients with enteral feeding tubes, however there are limited data on the sustainability of these interventions.
- Retrospective mapping of the Theoretic Domains Framework (TDF) to the evaluated interventions provided insights into the aspects of the interventions which may contribute to their sustainability.

The principle of the five ‘rights’ have always underpinned effective medicines management; Right patient, right drug, right dose, right route and right time (NMC, 2010) , Jennifer Kelly in

her doctoral thesis referred to the 6th right, that of right formulation (Kelly, 2012) a key aspect also postulated by Elliott in the extension to nine 'rights'(Elliott and Liu, 2010).

This research highlights that there are overlooked opportunities to influence medication choice earlier in the prescribing process to reduce administration issues. This new data can be used to simplify administration processes through the proactive use of liquid preparations that do not need further dilution, and solid dosage form administration using dispersion rather than crushing techniques. This would reduce nursing, carer and patient workload, reduce occupational exposure and improve dosing accuracy without increasing the risk of tube blockage.

Knowledge of and access to the 'right formulation' is the key to safe and effective medication administration to dysphagic patients or those with an enteral feeding tube. As can be seen throughout this thesis, this is not just about the pharmaceutical properties of the formulation but also the ability to accurately dose a convenient to use and a cost-effective option.

This research provides new insights into potential strategies and targets to improve the dysphagic patient's experience of drug administration. In this modern era of healthcare research we should turn the spotlight onto the right outcome and look towards patient focussed outcome measures.

## Right knowledge, right resources, right outcome.

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# Appendices

## Appendix 2.1aCovering letter for professional questionnaire


Oxford Radcliffe Hospitals NHS
NHS Trust

Rebecca White
Pharmacist
Churchill Hospital
Headington
Oxford
OX3 7LJ
Tel: 01865 741166 Bleep:4373

January 2010

**A study to determine the ideal medication characteristics for the safe and effective administration of medications via enteral feeding tubes**

Dear Colleague,

I am a researcher, undertaking a PhD, who is interested in the administration of medication via enteral feeding tubes. This research project, exploring the issues relating to the practical aspects of medication administration via enteral feeding tubes, is part of a larger project supported by a research grant from the Department of Health. This questionnaire has been sent to you by The Parenteral and Enteral Nutrition Group (PENG) and the National Nutrition Nurses Group (NNNG) on my behalf.

The aim of my research is to improve the quality of guidance available for healthcare professionals when administering medicines via enteral feed tubes. The questionnaire is designed to identify the issues faced by health care professionals when administering or advising on the administration of medication via enteral feeding tubes and therefore enable me to focus my future research for your benefit.

The project outcome is to develop evidence based national advice and a formulary document for this route of medication administration.

The enclosed questionnaire explores issues relating to medication administration via enteral feeding tubes; it should take no more than 15 minutes to complete and is completely anonymous. To enable me to be able to identify whether you have completed it or not I have also included a separate postcard which you can return separately, which does identify you. When I receive the postcard I will know not to send you a follow up questionnaire.

You are under no obligation to complete the questionnaire, and can indicate this using the separate post card enclosed. A reminder will be sent out to non-responders 6 weeks after this mailing. Please send the questionnaire and postcard separately.

Please note that all data collected as part of this project will be handled anonymously, in a confidential manner and will not be disclosed to third parties. Any information that is held on computers will be password-protected.

I would very much appreciate your involvement in this study.

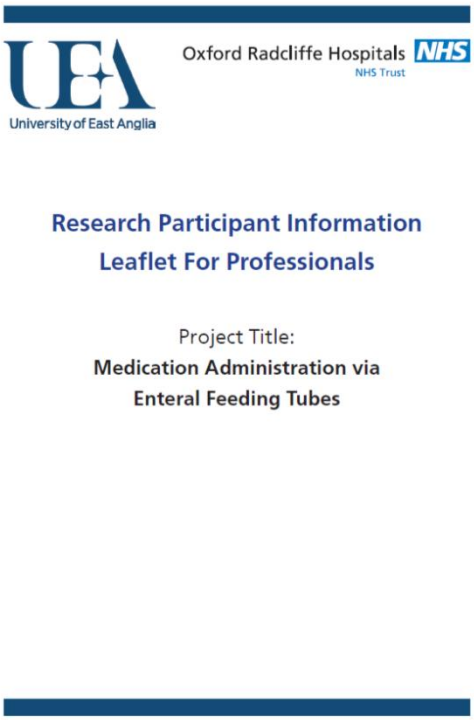
Thank you for your co-operation.
Yours sincerely,

Rebecca White
Pharmacist

*Prof_Invitation_Letter_Version4 08/12/2009*
*Mid & South Bucks Ethics Ref: 08/H0607/80*

OMI 1403.1

## Appendix 2.1b Research participant information leaflet for professionals




### PARTICIPANT INFORMATION SHEET
### PROFESSIONAL PERSONNEL

You are being invited to take part in a research study. Before you decide whether to participate, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Please contact the researcher if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

**What is the study about?**

This study is part of a larger project looking at medication administration via enteral feeding tubes. This first part of the study will help to identify how frequently medication are administered via enteral feeding tubes, which medication are commonly used and what methods are used to administer them. This study will be used a part fulfilment of a PhD.

**Why have I been chosen?**

This questionnaire has been sent to all members of the National Nutrition Nurses Group (NNNG) and Parenteral and Enteral Nutrition Group (PENG) on behalf of the researcher.

**What would I have to do?**

The simple questionnaire should take no more than 15 minutes to complete. A responder postcard is included to allow for anonymous completion, this should be posted separately to the questionnaire.

**Will I see the results of the study?**

This is the first part of a much larger study. Initial findings from this part of the study will be published and be used to inform the later parts of the study.

**What happens to information about me?**

No personal identifiers will be recorded during the data collection.

**What are the possible advantages of taking part?**

The data collected will be more representative if a large number of participants respond.
Guidelines produced from the data will be more robust and reflect current clinical practice.

**What are the possible disadvantages of taking part?**

There are none.

**Who is organising and funding the research?**

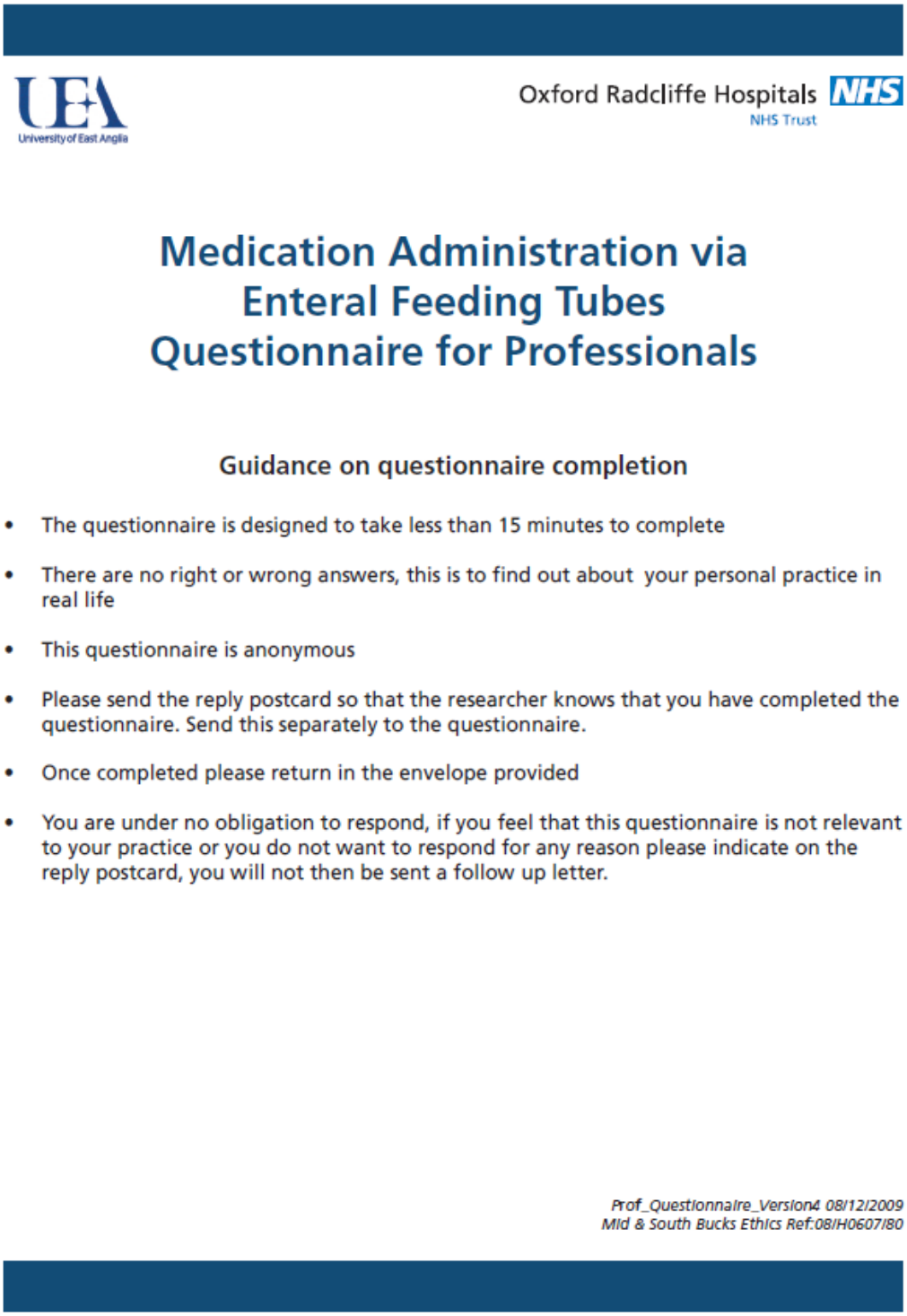
This research is being organised by Rebecca White, a pharmacist from the Oxford Radcliffe Hospitals NHS Trust, with academic support from the University of East Anglia. The researcher has been awarded a grant through the Research for Patient Benefit scheme by the Department of Health.

**How can I obtain more information?**

The researcher can be contacted, via the methods below, if there is anything which is unclear or if you would like more information regarding the study.

Rebecca White
Pharmacy Department
Churchill Hospital
Oxford, OX3 7LJ
Email: Rebecca.white@orh.nhs.uk or r.white@uea.ac.uk
Telephone: 01865 741166 pager number 4373 during normal working hours

**Appendix 2.1c Questionnaire for Professionals**



UEA
University of East Anglia

Oxford Radcliffe Hospitals NHS
NHS Trust

# Medication Administration via Enteral Feeding Tubes Questionnaire for Professionals

## Guidance on questionnaire completion

- The questionnaire is designed to take less than 15 minutes to complete
- There are no right or wrong answers, this is to find out about your personal practice in real life
- This questionnaire is anonymous
- Please send the reply postcard so that the researcher knows that you have completed the questionnaire. Send this separately to the questionnaire.
- Once completed please return in the envelope provided
- You are under no obligation to respond, if you feel that this questionnaire is not relevant to your practice or you do not want to respond for any reason please indicate on the reply postcard, you will not then be sent a follow up letter.

*Prof_Questionnaire_Version4 08/12/2009*
*Mid & South Bucks Ethics Ref:08/H0607/80*

OMI 1403.6

## Section 1 – About you

1. Please indicate your responder group

Nutrition Nurse ☐ Dietitian ☐

Other nurse ☐ Other ☐

2. Which groups of patients do you care for/advise on? (tick as many as apply)

Adult ☐ Paediatric ☐

In which sector do you primarily work?

Community ☐ Secondary Care ☐

## Section 2 – Tube flushing

3. Do you use/recommend a water flush when the feed is stopped?

Yes ☐ No ☐ Not applicable/not my role ☐

If yes, what volume do you recommend? _____mL

If the volume is variable please describe the usual volume used and details of why this may vary

_____

_____

_____

_____

4. Do you use/recommend a water flush before medication is given?

Yes ☐ No ☐ Not applicable/not my role ☐

If yes, what volume do you recommend? _____mL

If the volume is variable please describe the usual volume used and details of why this may vary

_____

_____

_____

5. Do you use/recommend a water flush between medication?

Yes ☐ No ☐ Not applicable/not my role ☐

If yes, what volume to you recommend? _____ mL

If the volume is variable please describe the usual volume used and details of why this may vary

## Section 3 – Medication via Feeding Tubes

6. Do you give/recommend liquid medicines for use via feeding tubes?

Yes ☐ No ☐ Not applicable/not my role ☐

If yes, describe the method you use/recommend

7. Do you give/recommend administering tablets via feeding tubes?

Yes ☐ No ☐ Not applicable/not my role ☐

If yes, describe the method you use/recommend

8. Do you have administration problems with particular medicines?

Yes ☐ No ☐ Not applicable/not my role ☐

If yes, which ones and why? Please give as many examples as possible

| Medicine and Formulation | Details of problem |
|---|---|
| | |
| | |
| | |
| | |
| | |
| | |
| | |
| | |
| | |
| | |

9. Are there any medication that you associate with tube blockage?

Yes ☐ No ☐

If yes, please describe. (Please give as many examples as possible)

10. Do you ever mix medication together prior to administration via a feeding tube?

Yes ☐ No ☐ Not applicable/not my role ☐

If you answered yes, then please state below which ones and how?

11. Who decides on which formulation you use e.g. liquid, tablet?

12. If a tube blocks what do you usually do/recommend?

13. Do you use/recommend purple/ enteral syringes?

Yes ☐ No ☐

Please describe any problems which you have had with these?

14. Do you recommend a specific size of syringe for flushing?

Yes ☐ No ☐ Not applicable/not my role ☐

If yes, what size? _____

15. Do you recommend a specific size of syringe for administering medicines?

Yes ☐ No ☐ Not applicable/not my role ☐

If yes, what size? _____

## Section 4 – Further comments

If you have any further information you wish to include or expand on any of the questions above, please do so in the box below. Thank you.

Thank you for taking the time to complete this questionnaire.
Please return using the envelope provided.

Please complete the reply postcard and send separately.

*Prof_Questionnaire_Version4 08/12/2009*
*Mid & South Bucks Ethics Ref:08/H0607/80*

**Appendix 2.2aCovering letter for patient questionnaire**

University of East Anglia

Oxford Radcliffe Hospitals NHS
NHS Trust

Rebecca White
Pharmacist
Churchill Hospital
Headington
Oxford
OX3 7LJ
Tel: 01865 741166 Bleep:4373

January 2010

## Giving Medicines through Enteral Feeding Tubes

Dear Sir/Madam,

I am a researcher, undertaking a PhD, who is interested in giving medicines through feeding tubes. This research project is funded by the Department of Health, with support from PINNT. This questionnaire has been sent by PINNT on my behalf.

This project is finding out the issues that affect giving medicines through enteral feeding tubes such as gastrostomy and PEG tubes. I am inviting you to help with this study by completing the survey that is attached.

The aim of this project is to develop better advice for healthcare professionals and patients through the production of a national advice and formulary document for this method of giving medicines.

The attached survey will ask you about your experience as a patient or carer. If you can't answer a question or don't want to answer just leave the section blank.

You don't have to give your name. You don't have to complete the survey, just tick the box on the separate post card enclosed.

None of your personal information will be recorded. Any information that is held on computers will be password-protected.

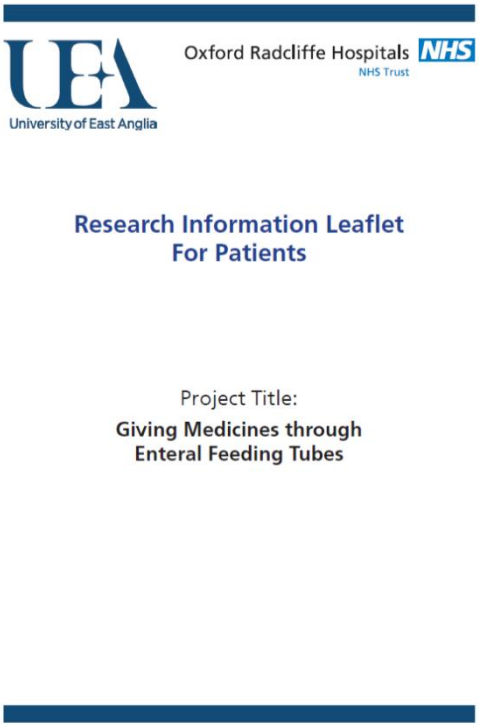
I would be grateful for your reply to this survey.

Thank you for your co-operation.
Yours sincerely,

Rebecca White

*Prof_Invitation_Letter_Version4 08/12/2009*
*Mid & South Bucks Ethics Ref: 08/H0607/80*
OMI 1403.2

## Appendix 2.2b Information leaflet for patient questionnaire




**RESEARCH INFORMATION SHEET – PATIENT**

You are being asked to take part in a research study. Before you decide whether to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully, if you are a patient you may wish to discuss it with friends and relatives. Ask me if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

**What is the study about?**
This study is part of a larger project looking at giving medicines through enteral feeding tubes e.g. PEGS or buttons. This first part of the study will help to find out how often medicines are given via enteral feeding tubes, which medicines are commonly used and what methods are used to administer them.

**Why have I been chosen?**
This questionnaire has been sent out by PINNT, on behalf or the researcher, to all members who have an enteral feeding tube or care for a patient with an enteral feeding tube.

**What would I have to do?**
The simple questionnaire should take no more than 20 minutes to complete.

**Will I see the results of the study?**
This is the first part of a much larger study. Information from this part of the study will be published and be used to design the later parts of the study.

**What happens to information about me?**
No information about you will be recorded during the data collection.

**What happens to information about me?**

No information about you will be recorded during the data collection.

**What are the possible advantages of taking part?**

The data collected will be better if a large number of people respond. The guidelines produced from the data will be better.

**What are the possible disadvantages of taking part?**

There are none.

**Who is organising and funding the research?**

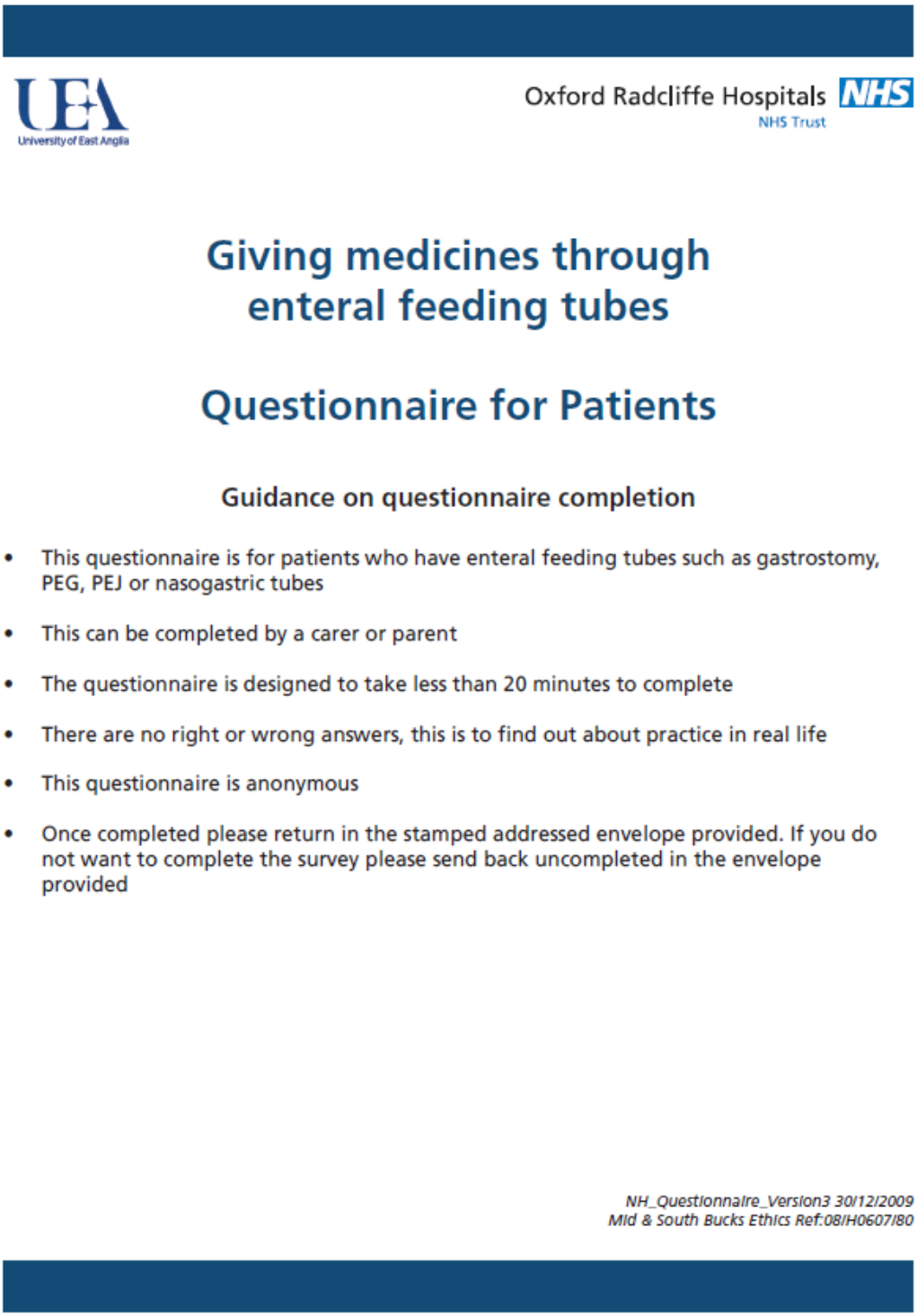
This research is being organised by Rebecca White, a pharmacist from the Oxford Radcliffe Hospitals NHS Trust, with academic support from the University of East Anglia.

The researcher has been given a grant through the Research for Patient Benefit scheme by the Department of Health.

**How can I obtain more information?**

Please contact me, via the methods below, if there is anything which is unclear or if you would like more information regarding the study.
Rebecca White
Pharmacy Department
Churchill Hospital
Oxford, OX3 7LJ
Email: Rebecca.white@orh.nhs.uk
Telephone: 01865 741166 pager number 4373 during normal working hours

**Appendix 2.2c Questionnaire for patients**



UEA
University of East Anglia

Oxford Radcliffe Hospitals NHS
NHS Trust

# Giving medicines through enteral feeding tubes

# Questionnaire for Patients

## Guidance on questionnaire completion

- This questionnaire is for patients who have enteral feeding tubes such as gastrostomy, PEG, PEJ or nasogastric tubes
- This can be completed by a carer or parent
- The questionnaire is designed to take less than 20 minutes to complete
- There are no right or wrong answers, this is to find out about practice in real life
- This questionnaire is anonymous
- Once completed please return in the stamped addressed envelope provided. If you do not want to complete the survey please send back uncompleted in the envelope provided

*NH_Questionnaire_Version3 30/12/2009*
*Mid & South Bucks Ethics Ref:08/H0607/80*

OMI 1403.7

## Section 1 – Medication Administration

How old are you?

0-18 years ☐ 19 - 40 years ☐

41 – 65 Years ☐ 66 or over ☐

What sort of tube do you have? _____/ Don't know ☐

What size tube do you have? _____/ Don't know ☐

## Section 2 – Tube Flushing

1. Do you flush your tube when the feed is stopped?

   Yes ☐ No ☐

If yes, how much water do you use? _____mL

If the volume varies please describe the normal volume used and explain why you might change this

_____

_____

_____

_____

_____

2. Do you flush your tube before giving medication?

   Yes ☐ No ☐

If yes, how much water do you use?

_____mL

If the volume is variable please describe the usual volume used and details of why this may vary

_____

_____

_____

_____

_____

3. Do you flush between medicines?

Yes ☐ No ☐

If yes, how much water do you use? _____mL

If the volume is variable please describe the usual volume used and details of why this may vary

_____

_____

_____

_____

_____

## Section 3 – Medicines

4. Which medicines do you give through your feeding tube?
Please complete the table below

| Medicine/Strength | Tablet/Capsule/Liquid | Comments |
|---|---|---|
| *e.g. Paracetamol 500mg* | *Soluble tablets* | *Dissolved in a full cup of water* |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |

5. Do you put liquid medicines down your feeding tube?

Yes ☐ No ☐

If yes, explain how you give them

6. Do you put tablets down your feeding tube?

Yes ☐ No ☐

If yes, explain how you give them

7. Do you ever mix medicines together before putting them down the tube?

Yes ☐ No ☐

If yes, which ones?

## Section 4 – Problems

8. Do you have any problems with putting your current medicines down your tube?

Yes ☐ No ☐

If yes, which ones and why?

_____

_____

_____

_____

_____

_____

_____

9. Are there any medicines that you think block the tube?

Yes ☐ No ☐

If yes, please describe.

_____

_____

_____

_____

10. Who recommends the formulation you use e.g. liquid, tablet?

GP ☐ Hospital Doctor ☐ Nutrition Nurse ☐

Dietitan ☐ Pharmacist ☐

Other _____

11. Who do you get advice about medicines from?

GP ☐ Hospital Doctor ☐ Nutrition Nurse ☐

Dietitan ☐ Pharmacist ☐

Other _____

12. If your tube blocks what do you do?

13. Do you use purple/ enteral syringes?

Yes ☐ No ☐

If Yes, Have you had any problems with these? Please describe below

If No, what do you use?

**Further comments section**

If you have any further information you wish to include to expand on any of the questions above, please do so in the box below. Thank you.

Thank you for taking the time to complete this questionnaire.
Please return using the envelope provided.

*NH_Questionnaire_Version3 30/12/2009*
*Mid & South Bucks Ethics Ref:08/H0607/80*

## Appendix 2.3aCovering letter for Nursing Home Questionnaire

University of East Anglia

Oxford Radcliffe Hospitals NHS
NHS Trust

Rebecca White
Pharmacist
Churchill Hospital
Headington
Oxford
OX3 7LJ
Tel: 01865 741166 Bleep:4373
Rebecca.white@orh.nhs.uk

December 2010

**A study to determine the ideal medication characteristics for the safe and effective administration of medications via enteral feeding tubes**

Dear Jan

As you care for patients with enteral feeding tubes at Saxon Way I would be grateful if you could assist me with this research project.

I am research pharmacist based at the Churchill Hospital in Oxford and funded by a Department of Health grant to undertake a PhD on the administration of medication via enteral feeding tubes (PEGs, PEJs and Nasogastric tubes).

The first part of my PhD is to develop a much greater understanding of how carers, patients and healthcare professionals administer medicines via enteral feeding tubes. This information will then be used in the laboratory to try to identify optimal ways of giving medicines via this route. My final aim is to develop national evidence based advice on this route of medication administration.

The enclosed questionnaire has been sent to all care and nursing homes in Oxfordshire and is designed to determine what medicines are currently being placed down enteral feed tubes and identify any issues you are facing when doing this. You are under no obligation to complete the questionnaire and if you do not wish to complete it or receive a follow up reminder then just place it uncompleted in the envelope provided. A reminder will be sent out to non-responders 6 weeks after this mailing.

**A copy of the 'Handbook of Drug Administration via Enteral Feeding Tubes' will be sent to all organisations that send back a fully completed questionnaire.**

I would very much like to be given the opportunity to watch medicines being administered down enteral feed tubes in primary care and therefore at the end of the questionnaire I have asked if you would allow me to undertake direct observation of medication administration via feeding tubes in your care home. **If you are happy to participate in the observational phase of the study please include your contact details in the final section of the questionnaire.**

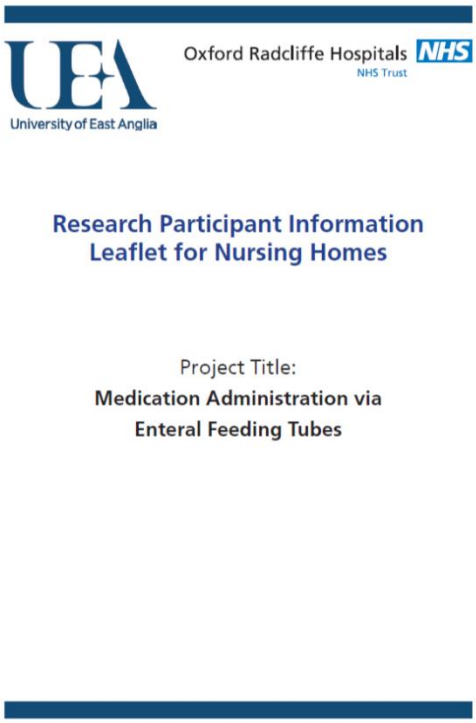
Please note that all data collected as part of this project will be handled anonymously, in a confidential manner and will not be disclosed to third parties. Any information that is held on computers will be password-protected.

I would very much appreciate your involvement in this study.

Thank you for your co-operation.
Yours sincerely,

Rebecca White
Pharmacist

## Appendix 2.3b Information leaflet for Nursing Home Questionnaire




### PARTICIPANT INFORMATION SHEET – NURSING HOME

You are being invited to take part in a research study. Before you decide whether to participate, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Ask me if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

**What is the study about?**

This study is part of a larger project looking at medication administration via enteral feeding tubes. This first part of the study will help to identify how frequently medication are administered via enteral feeding tubes, which medication are commonly used and what methods are used to administer them. This project will be used as part fulfilment of a PhD.

**Why have I been chosen?**

This questionnaire has been sent to all community care institutions within Oxfordshire.

**What would I have to do?**

The questionnaire should take no more than 60 minutes to complete.

If you consider participating in observational phase of study you will need to include your contact details on the reply card enclosed.

The observational phase of the study will take place at a mutually convenient time. The researcher will observe a medication administration round and record details of techniques used. No patient details will be recorded. The researcher will intervene and advise only if practice is

**Will I see the results of the study?**
This is the first part of a much larger study. Initial findings from this part of the study will be published and be used to inform the later parts of the study.

**What happens to information about me?**
No patient or participant identifiers will be recorded during the data collection. However the details of any participants in the observational part of the study will be recorded on the consent form. These will be stored in a secure location for the duration of the study.

Community Care Institution details will be recorded in code known to the investigator only.

**What are the possible advantages of taking part?**
The data collected will be more representative if a large number of participants respond. The guidelines produced from the data will be more robust.

Community Care organisations completing the questionnaire in full will receive a copy of the BPNG 'Handbook of Drug Administration via Enteral Feeding Tubes', once all the observational work has been done.

**What are the possible disadvantages of taking part?**
There are none.

**Who is organising and funding the research?**

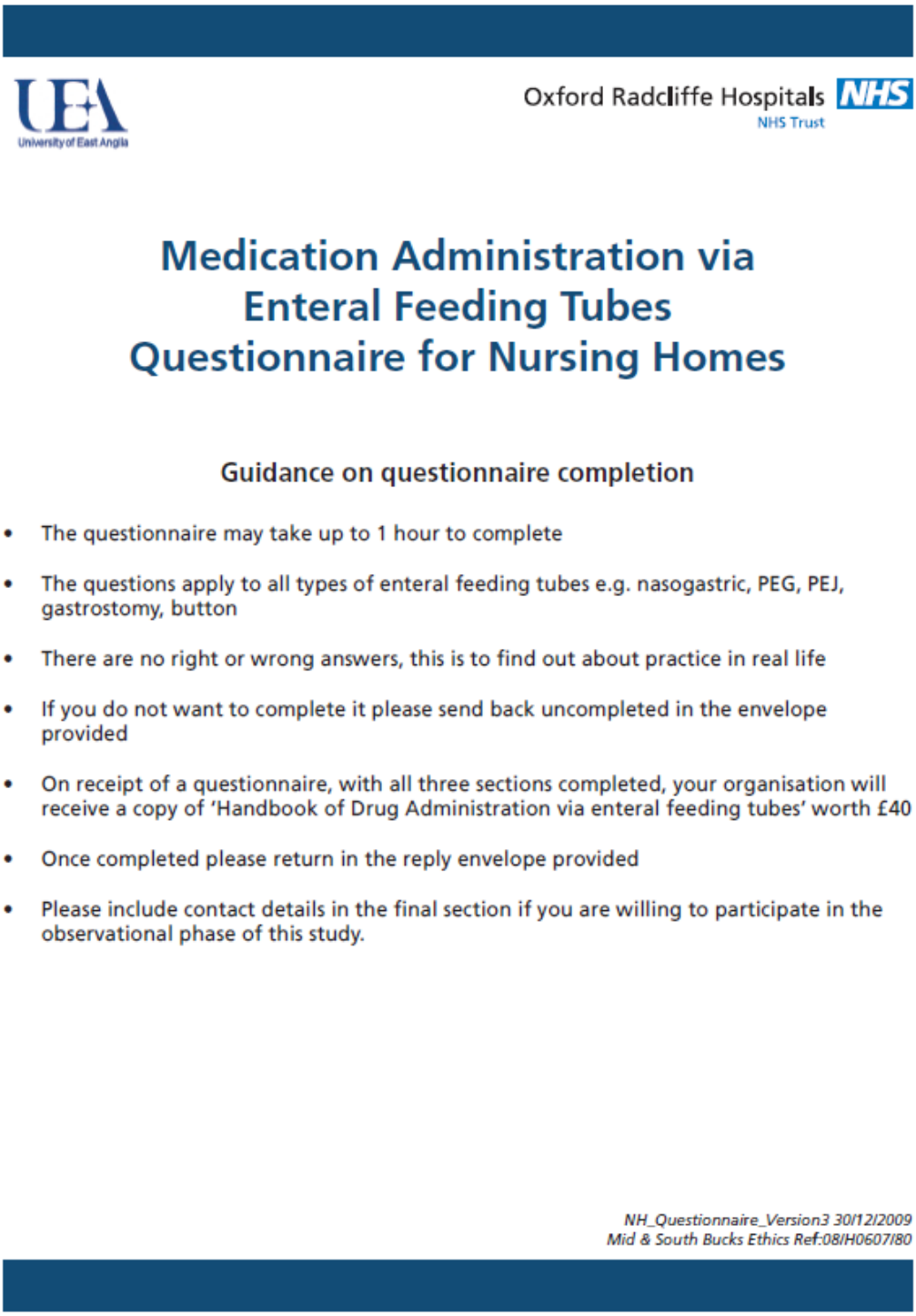
This research is being organised by Rebecca White, a pharmacist from the Oxford Radcliffe Hospitals NHS Trust, with academic support from the University of East Anglia. The researcher has been awarded a grant through the Research for Patient Benefit scheme by the Department of Health.

**How can I obtain more information?**

Please contact me, via the methods below, if there is anything, which is unclear or if you would like more information regarding the study.

Rebecca White
Pharmacy Department
Churchill Hospital
Oxford, OX3 7LJ
Email: Rebecca.white@orh.nhs.uk
Telephone: 01865 741166 pager number 4373 during normal working hours

**Appendix 2.3c Nursing Home Questionnaire**



University of East Anglia

Oxford Radcliffe Hospitals NHS
NHS Trust

# Medication Administration via Enteral Feeding Tubes Questionnaire for Nursing Homes

## Guidance on questionnaire completion

- The questionnaire may take up to 1 hour to complete
- The questions apply to all types of enteral feeding tubes e.g. nasogastric, PEG, PEJ, gastrostomy, button
- There are no right or wrong answers, this is to find out about practice in real life
- If you do not want to complete it please send back uncompleted in the envelope provided
- On receipt of a questionnaire, with all three sections completed, your organisation will receive a copy of 'Handbook of Drug Administration via enteral feeding tubes' worth £40
- Once completed please return in the reply envelope provided
- Please include contact details in the final section if you are willing to participate in the observational phase of this study.

*NH_Questionnaire_Version3 30/12/2009*
*Mid & South Bucks Ethics Ref:08/H0607/80*

OMI 1403

## Section 1 – Medication Administration

1. How many patients are there currently in the nursing/care home? _____

2. Do you currently have any patients with enteral feeding tubes in place?

   Yes ☐ No ☐

If you answered **No** to question 2 you do not need to answer any further questions. Thank you for taking the time to complete this questionnaire. Please return using the envelope provided.

3. How many patients have an enteral feeding tube in place? _____

4. Do any of these patients have medication administered via their feeding tubes?

   Yes ☐ No ☐

If you answered **No** to question 4 you do not need to answer any further questions. Thank you for taking the time to complete this questionnaire. Please return using the envelope provided.

5. How many patients currently have their medication via these tubes? _____

6. Do you flush the tube when the feed is stopped? Yes ☐ No ☐
   If **yes**, what volume of water do you use? _____mL

7. Do you flush the tube before medication is given? Yes ☐ No ☐
   If **yes**, what volume of water do you use? _____mL

8. Do you flush between medication? Yes ☐ No ☐
   If **yes**, what volume of water do you use? _____mL

9. Do you give liquid medicines through the feeding tubes? Yes ☐ No ☐

If **yes**, describe the method.

10. Do you give tablets through the feeding tubes? Yes ☐ No ☐

If **yes**, describe the method.

11. Do you have any problems with particular medicines? Yes ☐ No ☐

If **yes**, which ones?

12. Please describe the particular problems

13. Do you ever mix medication together prior to administration? Yes ☐ No ☐

If **yes**, which ones?

14. Who decides on which formulation you use e.g. liquid, tablet?

15. Where do you get advice from?

16. If a tube blocks what do you do?

17. Do you have a policy on medicine administration? Yes ☐ No ☐

18. Do you use purple / enteral syringes? Yes ☐ No ☐

If Yes, Have you had any problems with these?

## Section 2 – Tube and Medication data

This section only refers to patients receiving medication via their feeding tubes. Please complete as fully as possible.

**Tube Data**

| Tube Type or description | Size | Number of patients with this type of tube |
|---|---|---|
| e.g. Cor-flow Gastrostomy | 14 French | 2 |
| e.g. PEG with triangular retention plate with purple clamp | | 1 |
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**Medication data**

Please complete for any medication which you are currently administering through a pts feeding tube

| Medicine | Freq. | Dose | Formulation | Comments/Problems/Issues | Number of patients currently having this medicatio through feeding tube |
|---|---|---|---|---|---|
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**Additional copies of this page are supplied. If needed please attach to your completed questionaire**

*NH_Questionnaire_Version3 30/12/2009*
*Mid & South Bucks Ethics Ref:08/H0607/80*

**Further comments section**

If you have any further information you wish to include to expand on any of the questions above, please do so in the box below. Thank you.

**Observational Study**

**No**, I do not want to participate in the observational study (tick box) ☐
**Yes**, I do want to participate in the observational study (tick box) ☐

Please contact _____

on tel: _____ to arrange a convenient date and time.

Thank you for taking the time to complete this questionnaire.
Please return using the envelope provided.

*NH_Questionnaire_Version3 30/12/2009*
*Mid & South Bucks Ethics Ref:08/H0607/80*

## Appendix 5.1 Systematic review data extraction tool

| Section | Data Fields |
|---|---|
| **Citation Information** | First Author, summary, primary outcome, ethics approval |
| **Sampling** | Technique, power calculation, pre and post sample size intervention group, pre and post sample size control group, participant identification method |
| **Pre-intervention activities** | Prescribing practice evaluation, prescribing practice evaluation method, administration practice, administration practice method, knowledge assessment, knowledge assessment method, Outcome assessment, outcome assessment method, outcome assessment parameter, pre-baseline existing resource |
| **Intervention** | Intervention description, target, patient assessment and method |
| **Education component** | Y/N, delivered by, delivered to, method of delivery, assessment of knowledge, assessment of competence, method of assessment |
| **Documentation component** | Y/N, Guidelines, Protocol, specific drug protocols, patient level information, place of documentation, reference sources for documentation |
| **IT changes** | Use of IT systems to influence prescribing/administration, nature of IT modification |
| **Care communication pathway change** | Modification to communication process, description of modification |
| **Outcome** | Follow up period, control group information, follow up assessment technique, outcome measures, nurse knowledge, admin errors, tube blockage |
| **Bias Assessment** | Design bias, selection bias, randomisation, concealment, performance bias, detection bias, incomplete outcome data, adequacy of study power |
| **Cost benefit review** | Resources described, resources used, cost evaluation |
| **TDF mapping** | Knowledge, skills, social/professional roles and responsibility, belief about capabilities, optimism, beliefs about consequences, reinforcement, intentions, goals, memory/attention/decision process, environmental context/resources, social influences, emotion, behavioural regulation |

## Appendix 5.2 Risk of bias assessment tool (Higgins and Green, 2011)

| Domain | Low risk | High risk | Unclear |
|---|---|---|---|
| 1. Design bias (focus study question and design) | The study clearly described all of the following: Targeted population, The intervention, The comparator, Outcomes measures<br>The study design is the best to answer the questions, e.g. RCT for intervention<br>The study addressed the intended research question | The study is not fulfilling any of these criteria | Insufficient information to permit judgment of 'low risk' or 'high risk'. |
| 2. Selection bias (external and internal variations) | The study sample is representative of the intended population<br>There is nothing special about the sample with any potential to effect intervention or outcomes<br>All patients were included/excluded as per the stated inclusion and exclusion criteria<br>The study groups are comparable at baseline | The study is not fulfilling any of these criteria | Insufficient information to permit judgment of 'low risk' or 'high risk' e.g. groups were described as comparable but with no demographic to support assertion |
| 3. Selection bias (randomization) | The investigators describe a random component in the sequence generation process | The description of the sequence generation involve some systematic but non-random approach | Insufficient information to permit judgment of 'low risk' or 'high risk'. |
| 4. Selection bias (allocation concealment) | Participants and investigators enrolling participants could not forsee the study group assignment | Participants and investigators enrolling participants could possibly forsee the study group assignment | Insufficient information to permit judgment of 'low risk' or 'high risk'. |
| 5. Performance bias (standardised intervention delivery) | The investigators used a standardised process which was followed by all the service providers delivering the intervention (e.g. intervention delivered by one individual only or some evidence of standardised delivery) | The process of intervention delivery was not standardised | Insufficient information to permit judgment of 'low risk' or 'high risk'. |
| 6. Performance bias (standardised outcome measurement) | The investigators use a standardised process which was followed by all investigators recording and measuring outcomes e.g. appropriate training or use of standardised documentation for data collection | The process for recording outcomes was not standardised | Insufficient information to permit judgment of 'low risk' or 'high risk'. |
| 7. Detection bias (blindness of outcomes) | Blinding of outcome assessment ensured, and unlikely it was broken.<br>No blinding of the outcome assessment, but this is unlikely to influence outcome assessment | Outcome measurement was not blind | Insufficient information to permit judgment of 'low risk' or 'high risk'. |
| 8. Incomplete outcome data | No missing outcome data and all study participants accounted for at conclusion<br>All pre-specified primary and secondary outcomes have been reported<br>The reported outcomes are appropriate to answer the study question | The study is not fulfilling any of these criteria | Insufficient information to permit judgment of 'low risk' or 'high risk'. |
| 9. Adequacy of study power (appropriate statistical analysis) | The study used appropriate/justifiable statistical testing<br>Power calculation or sample size calculation was performed | The study is not fulfilling any of these criteria | Insufficient information to permit judgment of 'low risk' or 'high risk'. |

## Appendix 5.3 TDF mapping guidance

(adapted from Cane et al. 2012 (Cane et al., 2012))

| Domain | Definition | Constructs | Examples of evidence of component of intervention |
|---|---|---|---|
| Knowledge | An awareness of the existence of something | knowledge, procedural knowledge, knowledge of task environment | Evidence of teaching or transfer of information |
| Skills | An ability or proficiency acquired through practice | skills, skills development, competence, ability, interpersonal skills, practice, skill assessment | Evidence of teaching of skills or of structured support for skill development |
| Social/professional role and responsibility | A coherent set of behaviours and displayed personal qualities of an individual in a social or work setting | professional identity, professional role, social identity, professional boundaries, confidence, leadership, organisational commitment | Evidence of formalisation or articulation of professional role, responsibilities<br>Evidence of organisational leadership of intervention<br>Evidence of permanent change to implement intervention as an indication of organisational commitment |
| Belief about capabilities | Acceptance of the truth, reality, or validity about an ability, talent or facility that a person can put to constructive use | self-confidence, perceived competence, self-efficacy, perceived behavioural control, beliefs, self-esteem, empowerment, professional confidence | Evidence of contribution to individuals confidence or self-belief, e.g. assessment feedback and support |
| Optimism | The confidence that things will happen for the best or that desired goals will be attained | Optimism, pessimism, unrealistic optimism, identity | Evidence of subject of intervention being confident that their actions will result in the expected outcomes e.g. attitude assessment |
| Beliefs about consequences | Acceptance of the truth, reality, or validity about outcomes of a behaviour in a given situation | outcome expectancies, anticipated regret, consequents | Explicit use of incidents and consequences within teaching materials<br>Evidence of RCA as learning tool |
| Reinforcement | Increasing the probability of a response by arranging a dependent relationship, or contingency, between the response and a given situation | rewards, incentives, punishment, reinforcement | Evidence of cue's or prompts embedded in the intervention which serve to reinforce correct action<br>Evidence of reward or incentives for following protocol<br>Evidence of follow up/action when protocol not followed |
| Intentions | A conscious decision to perform a behaviour or a resolve to act in a certain way | stability of intentions<br>stability of change model<br>transtheoretical model and stages of change | Evidence of intent |
| Goals | Mental representation of outcomes or end states that an individual wants to achieve | goal priority, automous goals, implementation intention | Evidence of target set<br>Inclusion in Dashboard |
| Memory, attention and decision process | The ability to retain information, focus selectively on aspects of the environment and choose between two or more alternatives | Memory, attention control, cognitive overload/ tiredness | Aspects of intervention that reduce need for an individual to remember information and provide it a point of use<br>Aspects of intervention that reduce distraction |
| Environmental | Any circumstance of a | Environmental stressors | Evidence of aspect that encourages |

| Domain | Definition | Constructs | Examples of evidence of component of intervention |
|---|---|---|---|
| context and resources | person's situation or environment that discourages or encourages the development of skills and abilities, independence, social competence and adaptive behaviour | resources, organisational culture, critical incidents, barriers and facilitators | and facilitates knowledge and skill development e.g. routine availability of on-line learning tools Resources/information embedded into routinely used documentation |
| Social influences | Those interpersonal processes that can cause individuals to change their thoughts, feelings or behaviours | group norms, social norms | Evidence of leadership and fostering leadership e.g. train the trainer implementation process |
| Emotion | A complex reaction pattern, involving experiential, behavioural and physiological elements | fear, anxiety, stress | Use of tragic example of errors to emotionally connect trainee to consequence of protocol deviation |
| Behavioural regulation | Anything aimed at managing or changing objectively observed or measured actions | self-monitoring, breaking habit, action planning | Evidence of feedback, experiential learning |

Appendix 5.3 TDF mapping guidance continued

## Appendix 6 Conference abstracts/posters and presentations

| Conference Title | Date/Venue | Abstract/Presentation Title |
|---|---|---|
| **NNNG (National Nutrition Nurses Group) Annual Conference** | June 2011 Manchester | Presentation Drugs and tubes: What nurses say and what patients do |
| **EAHP (European Association of Hospital Pharmacists) Annual Conference** | March 2013 Paris | Abstract/Poster Evaluation of dose recovery from tablet manipulation for enteral tube administration |
| **HSRPP (Health Services Research and Pharmacy Practice) Conference** | May 2013 Lancaster | Abstract/Poster Enteral feeding tubes as a route of drug administration in residential care facilities |
| **BAPEN (British Association for Enteral and Parenteral Nutrition) Annual Conference** | November 2013 Harrogate | Abstract/Poster Tube flushing and drug administration practice in patients in the community on enteral feeding |
| **UKCPA (UK Clinical Pharmacy Association)/GHP (Guild of Hospital Pharmacists) joint conference** | November 2013 Leeds | Abstract/Poster Drug administration practice in patients in the community on enteral feeding |

Technical information from chapters 3 and 4 included in 3rd Edition (2015) of Handbook of Drug Administration via Enteral Feeding Tubes. Eds: R.White and V.Bradnam.
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