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Oral dosage form modifications for older adults: a mixed methods investigation

Aoife Mc Gillicuddy BPharm MPharm MPSI

A thesis submitted to the National University of Ireland, Cork for the degree of Doctor of Philosophy in the School of Pharmacy

September 2018

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Declaration

I declare that the work contained within this thesis has not been previously submitted for a degree at this or any other university. All the work contained within this thesis is entirely my own work, apart from due acknowledgements. I give my permission for the library to lend or copy this thesis upon request.

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Glossary

AC: Acute Care

ACF: Aged Care Facility

ATC: Anatomical Therapeutic Chemical

BNF: British National Formulary

BPG: Best Practice Guideline

CASP: Critical Appraisal Skills Programme

CC: Continuing Care

CDSR: Cochrane Database of Systematic Reviews

CENTRAL: Cochrane Central Register of Controlled Trials

CMI: Case Mix Index

CNM: Clinical Nurse Manager

CNS: Central Nervous System

COREQ: Consolidated Criteria for Reporting Qualitative Research

CVS: Cardiovascular System

ECTS: European Credit Transfer System

EMA: European Medicines Agency

ENTREQ: Enhanced Transparency in Reporting the Synthesis of Qualitative Research

EU: European Union

FDA: Food and Drug Administration

FPM: First Pass Metabolism

GABA: *gamma*-Aminobutyric Acid

GDP: Gross Domestic Product

GMS: General Medical Services

GP: General Practitioner

HIQA: Health Information and Quality Authority

HPRA: Health Products Regulatory Authority

HSE: Health Service Executive

ICH: International Conference on Harmonisation

IQR: Interquartile Range

LTC: Long Term Care

LTCF: Long Term Care Facility

MDT: Multi-Disciplinary Team

MIMS: Monthly Index of Medical Specialities

N/A: Not Applicable

NHS: National Health Service

NHSS: Nursing Homes Support Scheme

NICE: National Institute for Health and Care Excellence

NMBI: Nursing and Midwifery Board of Ireland

NTI: Narrow Therapeutic Index

OECD: Organisation for Economic Co-operation and Development

ODF: Oral Dosage Form

PEG: Percutaneous Endoscopic Gastrostomy

Ph.Eur.: European Pharmacopoeia

PIP: Paediatric Investigation Plan

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PRN: Pro Re Nata i.e. when required

PROSPERO: International Prospective Register of Systematic Reviews

RC: Respite Care

SD: Standard Deviation

SDU: Specialist Dementia Unit

SPC: Summary of Product Characteristics

SPSS: Statistical Package for the Social Sciences

STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

SWAMECO: “SWAllowing difficulties with MEdication intake and COping strategies”

TILDA: The Irish Longitudinal Study on Ageing

TRIP: Turning Research Into Practice

T2DM: Type 2 Diabetes Mellitus

UK: United Kingdom

UN: United Nations

USA: United States of America

USP: United States Pharmacopoeia

WHO: World Health Organisation

Publications

Peer-reviewed publications

Mc Gillicuddy A, Kelly M, Crean AM, Sahm LJ. Understanding the knowledge, attitudes and beliefs of community-dwelling older adults and their carers about the modification of oral medicines: A qualitative interview study to inform healthcare professional practice. Research in Social and Administrative Pharmacy. 2019; Article In Press. doi: https://doi.org/10.1016/j.sapharm.2019.01.004

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Presentations

Oral presentations

Mc Gillicuddy A, Crean A, Kelly M, Sahm LJ. Optimising oral medicines for older adults: what role can pharmacists play? 8th All-Ireland Pharmacy Healthcare Conference, Dundalk. 17th October 2017.

Mc Gillicuddy A, Kelly M, Crean A, Sahm LJ. The knowledge, attitudes and beliefs of nurses about the modification of oral medicines for older adults: a qualitative interview study. 39th All-Ireland Schools of Pharmacy Conference, University College Cork. 24th - 25th April 2017.

Mc Gillicuddy A, Kelly M, Sweeney C, Carmichael A, Crean AM, Sahm LJ. Oral medicines: are we meeting the needs of older adults? Lunchtime Education Session, Marymount University Hospital and Hospice, Cork. 4th October 2016.

Mc Gillicuddy A, Crean A, Kelly M, Sweeney C, Carmichael A, Sahm LJ. Oral dosage forms for older adults: is there an unmet need? 38th All-Ireland Schools of Pharmacy Conference, Royal College of Surgeons in Ireland, Dublin. 21st - 22nd March 2016.

Poster presentations

Sahm LJ, Crean AM, Kelly M, **Mc Gillicuddy A.** Oral dosage form (ODF) modifications for older adults: a direct observation of practice in aged care facilities in Ireland. Prescribing in Research and Medicines Management (UK & Ireland) Conference, London. 14th December 2018.

Mc Gillicuddy A, Crean AM, Kelly M, Sahm LJ. Oral medicine modifications to meet the needs of older adults: the views of community-dwelling older adults and their carers. Prescribing in Research and Medicines Management (UK & Ireland) Conference, London. 26th January 2018.

Mc Gillicuddy A, Crean AM, Kelly M, Sahm LJ. Pharmacists' role in medicine modification: a qualitative exploration of nurses' views. European Society of Clinical Pharmacy International Workshop, Leiden, The Netherlands. 15th - 16th June 2017.

Mc Gillicuddy A, Kelly M, Crean A, Sahm LJ. The knowledge, attitudes and beliefs of patients and healthcare professionals around oral medicine modification: a qualitative systematic review. SPHeRE Network 3rd Annual Conference, Royal College of Surgeons in Ireland, Dublin. 12th January 2017.

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literature. Irish Gerontological Society 64th Annual & Scientific Meeting 2016, Killarney. 30th September to 1st October 2016.

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  3rd and 10th December 2014.

Thesis Abstract

Introduction

Oral dosage forms (ODFs), particularly solid ODFs, are the most popular and most commonly prescribed of all medication formulations. Older adults are the highest consumers of prescription medication. However, age-related pharmacokinetic, pharmacodynamic and physiological changes can complicate the administration of oral medicines to older adults and may result in these ODFs being modified (e.g. tablets crushed or split, or capsules opened) in order to facilitate administration of the appropriate dose or to overcome swallowing difficulties. These modifications may impact on the safety and/or efficacy of the medication, which could have clinical consequences for patients. In addition, many of these modifications represent an off-licence use of the medication, which has subsequent legal implications for healthcare professionals. Despite guidelines advocating that the modification of ODFs should be avoided, it appears to be common practice. Therefore, there is a need to gain a greater understanding of ODF modifications for older adults.

Aim

The overall aim of this research was to investigate ODF modifications for older adults in an Irish setting and to gain an understanding of the factors influencing this practice.

Methods

A mixed methods approach, using both quantitative and qualitative research methods, was used. Initially, a quantitative systematic review was conducted to

identify the available evidence on the prevalence of difficulty swallowing ODFs and the modification of ODFs to overcome swallowing difficulties amongst the older cohort. Secondly, a qualitative systematic review was undertaken to determine the knowledge, attitudes and beliefs of patients, healthcare professionals and carers about ODF modifications. The findings of these reviews served to guide the generation of research questions for the empirical, primary research studies. A retrospective audit of drug charts in one aged care facility (ACF) in Ireland was completed to provide preliminary data on ODF modifications in an Irish setting. Following this, a qualitative, semi-structured interview study was conducted with nurses working in acute and long-term care settings, to elucidate their knowledge, attitudes and beliefs about ODF modification and administration for older adults. Based on the findings of these studies, a direct observation of medication administration to older adults in five ACFs was conducted to provide more in-depth information on ODF modifications. Finally, the views and experiences of community-dwelling older adults and their carers around ODF modifications were explored using qualitative, semi-structured interviews.

Results

The quantitative systematic review highlighted the paucity of studies investigating ODF modifications, with only three studies describing modifications in care settings, which when combined with the limitations of the data collection methods used, demonstrated the requirement for further research investigating this issue. The qualitative systematic review provided useful insights into the factors that influence the knowledge, attitudes and beliefs of healthcare professionals and patients about

ODF modifications; highlighting that (i) the variability of individual patient's requirements, (ii) poor communication practices and (iii) lack of knowledge about modifications, when combined with (iv) the complex healthcare environment, complicate decision-making regarding ODF modification. Results from the retrospective audit emphasised that modifications were commonly required to ensure patients' needs could be met, particularly for fractional dosing. Whilst there was a lack of evidence-based information to support decision making around modifications, in many cases no suitable alternatives were available. This was echoed in the nurse interview study, with modifications seen to be a routine and necessary occurrence in older patient care. The nurses' role as patient advocate however, helps to optimise formulation suitability within current limitations. The direct observation study once again demonstrated the ubiquity of ODF modifications, providing detailed insights into ODF modification practices in an Irish setting but also highlighting the challenges encountered when administering oral medicines to older adults. Finally, the challenges encountered in the community-setting were elucidated, and there is a clear need for greater engagement with the issue of ODF suitability for community-dwelling older adults.

Conclusions

This thesis has made a significant contribution to understanding ODF modifications for older adults. It is clear that ODFs are not meeting the needs of the older cohort. Modifications are common and necessary, due to age-related changes combined with limitations of currently available formulations. This thesis has provided important information about current practices, but has also highlighted the

complex factors that give rise to the need to modify ODFs for older adults. There is a need to prioritise engaging with this issue in order to optimise ODF suitability for older adults. This will necessitate input from a wide variety of key stakeholders, including healthcare professionals, industry and regulatory bodies, as well as patients and carers. The findings of this thesis provide direction and important insights that will guide this process.

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Chapter 1: Introduction

1.1 Introduction

Globally, the fact that we are living longer is a tribute to the strides that have been made in public health. However, this ageing demographic profile presents challenges from a healthcare perspective, and this served as the impetus for this thesis. Medicines optimisation for older adults has been a key focus of research and policy with significant advances reported in the appropriateness of prescribing for the older person. Whilst these improvements must be acknowledged, there is still a dearth of research examining the suitability of medications for older adults. Ultimately for a medication to be effective, it must be capable of being safely administered to the patient using an appropriate formulation. Oral dosage forms (ODFs), particularly solid ODFs, are the most commonly prescribed of all formulations. However, age-related changes complicate administration and may result in ODFs being modified, e.g. tablets being crushed or split or capsules being opened, to "tailor" them to the needs of individual older patients. These modifications can alter the pharmacological profile of the drug *in vivo* and consequently, the safety and efficacy of the medication. In addition, the potential legal implications of using a medication outside the terms of the product licence are an important consideration.

The research undertaken focused on the practical suitability of ODFs for older adults by investigating ODF modifications in an Irish setting. In order to comprehensively address this topic, a mixed methods approach was used for this thesis, which comprises: two systematic reviews (one quantitative and one

qualitative); two primary quantitative research studies and; two primary qualitative research studies. This introductory chapter will begin by providing a background to the research area which will highlight the rationale for, and the importance of, this research. Salient features of the Irish healthcare landscape will be detailed. Following this, the hypothesis underpinning the research will be described along with the overall aim of the thesis. The specific objectives defined to achieve this aim will be outlined. Based on the aim and objectives, the methodological approach utilised will be justified. Finally, a brief overview of the thesis will be provided.

1.2 Background

1.2.1 The ageing population

Providing medication for the growing older population is one of the most significant challenges facing the healthcare sector and optimising its use is complicated by many factors including, age-related physiological changes, non-adherence and cost. The ageing population profile is a global reality that has arisen due to a decline in birth rates coupled with an increase in life expectancy (1). In 2017, the global population aged 60 years and older, was estimated to be 962 million, a substantial increase from 382 million in 1980 (2). This trend in population ageing is set to continue worldwide with current estimates suggesting that the population aged 60 years and older will double to 2.1 billion by 2050, while the population aged 80 years and older is expected to triple from 137 million in 2017 to 425 million by 2050 (1, 2).

While the United Nations (UN) use 60 years to define the beginning of old age, in Ireland and other developed nations, the older population is generally considered to include those aged 65 years and older (3, 4). In Ireland, the 2016 Census found that there were 637,567 people aged 65 years and older, representing 13.4% of the total population (5). However, substantial growth is anticipated in the coming decades with projections suggesting that by 2046 there will be 1.4 million people aged 65 years and older (6). The expansion in the "very old" cohort (aged ≥80 years) will be even more dramatic, with estimates suggesting an increase from 128,000 in 2011 to 484,000 by 2046 (6).

Population ageing and the increase in life expectancy worldwide has been described as *"one of humanity's greatest triumphs"* (7). However, this success is accompanied by substantial challenges from socioeconomic and healthcare perspectives. A coherent, proactive, timely and co-ordinated approach to policy development and planning will be required to address the social, economic and healthcare implications brought about by this expansion in the older cohort. As highlighted by the World Health Organisation (WHO), consideration of the *"rights, needs, preferences and capacities of older people"* (7) is of particular importance to ensure that the challenges inherent in this triumph do not overwhelm the success story of population ageing. This approach will be critical in the healthcare sector, where, in the past, the requirements of older adults have often been neglected (8).

1.2.2 Healthcare utilisation amongst the older cohort

Understanding the needs, preferences and capacities of older adults from a healthcare perspective is vital given the significant pressures already placed on healthcare systems coupled with the increased demands that will be encountered by these already stretched systems due to the expansion of the older population.

1.2.2.1 Health service utilisation

The older cohort represents a heterogeneous population with significant inter-individual variability in health status and functional capacity. While chronological age alone is not a good predictor of health status or level of dependence of an older individual (7, 9), it is clear from the literature that the older population are the most frequent users of healthcare services at all levels of care provision (10-12).

In the acute care sector, managing acute exacerbations of chronic conditions, as well as treating acute, episodic illnesses experienced by older adults, contributes substantially to resource utilisation. Internationally, it is consistently demonstrated that the older cohort have the highest rates of hospitalisation (13, 14). Within the Irish context, in 2015, 52% of in-patient bed days and 39% of day cases in acute hospitals were used by patients aged ≥65 years (15). Given that of the €19.9 billion total healthcare expenditure, 35% is accounted for in the hospital sector, the financial implications of high rates of acute hospital utilisation become clear (16). Further insights into the costs specifically pertaining to the older cohort can be gained by examining the Case Mix Index (CMI) (17). Higher CMI scores indicate

increased complexity which in turn results in greater expenditure (17). Data from the Department of Health have shown that CMI inpatient activity scores ranged from 1.59 to 1.61 for patients aged 65 years and older in 2015 (17), compared to between 0.68 and 1.47 for individuals aged 15 to 64 years (17). Therefore, older patients are generally more complex and hence, more costly to treat than younger patients (17).

Higher rates of service utilisation are also evident in primary care, with national and international literature consistently demonstrating higher General Practitioner (GP) consultation rates amongst older adults (18-21). Research in Ireland has found that the average number of GP consultations for all individuals aged 15 years and older is 4.3 per year, however for older adults this rises to 7.1 consultations per annum (22).

As the population continues to age, the demand for long-term care (LTC) is likely to grow. In 2015, across "Organisation for Economic Co-operation and Development" (OECD) countries, government spending on LTC provision accounted for 1.7% of the gross domestic product (GDP) (23). However, by 2060, this figure is expected to double (23). In 2016, 22,762 people aged ≥65 years in Ireland (3.7% of the older population) were resident in nursing homes, an increase of 9.4% since 2011 (24). The nursing home sector in Ireland includes public, private and voluntary nursing homes which differ based on their funding and governance structures (25).

However, regardless of the type of nursing home, all those requiring long-term nursing home care are entitled to apply for financial support from the Government's Nursing Homes Support Scheme (NHSS), more commonly known as the "Fair Deal" scheme. This scheme was introduced in 2009 with the aim of facilitating access to long-term residential care for those in need. Under this means tested scheme, individual residents make a contribution to their care (80% of disposable income and 7.5% of the value of any assets per annum), with the outstanding balance paid by the State (26). In 2016, 23,002 people received support under the NHSS, with the majority (70.5%) aged 80 years and older (27). During this time, the total expenditure on care provision for NHSS clients was €1.26 billion (€921 million from exchequer funding and €337 million from client contributions), an increase from €1.17 billion in 2014 (27). The demand for LTC beds is projected to increase by 40% by 2030 (28), again highlighting the challenges faced by the healthcare system in meeting the needs of the older population.

It is clear that the high rates of health service utilisation by the older cohort present significant challenges for the healthcare sector from both capacity and expenditure perspectives. Age-related changes in the prevalence of disease are a key factor driving this utilisation. The prevalence of chronic disease increases with age (10, 29). A study involving a group of community-dwelling older adults conducted as part of "The Irish Longitudinal Study on Ageing" (TILDA) found that participants had a median of three doctor diagnosed chronic conditions (30). Similarly, the Health Service Executive (HSE) estimated that in 2016, 542,400 people aged ≥65 years in

Ireland had at least one chronic disease, while 404,470 (65%) had two or more chronic illnesses (31). Multimorbidity, defined as the co-existence of two or more chronic diseases, has been shown to increase substantially with age (32-36), and is associated with increased healthcare utilisation rates and expenditure (37-39). Healthcare systems have traditionally focused on specialisation and disease-specific treatment approaches (40-42). This has been reflected in the organisation and delivery of healthcare, and the education of healthcare professionals. Clinical practice guidelines are generally developed based on the management and treatment of single diseases in isolation and therefore, are of limited use for healthcare professionals managing multi-morbid patients (40, 42-46). Therefore, providing holistic, person-centred and evidence-based care to the growing cohort of multi-morbid older adults is a challenge that healthcare systems must address, particularly in light of findings that healthcare professionals have reported feeling ill-equipped and unsure of how to manage these multi-morbid patients (47, 48).

1.2.2.2 Medication utilisation

As a consequence of the high prevalence of chronic illness and multimorbidity, older adults are the highest consumers of prescription medications. It has been estimated that, despite accounting for only 12-18% of the population of developed countries, people aged 60 years and over consume approximately 50% of all prescribed medicines and are responsible for 60% of medication related costs (49). Studies investigating medication usage amongst older Irish patients have shown that community-dwelling older adults are prescribed a median of 5 to 6 regular

medications (30, 50), whilst those in nursing homes are prescribed a median of 8 (51, 52).

In Ireland, payment for medications is provided through a number of drug schemes, the most significant of which, from a cost perspective, is the General Medical Services (GMS) Scheme. Within the GMS or "medical card" scheme, eligible individuals are entitled to free GP care and pay a co-payment for prescription medicines (currently €2 per item up to a maximum of €20 per family, per calendar month) (53). Eligibility for this scheme is based on means testing (54). Previously, individuals aged 70 years and older were automatically entitled to a medical card regardless of income (55). This automatic entitlement was removed on the 1st of January 2009 (55), however the income thresholds differ for those aged <70 years compared to those aged ≥70 years (56). In 2016, 35.4% of the Irish population were covered on the GMS scheme, with individuals aged ≥65 years accounting for 25.7% of the total GMS population (57).

In 2016, of the €1,343.3 million paid to pharmacists under the community drugs schemes, €1,026.7 million related to the GMS scheme (57). In total, the average pharmacy cost paid by the Government for a GMS patient per year was €613.67 (57). However, the average pharmacy cost was substantially higher for older patients than younger patients as outlined in Table 1.1. Therefore, it is clear that

the high rates of medication use amongst the older cohort have significant economic implications.

Table 1.1 Average pharmacy cost per GMS eligible person

Age Group	Average Cost per Eligible Person (€)
<5 years	118.08
5-11 years	77.95
12-15 years	81.38
16-24 years	167.27
25-34 years	287.04
35-44 years	371.62
45-54 years	566.20
55-64 years	892.25
65-69 years	1,074.60
70-74 years	1,169.52
≥75 years	1,594.47
All Eligible Persons	613.67

Adapted from: Primary Care Reimbursement Service Statistical Analysis of Claims and Payments 2016 (57)

1.2.3 Age-related changes complicate medication use

Given the high rates of medication utilisation, combined with the projected expansion of the older cohort, it is unsurprising that much research in the medical and pharmacy fields has focused on optimising medication use for older adults. The impetus for this research has also been driven by the fact that due to age-related physiological, pharmacokinetic and pharmacodynamic changes, older adults are particularly susceptible to medication related problems including drug-drug

interactions, drug-disease interactions and adverse drug reactions (58, 59). The National Institute for Health and Care Excellence (NICE) in the United Kingdom (UK) has defined "Medicines Optimisation" as: "*A person-centred approach to safe and effective medicines use, to ensure people obtain the best possible outcomes from their medicines"* (60). Medicines optimisation has also been defined as: *"The process by which healthcare professionals engage with individual patients to understand their views, opinions and beliefs, to share their clinical and medicines knowledge so that the most appropriate evidence based care for each individual can be agreed,"* (61) or simply, "*engaging with individual patients to get their medicines right for them*" (61). Ensuring that medication meets the unique needs of the individual patient is a key component of medicines optimisation (61).

To date, medicines optimisation research has focused on inappropriate prescribing and selecting the most clinically appropriate drugs to reduce adverse outcomes. Significant improvements have been seen, with Moriarty *et al.* (62) reporting that despite an increase in polypharmacy, the quality of prescribing for older adults in Ireland has improved, with a 60% decrease in the risk of potentially inappropriate prescribing. While selecting the most clinically appropriate drug is a vital first step in the medicines optimisation process, other important considerations, including the practical suitability of the medication, have been neglected in research and practice. There is growing awareness that commercial dosage forms can prove problematic and unacceptable for older adults (8, 63, 64). This thesis investigates if oral medicines are meeting the needs of older adults at a practical level as a

number of age-related changes can complicate ODF administration and may result in ODFs being modified to tailor them to individual patient's needs.

1.2.3.1 Oral dosage forms

The oral route of drug administration is preferred as it is the simplest, most convenient and safest route of drug administration (65). There are a wide variety of ODFs available but the most popular, from a patient and healthcare professional perspective, are solid ODFs i.e. tablets and capsules. Solid ODFs are preferred as they are convenient and safe dosage forms that facilitate accurate drug dosing, in an easy to administer formulation that ensures the chemical and physical stability of the drug (65). Tablets and capsules also offer advantages for the pharmaceutical industry as they can be mass produced using well-defined and controlled procedures to produce dosage forms of consistent quality at comparatively low price (65). However, for some patients, ODFs and the one-size-fits-all approach may prove problematic. This may result in ODFs being modified, which has previously been defined by Richey *et al.* (66) as, "*any alteration of an oral dosage form that can be performed at the point of administration*"(66). This definition will also be used to describe modifications throughout this thesis.

1.2.3.2 ODF modifications for swallowing difficulties

The first step in the administration of ODFs involves the patient swallowing the dosage form so that it passes safely from the oral cavity into the stomach via the oesophagus. Swallowing is a complex mechanism that involves the coordinated

action of more than 30 nerves and muscles (67). Swallowing centres in the brainstem coordinate the action of muscles in the mouth, pharynx, larynx and oesophagus during the swallowing process. These swallowing centres in the brainstem receive sensory input from afferent cranial nerves, while modulatory input is received from higher centres in the brain (68). The physiology of a normal swallow is divided into three distinct phases: (i) the oral phase; (ii) the pharyngeal phase and; (iii) the oesophageal phase (67, 68). The oral phase is the volitional component of the swallow and involves the formation of a suitable bolus and the transfer of this bolus into the pharynx (67). During the pharyngeal phase, the bolus is propelled through the pharynx into the oesophagus via the upper oesophageal sphincter. This is a reflex (involuntary) action that occurs rapidly, in less than one second (67, 69). During the pharyngeal phase, the epiglottis covers the larynx to protect the airway (67). The oral and nasal cavities are also sealed off to prevent regurgitation of the bolus (67, 70). The oesophageal phase begins when the bolus passes through the upper oesophageal sphincter and the peristaltic wave carries the bolus through the oesophagus and the lower oesophageal sphincter into the stomach (71).

Ageing is associated with natural alterations in the anatomic, physiological, neural, motoric and sensory mechanisms that underpin swallowing (63, 67, 72). These age-related changes are evident in all three phases of deglutition and include: decreased isometric tongue pressure, reduction in muscle mass and strength, reduced receptor density and responsiveness, decreased pharyngeal sensation,

prolongation of the oropharyngeal swallowing phase, slow bolus velocity and prolongation of the time for upper oesophageal sphincter relaxation (63, 68, 70, 73). Presbyphagia is the term used to describe these characteristic changes in the swallowing mechanism of otherwise healthy older adults (63, 72, 73). These changes are not inherently pathological and, in isolation do not result in any clinically relevant swallowing impairment (63). However, presbyphagia reduces the functional swallowing reserve which partly explains why older adults are at increased risk of developing dysphagia (difficulty swallowing) (72, 73). In addition, dysphagia is a common co-morbidity associated with many age-related diseases and many of the medications prescribed to older adults can disrupt the swallowing function by: (i) causing xerostomia, (ii) directly damaging the oesophagus or; (iii) dysphagia may arise as an adverse effect associated with the pharmacological action of the drug (63, 72). Therefore, the presence of these additional risk factors for dysphagia can ultimately affect the swallow beyond the normal effects of ageing, which accounts for the observation that older adults are more likely to experience dysphagia than the general population. Table 1.2 summarises some of the common age-related diseases and medication classes that are frequently implicated in the development of dysphagia and swallowing disorders amongst older adults (63, 68, 71). Whilst the prevalence of dysphagia is known to increase with age (67), it has also been shown that amongst the older population, the prevalence of dysphagia increases with increased levels of care (63). It is estimated that between 11% and 33% of community-dwelling, independently-living older adults experience dysphagia (74-78) compared to between 31% and 68% of nursing home residents (67, 79-81).

Table 1.2 Age-related medical conditions and drug classes that contribute to dysphagia (63, 68, 71)

Medical Conditions with Dysphagia as a Co-morbidity (list not exhaustive)		
Neurological Disorders	**Musculoskeletal**	**Neoplastic**
Stroke	Myasthenia gravis	Brain tumours
Alzheimer's Disease	Connective tissue disease	Neck tumours
Parkinson's Disease	Osteoarthritis	Oropharyngeal tumours
Motor Neurone Disease	Sarcoidosis	
Drug Classes that can Impair Swallowing Function (list not exhaustive)		
Drug classes associated with xerostomia	**Drug classes associated with oesophagitis**	**Drug classes with dysphagia as a complication**
Anticholinergics	Bisphosphonates	Analgesics
Antidepressants	Iron salts	Anticholinergics
Antipsychotics	Non-steroidal anti-inflammatory drugs	Antipsychotics
Diuretics	Tetracycline antibiotics	Cytotoxics

Dysphagia complicates the administration of medicines to older adults (63) and the use of solid ODFs in patients with dysphagia has been shown to increase the risk of penetration and aspiration (82). Therefore, in order to overcome the challenges associated with administering medication to patients with dysphagia, ODFs may be modified.

Swallowing medication is a learned response, accounting for the difficulties often experienced by children and adolescents (83). Adults may also report difficulty swallowing medication in the absence of objective evidence of swallowing

dysfunction. ODFs may be modified to overcome the difficulty experienced by these individuals. Reports on the prevalence of difficulty swallowing ODFs vary. It has been reported that between 9 and 60% of community-dwelling adult patients experience difficulty swallowing ODFs (84-87). There is a paucity of data from an Irish setting and data specifically pertaining to the older cohort. However, it is highlighted by these studies that, of those who experience difficulty swallowing medication, between 27% and 68% modify medicines to facilitate intake (84-87). Therefore, it is clear that individuals who find it difficult to take oral medicines frequently resort to modifying ODFs. Given the increased prevalence of both dysphagia and polypharmacy with increased age (67, 88), it is anticipated that difficulty swallowing ODFs is likely to be a substantial issue amongst older adults, which is a significant cause for concern.

1.2.3.3 ODF modifications for fractional dosing

Selecting and administering the correct dose of a medication is vital to optimise therapeutic outcomes and minimise adverse events. Dosing requirements for older adults, however, are complicated by age-related physiological changes that alter the pharmacokinetic and pharmacodynamic properties of medicines. The magnitude of the effect that a drug elicits in the body is dependent on: (i) the concentration of the drug at the site of action; (ii) the number of receptors and their affinity for the drug at the site of action; (iii) signal transduction mechanisms and; (iv) homeostatic regulation (89, 90). Pharmacokinetics relates to the rate and extent of drug absorption, distribution, metabolism and excretion. Age-related

pharmacokinetic changes result in altered drug concentrations at the site of action, which has implications for both therapeutic and adverse effects (90). Table 1.3 summarises some common age-related pharmacokinetic changes and the potential effect of these changes on various drugs (89-94).

Table 1.3 Age-related pharmacokinetic changes (89-94)

Stage	Age-Related Change	Potential Effect	Drug Examples
Absorption	↓ Gastric motility	↓ Rate of absorption	Digoxin, Allopurinol
	↓ Carrier-mediated transport	↓ Extent of absorption	Calcium, Iron, Vitamins
Distribution	↓ Total body water	↑ Plasma concentration of hydrophilic drugs	Digoxin, Theophylline
	↑ Body fat	↑ Half-life of lipophilic drugs	Diazepam, Amiodarone
	↓ Plasma albumin levels	↑ Concentration of unbound acidic drugs	Coumarins, Phenytoin
Metabolism	↓ First Pass Metabolism (FPM)	↑ Plasma concentration of drugs that undergo extensive FPM	Propranolol, Verapamil, Nifedipine
		↓ Bioavailability of pro-drugs that require FPM for activation	Enalapril, Perindopril
	↓ Phase I metabolism	↓ Metabolic clearance	Amitriptyline, Lidocaine
Excretion	↓ Renal blood flow	↓ Clearance and ↑ plasma concentration of renally eliminated drugs	Diuretics, Digoxin, Lithium, Aminoglycosides
	↓ Glomerular Filtration Rate		
	↓ Tubular secretion		

Legend: FPM = First Pass Metabolism

Pharmacodynamics relates to the action or effect that a drug elicits in the body. Age-related pharmacodynamic changes are associated with altered sensitivity to drugs and arise due to alterations in receptors, signal transduction or homeostatic mechanisms (92). Whilst the clinical implications of age-related pharmacodynamic changes are often more difficult to predict than the pharmacokinetic changes, numerous examples have been documented in the literature (Table 1.4) (89, 90, 92, 94).

Table 1.4 Clinical implications of age-related pharmacodynamic changes (89, 90, 92, 94)

Drug/ Drug Class	Effect of Pharmacodynamic Change	Mechanism of Pharmacodynamic Change
Benzodiazepines	↑ Central Nervous System (CNS) sensitivity including sedation, confusion, falls etc.	Receptor changes: changes in $GABA_A$-benzodiazepine receptor complex number and composition
Sulfonylureas	↑ Risk of hypoglycaemia	Homeostatic mechanisms: age-dependent impairment of glucose counter-regulation
Antihypertensives/ Diuretics	↑ Risk of postural hypotension	Homeostatic mechanisms: ↓ Baroreceptor reflex sensitivity and responsiveness
Antipsychotics	↑ Risk of extrapyramidal symptoms ↑ Risk of anticholinergic effects	Homeostatic mechanisms: Age-related ↓ in dopamine content in CNS Age-related ↓ in acetylcholine content in CNS

Legend: CNS = Central Nervous System; GABA = *gamma*-Aminobutyric acid.

Therefore, when prescribing medication for older adults, clinicians need to be cognisant of the potential for altered responses to medications due to changes in the pharmacokinetic profile of the drug or due to alterations in pharmacodynamic

properties. As a result, a policy of “start low and go slow” is commonly advocated when using medication in the older patient. However, as highlighted by Rochon *et al.* (95), this can prove challenging when using commercially available solid ODFs. These ODFs are routinely marketed based on the results of clinical trials that exclude older patients and therefore, the appropriate dose may not be available, or indeed, the evidence-base for the optimal dose in the older cohort may be absent. Therefore, in practice, when pursuing a policy of “start low and go slow” in an attempt to meet the unique dosing requirements of older adults, fractional dosing may be required (e.g. administration of half or quarter of a tablet).

While for the reasons outlined above, fractional dosing may be routinely required, there are limited data on the prevalence of this practice, particularly in the older cohort. Studies conducted in community settings in Germany, the Netherlands and Sweden have suggested that between 10% and 31% of prescribed tablets are required to be split (96-98). These studies investigated tablet splitting in the general adult population and did not provide data on tablet splitting specifically for older adults (96-98). A Taiwanese study reported that 36% of prescriptions for narrow therapeutic index (NTI) drugs involved tablets being split, and stated that the prevalence of fractional dosing was high for older patients, particularly for digoxin and warfarin (99). One of the few studies specifically investigating fractional dosing in an older cohort, undertaken by Fischbach *et al.* (100) in a Canadian nursing home setting, found that 35% of all residents received at least one split tablet. Of the 157 medications split, psychotropic medications (36.3%) were modified most

commonly, followed by cardiovascular medications (19.1%). A study conducted in a geriatric outpatients department in Brazil found that 35% of patients with dementia required fractionally dosed medicines compared to 24% of patients without dementia (101). There are no data on ODF modifications for fractional dosing in an Irish setting, for either the general adult population or the older cohort specifically.

1.2.3.4 Implications of modifications

For the reasons outlined previously, ODFs may need to be modified to meet the needs of older adults. These modifications may include: cutting or splitting tablets, crushing or grinding tablets, opening capsules or mixing the medication with food or liquid. While the intention underlying these modifications, to tailor the dosage form to meet the needs of the patient, is admirable, there are numerous potential consequences of modifications that are a cause for concern. ODFs are becoming increasingly complex with the dosage form controlling factors including the rate, extent and site of drug release and absorption as well as drug stability, both in the dosage form and the gastrointestinal tract (65). Therefore, there are potential clinical implications associated with modifications for either fractional dosing or swallowing difficulties. In addition, there are a number of legal and ethical considerations which healthcare professionals should be cognisant of, prior to authorising or undertaking any modifications.

1.2.3.4.1 Modifications for difficulty swallowing

ODF modifications that are undertaken to facilitate administration to individuals with difficulty swallowing the intact dosage form include tablet crushing, splitting, or chewing, capsule opening, mixing medication with food or dispersing in liquid. Modifications such as these have been reported in community, long-term and acute-care settings (84-87, 102, 103). However, various commentators have highlighted potential concerns around ODF modifications including: the risk posed to healthcare professionals and carers due to exposure to powdered drug substances; drug instability; the potential for altered pharmacokinetic profiles and hence changes in drug bioavailability; oesophageal or gastric irritation; inaccurate drug dosing due to drug loss and; impact on palatability (104). The likelihood that modifying a dosage form can potentially lead to harmful outcomes depends on numerous factors including: the method of modification used; the characteristics of the dosage form and; the therapeutic index of the drug. As a result, it can be difficult to make general recommendations around ODF modifications. However, it is widely acknowledged that certain classes of medications and dosage forms should never be altered. For example, it is generally advised that carcinogenic, teratogenic, hormonal and steroidal products should not be modified due to the potential risk posed to carers by exposure to aerosolized drug particles. Table 1.5 describes some commonly used dosage form types and the reasons that they should not be modified (104, 105).

Table 1.5 Examples of drug classes that should not be modified

Dosage Form Type	Potential Consequence of Modification	Examples
Enteric coated formulations	Drug degradation or inactivation in the gastric acid and therefore diminished therapeutic efficacy	Acid-labile drugs e.g. omeprazole, pancreatic enzymes
	Stomach or oesophageal irritation	Corticosteroids, non-steroidal anti-inflammatory drugs e.g. diclofenac, aspirin
	Premature drug release resulting in lower drug concentrations at site of action and reduced efficacy	Drugs intended to be released at specific location in the gastrointestinal tract e.g. sulfasalazine
Extended release formulations	Altered drug release and hence absorption *in vivo* resulting in possible over dosing and toxicity initially followed by under dosing and loss of therapeutic efficacy	Extended release carbamazepine, verapamil, opioid analgesics
Some film or sugar coated drugs	Drug instability	Photosensitive drugs e.g. nifedipine
	Palatability issues	Bitter tasting drugs e.g. ciprofloxacin

For the categories of dosage forms mentioned above, healthcare professionals are generally cognisant of the need to administer these formulations whole. However, for other dosage forms, there can be ambiguity around whether modifications will have any unintended, negative clinical consequences. The need for healthcare professionals to be alert to the potential risks associated with ODF modification is highlighted in the case reported by Schier *et al.* (106) in which a fatality arose due

to the inappropriate crushing of an extended release formulation of nifedipine, prior to administration to a patient in hospital. There are numerous studies in the scientific literature reporting on the impact of crushing tablets or opening capsules on *in vitro* dissolution profiles (107-110) or *in vivo* pharmacokinetic behaviour (109-113). The results of these studies highlight the variable effect of ODF modifications, for example, Song *et al.* (111) showed that apixaban tablets can be administered whole or crushed in either water or apple sauce with no difference in bioequivalence observed. In contrast, Cattaneo *et al.* (110) found significant differences in both *in vitro* dissolution behaviour and *in vivo* pharmacokinetic profiles between whole raltegravir tablets and modified (crushed or chewed) tablets.

When ODFs are modified to overcome swallowing difficulties they are frequently mixed with food or liquid to facilitate administration. The potential for the administration vehicle to affect the pharmacokinetic properties of the drug *in vivo* must also be considered. Drug-food interactions can potentially affect drug absorption e.g. calcium interferes with the absorption of quinolone antibiotics, therefore it is recommended not to take milk or dairy products for two hours before or after ingestion of ciprofloxacin (114). A number of studies have investigated the *in vitro* effects of administering modified medicines in food on drug stability, disintegration and dissolution characteristics (107, 108). Both Carrier *et al.* (107) and Wells and Losin (108) found that certain vehicles negatively impacted on the stability and dissolution profile of medication, which could potentially alter drug

action *in vivo*. In general, most medicines are designed to be administered with water. Older adults with swallowing difficulties are often prescribed thickened fluids in order to minimise the risk of aspiration. This has led to interest in the use of thickened fluids for administering medication to patients with dysphagia. However, recent literature reports have demonstrated that the administration of modified medicines in thickened liquids can alter the dissolution characteristics of some medications (115, 116).

Depending on the ODF and the administration vehicle used, modifying an ODF can potentially impact on drug release and absorption *in vivo*, which could potentially impact on therapeutic outcomes. In addition, Thong *et al.* (117) recently highlighted that the type of crushing device used could affect the amount of the active ingredient that can be delivered to the patient, which has obvious implications for dosing accuracy and therapeutic effect.

In addition to the pharmacological concerns, the palatability and acceptability of modified ODFs from patient and carer perspectives must also be considered. The taste of modified medicines can be an issue that affects patient acceptance and adherence. Recent literature reports have highlighted that modifications often result in bitter or poor tasting formulations (118, 119). Greater consideration is being given to the palatability of medicines, particularly for paediatric patients (120), however for the older population the issue of palatability tends be neglected.

ODF modifications may, in addition, be difficult for older adults or carers to perform given the requirement for manual dexterity, visual acuity and knowledge around performing the modification. These factors are of importance when considering the appropriateness of ODFs and ODF modifications for older adults.

1.2.3.4.2 Modifications for fractional dosing

Modifications of ODFs for fractional dosing generally involve the administration of half or quarter of a tablet. Numerous methods of modification are used including commercial pill splitting devices, manual splitting by hand, using a knife or, getting a pharmacy to split a medication in advance, with both scored and unscored tablets reportedly being split (96, 121). The most significant concern is that the dose the patient receives may not be accurate. Studies investigating the accuracy of tablet splitting are numerous (122-127), however the results vary considerably, complicating the interpretation of the clinical implications of these findings (Table 1.6). Initially, studies used the weight of split tablets as a surrogate indicator of dosing accuracy (122-126), however later studies used adapted United States Pharmacopoeia (USP) or European Pharmacopoeia (Ph.Eur) tests for uniformity of dosage units to evaluate the accuracy of tablet splitting (123, 124). Extrapolating uniformity of weight data to infer uniformity of drug content and hence dosing accuracy assumes that the active ingredient is homogenously distributed throughout the dosage form. However, this is often not the case, as demonstrated by Zhao *et al.* (128). To address this, a number of studies have sought to determine

whether tablet fractions contain the desired amount of active ingredient (127, 129, 130).

Table 1.6 Summary of studies investigating the accuracy of fractional dosing

Study	Medication	Method of Modification	Method of Evaluation	Criteria	Findings
McDevitt *et al.* (122)	Hydrochlorothiazide	Manually split by hand (n=876 tablets) Tablet splitter (n=51 tablets) 94 healthy volunteers	Variation from ideal weight	N/A	Manually split tablets: 41.3% of tablet halves deviated from ideal weight by more than 10% and 12.4% deviated by more than 20% Tablet splitter: 37.3% deviated from ideal weight by more than 10%
Peek *et al.* (125)	Warfarin, Lisinopril, Metoprolol, Simvastatin	2 tablet splitters 30 men aged ≥50 years	Deviation from expected weight	N/A	Doses deviated by between 9 and 37% from the intended dose
Verrue *et al.* (126)	Warfarin, Digoxin, Metformin, Levodopa and Carbidopa, Fenprocoumon, Spironolactone, Methylprednisolone, Lisinopril	3 methods of modification used: tablet splitter; hand-splitting for scored and scissors for unscored tablets and; a kitchen knife 5 volunteers	Deviation from theoretical weight	N/A	Deviations from expected weights ranged from 5.5% to 18.9%

Study	Medication	Method of Modification	Method of Evaluation	Criteria	Findings
Polli *et al.* (123)	Atorvastatin, Citalopram, Furosemide, Glipizide, Metoprolol, Paroxetine, Sertraline, Warfarin, Lisinopril, Lovastatin, Rofecoxib, Simvastatin	Tablet splitter Trained pharmacy student	Weight Uniformity	Adapted USP Test for Uniformity of Dosage Units	Eight products passed: atorvastatin, citalopram, furosemide, glipizide, metoprolol, paroxetine, sertraline and warfarin Four products failed: lisinopril, lovastatin, rofecoxib and simvastatin
Rosenberg *et al.* (124)	22 prescriptions returned unused from long term care facilities	Method unknown Pharmacists	Weight Uniformity	Adapted USP criteria	Seven dispensed prescriptions (31.8%) met adapted weight uniformity standards
Hill *et al.* (127)	Warfarin, Simvastatin, Metoprolol succinate, Metoprolol tartrate, Citalopram and Lisinopril	Tablet splitter Pharmacy students	Weight uniformity and drug content	Adapted USP specifications	23.9% of tablet halves differed from sample mean values for drug content by more than specification limits

Study	Medication	Method of Modification	Method of Evaluation	Criteria	Findings
Helmy (129)	16 medications	A knife 5 volunteers (2 men and 3 women; aged 25-44 years)	Weight and content uniformity	Adapted USP specifications	16.2% fell outside weight limits, 15.0% fell outside content uniformity specifications and overall 6 medicines failed the test.
Zaid (130)	Lorazepam	Method unknown	Weight variation and drug content	Adapted Ph.Eur Tests for Uniformity of Mass and Uniformity of Content	Split lorazepam tablets met the adapted Ph.Eur criteria

Whilst numerous studies have investigated the potential impact of fractional dosing on uniformity of weight or content, there is limited evidence on the effect of fractional dosing on clinical outcomes. Three studies investigated the effect of a tablet splitting programme for statins on clinical laboratory measurements and in all three studies no clinically relevant differences in lipid parameters were observed between split tablet dosing and whole tablet dosing (131-133). Similarly, Rindone *et al.* (134) conducted a randomized crossover trial which found no significant differences in blood pressure when taking a full tablet of lisinopril compared to fractional dosing to provide an equivalent dose of anti-hypertensive.

The studies on uniformity of weight and content for split tablets have demonstrated equivocal results (Table 1.6). Although the number of studies is limited, fractional dosing was not shown to adversely affect clinical outcomes in the four studies that investigated the short-term impact of fractional dosing (131-134). Given the ambiguity of the literature findings, it is unsurprising that debate exists around the appropriateness of modifying medicines for fractional dosing, with some authors advising that it is of limited clinical consequence or only of concern for NTI drugs while others advise caution (135-137). Various factors have been shown to impact the accuracy of fractional dosing. The method of modification used affects the dosing accuracy with splitting devices performing better than manual splitting by hand (138), while some tablet splitters performed better than others (125). Dosage form related factors play a role including: the shape of the tablet (123, 125); presence or absence of a score line (127); depth of the score line

(139) and; tablet hardness (123). Patient-related factors that have been shown to influence the accuracy of fractional dosing include: whether training or instructions were provided (125) and; the age of the patient, with older patients in particular experiencing difficulty (140). In addition, the clinical relevance of any potential alteration in the accuracy of dosing may be influenced by the therapeutic range of the medication, the half-life of the drug and whether the medication is for acute or chronic use (135-137). The sheer number of variables that can play a role makes the provision of guidelines and general recommendations in this area difficult.

Another issue that must be considered is the acceptability of fractional dosing from a patient perspective as well as the ability of patients to perform modifications. Again, results vary with some studies reporting that patients experienced difficulty when breaking tablets (134, 141, 142) and found that tablets did not break evenly (121, 134, 141, 142), whilst other patients found tablet splitting to be acceptable and satisfactory (131).

1.2.3.4.3 General considerations around modifications

For healthcare professionals who prescribe, dispense or administer modified ODFs, the legal implications of the modification must also be considered. In order to have a medication placed on the market, pharmaceutical companies must apply for a marketing authorisation from a relevant competent authority: the Health Products Regulatory Authority (HPRA) for Ireland or; the European Medicines Agency (EMA)

for the European Union (EU) (143). During this process, the regulatory authorities evaluate whether the product meets the necessary standards of quality, safety and efficacy. The Summary of Product Characteristics (SPC) is an integral part of the application and contains essential information about the licensed use of the medicine: including details on the therapeutic indication, dose, contra-indications and method of administration. Any use of a product outside of the terms of the marketing authorisation is considered an "off-label" use of the medication (144). Therefore, unless a modification or a dose is expressly authorised in the SPC, it is considered an "off-label" use (145). The significance of this is that the pharmaceutical company do not bear any responsibility for harm that arises due to the off-label use of a medication, and the healthcare professionals bear responsibility for any adverse events that may occur (146). Off-label use of medication is a reality in paediatric (147), adult (148) and geriatric (149) medicine, however healthcare professionals must be aware of their legal responsibilities when prescribing, dispensing and administering modified medicines (104, 146). In particular, for pharmacists and nurses it is important to note that in the Republic of Ireland, only a registered medical practitioner, a registered dentist or a registered nurse prescriber can authorise an off-label use of a medication (104, 146).

1.2.4 Guidelines on medicine administration and medicine modification

Guidelines on medicine administration are issued by healthcare agencies and professional regulatory bodies. In addition, most healthcare settings, whether they provide acute or long-term care, have institution specific policies and protocols on

medicine administration, many of which provide direction on medicine modification.

An Bord Altranais agus Cnáimhseachais na hÉireann, also known as the Nursing and Midwifery Board of Ireland (NMBI), regulate the nursing and midwifery professions in Ireland. In 2007, the NMBI published guidance for their members on medication management which is applicable in all healthcare settings where nurses administer medication (150). In addition, the Health Information and Quality Authority (HIQA), an independent authority which develops standards for health and social care services in Ireland, published Medicines Management Guidance in 2015 which applies to providers of residential care services for older people and for children and adults with disabilities (151). The administration of modified medications is addressed in both publications with comparable recommendations provided in each (150, 151). These guidance documents highlight that if a medicine is modified and this modification is not authorised in the SPC, the medication has been used outside the terms of the product licence. It is advised that if a modification is required to facilitate administration to a patient, the medical practitioner and pharmacist should be contacted to discuss whether alternative preparations or forms of administration would be suitable for the patient. If following consultation it is deemed necessary to modify the medication, it must be authorised by the medical practitioner on the patient's medication chart or prescription sheet and appropriate advice should be sought from the pharmacist prior to modifying any medication (150, 151). Comparable guidance has been issued by regulatory bodies

in other jurisdictions (152, 153). These guidance documents recognise the key role of the pharmacist, recommending that a pharmacist's advice should be sought regarding the appropriateness of ODF modification. These guidance documents serve as the basis for the development of institution-specific policies and protocols on medicine administration and modification.

Whilst these guidance documents address ODF modifications in a generic manner, specific guidance on medicine modification is limited. Wright *et al.* (104) have published a consensus guideline on medicine administration to adult patients with swallowing difficulties which provides an algorithm to support decision making around medication use for such patients. It also details important points to consider in relation to ODF modifications including the potential for altered pharmacological effects, drug stability concerns, the potential risk associated with unintended exposure to healthcare staff and other patients etc. (104). In addition, various bodies including the UK Medicines Information Service of the National Health Service (NHS) have also issued general guidance on ODF modifications with a particular emphasis on types of ODFs that should not be modified e.g. modified release preparations or enteric coated formulations (154, 155). However, these documents do not provide specific recommendations for individual drug products or formulations. A variety of information sources are used by healthcare professionals when seeking information about the appropriateness of modifying specific drug formulations including consultation with peers or other healthcare professionals or the use of reference sources (156-158). Reference sources that

provide drug-specific recommendations include the SPC for the product, the NEWT Guidelines for Administration of Medication to Patients with Enteral Feeding Tubes or Swallowing Difficulties (159), the Handbook of Drug Administration via Enteral Feeding Tubes (160), The Australian Don't Rush to Crush Handbook (161) and organisation-specific "do not crush" lists. The reference source used depends on custom, practice and jurisdiction. While numerous references are available, many studies have shown that healthcare professionals are unsure what drug-specific information sources are available and where they can be found leading to substantial concerns about undertaking modifications (156, 157). In addition, it is important to note that any recommendation in a resource other than the SPC still represents an off-label use of the medication.

1.2.5 Regulatory perspective

Ensuring the dose and formulation suitability of medications is an issue of importance for all consumers of medication and as a consequence, a number of International Conference on Harmonisation (ICH) Guidelines address these topics (162, 163). The critical importance of considering formulation suitability in the drug development process is acknowledged in the ICH Q8 guideline which states, "*in all cases the product should be designed to meet patients' needs*", and that the choice of dosage form must be justified, "*The Pharmaceutical Development section should describe the knowledge that establishes that the type of dosage form selected and the formulation proposed are suitable for the intended use*" (162). The issue of dose suitability is addressed in the ICH E4 guideline which specifies that the impact of

age on the dose and dose-response should be assessed during the drug development process (163).

Whilst these guidelines highlight the importance of considering dose and formulation suitability in drug development (162, 163), no specific reference is made to the older adult. However, in recent years the need for patient-centric, age-appropriate dosage form development to meet the needs of older adults is increasingly being acknowledged (164-168). This has led regulatory agencies to reflect on whether the regulatory environment supports the development, approval and use of medications for this cohort. This growing awareness amongst the regulatory community of the unique needs of the older cohort can be traced back to 1993, when the ICH published a guideline, "Studies in support of special populations: geriatrics E7", which were adopted by regulatory agencies in Europe, the United States of America (USA) and Japan (169). This guideline highlighted that participants enrolled in clinical trials should be representative of the patient population that will be treated with the drug in clinical practice and as such, sought to encourage the inclusion of older patients in clinical trials (169). However, this guideline did not discuss the practical suitability of dosage forms for older adults nor did it require dose-response studies to be conducted for the older cohort unless the drug had effects on the CNS or if analyses indicated a potential for clinically significant, age-related differences in the effectiveness or adverse effect profile that could not be explained by age-related pharmacokinetic differences alone. Despite the adoption of this guideline, repeated commentators have voiced concern about

the sub-optimal inclusion of older adults in clinical trials (170, 171). The ICH E7 Guidelines were subject to a review and a supplementary Questions and Answers document was published in 2010, which reiterated the importance of ensuring appropriate representation of older patients in clinical trials and encouraged the inclusion of older patients from the entire age-range, including those with co-morbidities and concomitant therapies (172). Whilst the concept paper for this addendum raised the issue of difficulties with pill ingestion and dose adjustment and suggested that, *"the development of galenical formulations that facilitate the dose adjustment and enable both the patients and the carers to reduce the risk of medication errors and to improve compliance could also be considered"* (173), the subsequent Questions and Answers document made no reference to these issues (172).

The EMA in particular, has taken several steps to ensure that the needs of the older cohort are considered in the development and evaluation of new medicines with the publication in 2011 of the Geriatric Medicines Strategy (64). In this Strategy, the EMA stated their overall vision for geriatric medicines and their two key aims of: (i) ensuring that the medicines used by older patients are of high quality, and appropriately researched and evaluated, throughout the lifecycle of the product, for use in this population and; (ii) improving the availability of information on the use of medicines for older people, thereby helping informed prescription (64). In August 2017, the EMA further strengthened their commitment to encouraging the development of age-appropriate medicines with the publication, for public

consultation, of a reflection paper on the pharmaceutical development of medicines for use in the older population (174). This reflection paper discusses many factors that can affect the acceptability and suitability of medicines for older adults including the route of administration and dosage form choice, dosing frequency, container closure systems etc. (174). The key issues under consideration in this thesis, the modification of ODFs to facilitate administration due to difficulty swallowing or for fractional dosing, are described as being important factors that should be considered in the development of medications for older adults (174). At present, this document is a reflection paper however, at the end of the consultation process; guidelines may be developed, informed by the issues raised.

As outlined previously, if a modification or method of administration is not expressly authorised in the SPC, then it is considered an off-licence use of the medication. In the area of fractional dosing of medicines, concern has been expressed by regulatory agencies and academics alike about the presence of non-functional score lines on tablets (175, 176). It is often assumed by healthcare professionals and patients that the presence of such score-lines indicates that the tablet can be divided into equal halves for fractional dosing (141). However, this is not always the case and the score-line may only be present to allow breaking the tablet to facilitate swallowing (177). In 2013, the Food and Drug Administration (FDA) issued guidance for industry detailing specific criteria that should be reported to support an authorisation application for scored tablets (178). These recommendations cover issues including: the appropriateness of the presence of a

score line based on the dose achieved following splitting compared to the minimum licensed dose; the safety of the split tablet and the risks associated with unintended exposure; finished product testing requirements; stability of split tablet portions on storage and; the ease of tablet splitting. However, it is important to note that these recommendations are non-binding. As regards the EMA's position on tablet splitting, it is stated in the, "Guideline on pharmaceutical development of medicines for paediatric use", that tablet splitting for fractional dosing may not always be acceptable particularly for NTI drugs, and the suitability of subdivision should be assessed if tablet splitting is considered appropriate for a formulation (179). However, these guidelines only relate to paediatric medication development and do not apply to medicines for either adults or older adults.

Various pharmacopoeia requirements address the issue of splitting scored tablets for fractional dosing. The most recent version of the Ph.Eur. requires that tablets with a break mark, that is intended to divide the tablet into equal halves, must meet the requirements of the "Test for Uniformity of Mass of Subdivided Parts" however, this test is only required during product development and not for finished product release testing (180). In 2009, a stimulus article was published by the USP which proposed that loss of mass and accuracy of subdivision should be used as standards to evaluate the subdivision of scored tablets, but again it was recommended that this should only be required during the drug development process and not for product release testing (181). To date these standards have yet to be adopted in the USP.

These guidelines, concept papers and reflection papers highlight that regulatory agencies are engaging with the complex area of medication suitability for older patients. Many parallels have been made between the challenges encountered in the use, development and approval of medicines for paediatric and older patients (182-184). Issues such as the lack of evidence from clinical trials, the absence of age-appropriate dosage forms, difficulties with the administration of solid ODFs, the absence of dosage forms that facilitate administration of the correct dose, and the routine modification of commercially available ODFs to overcome these challenges, are common to both groups (182-184). In order to encourage the development of age-appropriate formulations for paediatric patients, numerous legislative and regulatory changes were implemented (185). Central to these changes was the requirement for a Paediatric Investigation Plan (PIP) to be submitted to regulatory agencies documenting the studies that would be undertaken to assess the suitability of the medication for the paediatric cohort (185). There has been debate as to whether a similar "Geriatric Investigation Plan" should be implemented for older patients (186). However, a predominant argument against the need for a similar approach is the recognition that older adults, unlike paediatric patients, do not represent a minority as regards medication use but rather are the main users of medicines (187). Therefore, special incentives should not be required to ensure that drug development meets the needs of this cohort (187). The increased acknowledgement of the needs of older patients, combined with recent regulatory and pharmacopoeia changes, should help to encourage the routine consideration of the needs of this cohort during drug development and approval. Recent research has shown, that despite

improvements, there is a need for greater input from geriatric experts in regulatory agencies (188). This must also be supplemented by increased research investigating the actual challenges faced by older patients and their carers when using medication on a daily basis.

1.3 Hypothesis, aim and objectives

1.3.1 Hypothesis

The hypothesis that underpins this research is that ODFs are not meeting the needs of older patients. This necessitates the routine modification of ODFs to tailor them to older patients' requirements. These ODF modifications are frequently outside the terms of the product licence and there may not be an evidence-base to support decision making around ODF modifications.

1.3.2 Aim

The overall aim was to investigate ODF modifications for older adults in an Irish setting and the factors influencing this practice.

1.3.3 Objectives

Three specific objectives were defined in order to achieve this aim. The objectives of this research were:

1. To generate an evidence-base describing current literature investigating ODF modification practices and the factors that influence this practice.
    - Systematically review the quantitative literature on the prevalence of ODF modifications for older adults due to swallowing difficulties (Chapter 2).
    - Systematically review the qualitative literature on ODF modifications (Chapter 3).

2. To examine and describe current ODF modification practices for older adults in an Irish setting.
    - To investigate the prevalence of ODF modifications for older adults in care settings in Ireland (Chapters 4 and 6).
    - To identify the most commonly modified medications and the rationale for modification (Chapters 4 and 6).
    - To ascertain if there is an evidence-base to support these modifications (Chapters 4 and 6).
3. To ascertain the knowledge, attitudes and beliefs of key stakeholders to elucidate the factors that influence ODF modifications in an Irish setting.
    - To investigate the knowledge, attitudes and beliefs of nurses about the modification of ODFs for older adults (Chapter 5).
    - To ascertain the knowledge, attitudes and beliefs of community-dwelling older adults and carers about ODF modifications (Chapter 7).

1.4 Methodological justification

A mixed methods approach, involving the use of both quantitative and qualitative methods, was chosen for this research based on the overall aim of the thesis and the complex nature of the topic of interest (189). This methodological approach is in keeping with the research paradigm of pragmatism that served as the philosophical approach to this thesis (190). It is increasingly recognised in healthcare research that neither positivist quantitative approaches nor

constructivist qualitative approaches alone can fully elucidate the complex phenomena observed and examined in healthcare (191, 192) As a result, pragmatism, which advocates the use of the most appropriate research method to interrogate a research question, be that quantitative, qualitative or mixed methods, has gained popularity in the field of healthcare research (190).

The primary purpose of using mixed methods in this thesis was for complementarity i.e. different methods were used to address different aspects of the same phenomenon with the goal being the generation of a detailed and comprehensive understanding of this complex phenomenon (189). The overall aim of this thesis was to investigate ODF modifications in an Irish setting and the factors that influence this practice. As with any area of healthcare research, undertaking research in this area is inherently complex and to generate sufficient understanding, not only of the extent of the problem but also the factors influencing this problem, mixed methods are required (189). The first step of this research involved systematically reviewing the quantitative (Chapter 2) and qualitative (Chapter 3) literature to identify the current evidence base in this area and to identify knowledge gaps that should be addressed in this thesis. The findings of these reviews went on to inform the development of the individual studies that formed this thesis. The quantitative studies investigated the extent of ODF modifications for older adults in nursing home settings and were conducted from a positivist epistemological approach. While these studies provided necessary information on the extent of the problem and elucidated concerns about the

practice in an Irish setting, there were limitations to the depth of understanding that could be obtained (193). Key criticisms of quantitative based studies include the limited input that key stakeholders, particularly patients, have in the research with the result that the knowledge base generated does not reflect the priorities and needs of end users (194). The result of this can be that the body of research-based knowledge can be at odds with the knowledge being used by patients, carers and other important stakeholders who manage these conditions in reality (194). To address this gap, qualitative research methods were used to investigate the knowledge, attitudes and beliefs of key stakeholders: nurses and; community-dwelling patients and carers. The ultimate effect of the utilisation of these complementary research methods was that it facilitated the generation of a deep understanding of ODF modifications and the factors influencing this practice in an Irish setting, as well as ensuring that the limitations of one method were overcome by the strengths of the other method (189, 195). In this thesis, a "composite analysis" approach to the conduct and presentation of the quantitative and qualitative studies was used, as described by Yardley and Bishop (196). In this approach, the quantitative and qualitative studies, which investigated different aspects of the phenomenon of medicine modification, were conducted and presented as individual studies, which can be judged on their individual merits. However, the findings are interpreted and inter-related in the discussion, to provide more insight than could be achieved by either method alone.

1.5 Thesis outline

This thesis consists of eight chapters which, when combined, provide a thorough and detailed investigation of ODF modifications for older adults and the factors influencing this practice in an Irish setting. Figure 1.1 provides an overview of the thesis and demonstrates how the aim and objectives are addressed by the individual studies undertaken as part of this doctoral research and how these studies combine to form the thesis.

Chapter One: This chapter introduces this research topic, as well as defining the overall aim and objectives of the thesis.

Chapter Two: This chapter consists of a systematic review of the quantitative literature to investigate the prevalence of difficulty swallowing ODFs amongst older adults and the prevalence of ODF modifications for older adults (Paper 1).

Chapter Three: Chapter Three presents the findings of a qualitative systematic review on the knowledge, attitudes and beliefs of healthcare professionals, patients and carers about the modification of ODFs (Paper 2).

Chapter Four: This chapter describes a retrospective review of drug charts in an aged care facility (ACF) in Ireland which sought to determine the extent of ODF modifications in an Irish setting, as well as elucidating the rationale and the evidence-base for these modifications (Paper 3).

Chapter Five: Chapter Five is a qualitative, semi-structured interview study undertaken with nurses working in acute and long-term care settings to explore their knowledge, attitudes and beliefs about ODF modifications (Paper 4).

Chapter Six: Chapter Six describes an undisguised, direct observation of medication administration in 5 ACFs throughout Cork in Ireland. This chapter provides more in-depth information on the extent of ODF modifications, as well as the methods of modification and administration of modified medicines (Paper 5).

Chapter 7: Chapter Seven describes a qualitative, semi-structured interview study conducted with community-dwelling older adults and carers of community-dwelling older adults. This chapter explores the knowledge, attitudes and beliefs, as well as the experiences, of these key stakeholders around ODF modifications (Paper 6).

Chapter 8: The final chapter of this thesis presents the overall discussion, taking into consideration the findings of each study that comprises this thesis (Chapters 2 to 7).

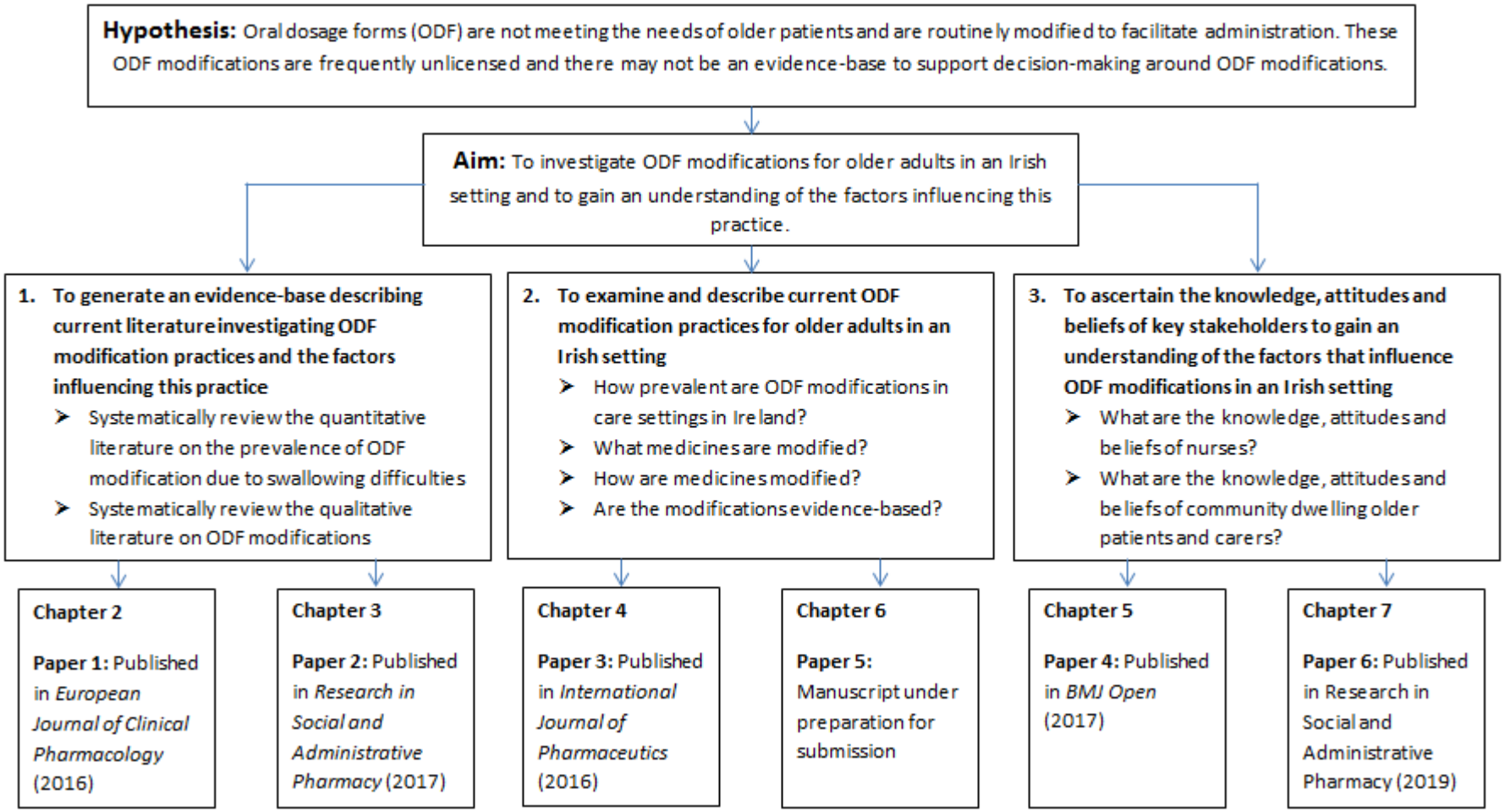

Figure 1.1 Thesis outline

Chapter 2: Older adults with difficulty swallowing oral dosage forms: a systematic review of the quantitative literature

Publication one:

Mc Gillicuddy A, Crean AM, Sahm LJ. Older adults with difficulty swallowing oral medicines: a systematic review of the literature. Eur J Clin Pharmacol. 2016;72(2):141-51. doi:https://doi.org/10.1007/s00228-015-1979-8

2.1 Abstract

2.1.1 Background

Swallowing ODFs may be challenging due to diagnosed swallowing disorders or patient self-reported difficulties. The prevalence of dysphagia increases with age due to an age-related decline in swallowing function combined with an increased prevalence of medical conditions that predispose to dysphagia. Medication use also increases with age; therefore, difficulty swallowing medication may complicate medicine administration to older patients. This may result in patients, carers or healthcare professionals modifying ODFs to facilitate administration. Modifying ODFs can impact on the safety, quality and efficacy of the medication.

2.1.2 Aim

The aim of this systematic review was to critically appraise the evidence regarding the prevalence of difficulty swallowing ODFs and the modification of ODFs to overcome swallowing difficulties in the older cohort.

2.1.3 Methods

A systematic search of PubMed, EMBASE, Medline, CINAHL, Scopus, Web of Science, The Cochrane Library, PsycINFO and ProQuest Databases was conducted from database inception to November 2014. Studies investigating the prevalence of difficulty swallowing ODFs or the modification of ODFs were eligible for inclusion. A narrative analysis of the results was conducted.

2.1.4 Results

Five studies met the inclusion criteria. The results suggested that approximately 14% of community dwelling older patients experienced difficulty swallowing

medicines. Between one quarter and one third of occasions of medicine administration to older patients in care facilities involved the modification of ODFs.

2.1.5 Conclusions

Difficulty swallowing ODFs and the modification of medicines were reported as being common issues in the older cohort. However, evidence to support such contentions was limited. Future research should investigate the prevalence of medicine modification for older patients in all settings and identify what medicines are modified. This would facilitate the targeting of interventions to optimise medicine administration to older patients.

2.2 Introduction

Current estimates suggest that the proportion of the global population aged 65 years and older will increase from 8.0% in 2013 to 15.6% by 2050 (197). This trend towards an ageing population is evident in both developing and developed countries (198, 199). The ageing population profile presents significant challenges for healthcare providers. Older people are the most frequent users of healthcare services; they suffer from more chronic diseases (10) and experience increased levels of multi-morbidity (34, 35). Consequently, older patients tend to require more prescribed medications (34, 200), with studies showing that the number of prescribed medications increases with age (201, 202). The appropriate use of medicines is crucial to increasing life expectancy, maintaining health and improving the quality of life in older patients. However, various age-related changes in pharmacokinetics, pharmacodynamics and physiological function need to be considered when treating this heterogeneous cohort (92-94). While issues such as inappropriate prescribing, increased susceptibility for adverse events and altered pharmacokinetics are widely acknowledged (8), practical issues, such as the "swallowability" of the pharmaceutical form for individual patients, are often overlooked (8).

The preferred route for drug administration is the oral route as it is a simple, convenient and non-invasive route that the majority of patients can safely manage with minimal input from healthcare professionals (65). However, the advantages of this route are lost if a patient cannot swallow the pharmaceutical form prescribed.

While the prevalence of dysphagia increases with age due to age-related decline in the swallowing mechanism (203) combined with increased prevalence of conditions that predispose to dysphagia (72), nonetheless the rates of dysphagia are setting-dependent. The prevalence in the older cohort increases from approximately 15%, in those who live independently in the community (74-76) to between 40 and 60% in nursing home residents (80). In addition, many patients without a clinical diagnosis of dysphagia will report difficulty swallowing oral medications due to an aversion to swallowing medication (83) which in severe cases may be considered a form of psychogenic dysphagia or "phagophobia" (204).

If a person experiences difficulty swallowing ODFs, they may resort to altering the dosage form or become non-compliant (87, 205). Modifying the dosage form is of particular concern as these physical changes e.g. crushing tablets, opening capsules etc., may affect the stability, efficacy and safety of the drug (106, 206). Administering medicines with food may also cause drug-food interactions which can affect drug stability or absorption of the drug *in vivo* (108, 207). In addition to the effect that modifications may have on the stability and therapeutic effectiveness of the drug, healthcare professionals need to be cognisant of their legal responsibilities in relation to these modifications (208).

Despite the issues associated with the modification of ODFs and the numerous guidelines and opinion pieces published regarding the administration of medicines

to patients with difficulty swallowing (104, 209), no systematic review was identified that investigated the prevalence of difficulty swallowing ODFs or the prevalence of medicine modification amongst the older cohort.

2.3 Aim of the systematic review

The aim of this systematic review was to identify and critically appraise the available evidence regarding oral medicine use amongst older patients with difficulty swallowing oral medicines. To achieve this aim, two specific objectives were investigated: (i) to determine the prevalence of difficulty swallowing ODFs amongst older patients and; (ii) to quantify the prevalence of ODF modifications to facilitate drug administration to older patients with difficulty swallowing intact dosage forms.

2.4 Methods

2.4.1 Search strategy

A search strategy was developed based on the use of index and free text terms related to (i) oral dosage forms, (ii) methods of modification and (iii) difficulty swallowing. The lack of index terms to describe methods of modification complicated the development of the search strategy. A comprehensive list of free text terms was devised to account for the numerous potential methods of modification. A qualified medical librarian reviewed and approved the search

strategy prior to undertaking the literature searches. The complete search strategy is provided in Appendix 1.

A comprehensive, systematic literature search was undertaken in November 2014. The following databases were searched: PubMed, EMBASE, Medline, CINAHL, Scopus, Web of Science, The Cochrane Library, PsycINFO and ProQuest Databases. Databases were searched from inception to 11th November 2014. No time restrictions were placed on the search and articles were not excluded based on the date of publication. No language restrictions were applied during the initial literature search. The reference lists of included full text articles were hand-searched to identify any further potentially relevant studies. Citation searching was undertaken to identify any potentially relevant articles that cited the papers included in the systematic review.

2.4.2 Study selection

Following removal of duplicates, two reviewers independently screened titles for relevance for inclusion (AMG and AMC). The abstracts of studies identified from the initial title screen were obtained and independently assessed by two reviewers (AMG and LJS) for potential inclusion in the review. Finally, the full text of studies identified from the abstract screen were obtained and reviewed independently by two reviewers (AMG and; LJS or AMC) to identify studies that met the inclusion criteria. In the case of disagreement between the two reviewers at any stage of the

selection process, the third researcher independently examined the study and following discussion, consensus was reached.

2.4.3 Eligibility criteria

For this review, similarly to Richey *et al.* (66), a modification was defined as; " *any alteration of an oral dosage form that can be performed at the point of administration*". The modification may be undertaken by patients, carers or healthcare staff. ODFs were defined as any dosage form that is to be administered orally by swallowing i.e. tablets, capsules and oral liquids. The purpose of the modification must have been to facilitate administration to a patient with difficulty swallowing the intact or unaltered dosage form. In contrast to the review undertaken by Richey *et al.* (66, 210), studies that investigated the modification of dosage forms to allow for fractional dosing were not considered.

People aged 60 years and older were, for the purposes of this review, defined as older persons. There is a debate surrounding the definition of old age, which is both region and demographic specific (211). Most developed countries accept 65 years as the standard definition of an older person, however, the UN use 60 years to define an older population (199). It was determined *a priori* that studies involving patients aged <60 years would only be included if the results for patients aged ≥60 years could be extracted and analysed separately.

The primary outcomes of interest were (i) the prevalence of difficulty swallowing ODFs amongst older patients in all settings and (ii) the prevalence of ODF modifications to facilitate administration to older patients with difficulty swallowing intact dosage forms. For this review, difficulty swallowing refers to difficulty swallowing oral medicines not to aberrations of swallowing function due to disease states or medical conditions. A detailed breakdown of the inclusion and exclusion criteria for the systematic review is provided in Table 2.1.

Table 2.1 Inclusion and exclusion criteria for the systematic review

Inclusion Criteria	Exclusion Criteria
Studies presenting the results of original research in English.	Systematic reviews, meta-analyses, conference abstracts, editorials and commentaries.
Studies investigating oral medicine administration to patients aged 60 years and older.	Studies investigating extemporaneous compounding of medicines by pharmacists.
Studies undertaken in primary, secondary and tertiary care.	Studies in which the purpose of the modification is to facilitate fractional dosing.
Studies in which modifications are undertaken to facilitate medication administration to patients with difficulty swallowing the unmodified dosage form.	Studies that solely investigate modifications to facilitate administration via enteral tubes.
Difficulty swallowing in this review refers to difficulty swallowing oral medicines, not dysphagia. Studies in which patients or carers identify patients as having difficulty taking oral medicines will be included, even if the patient has no clinical evidence of swallowing dysfunction.	Studies investigating the practice of covert administration of medications.
Examples of modifications include, but are not limited to, crushing, grinding, cutting or splitting tablets, breaking open capsules, dissolving or dispersing intact or modified dosage forms in food or liquid, diluting oral liquids or adding thickening agents to oral liquids.	Qualitative studies.
	Studies that describe the results of interventions or quality improvement programmes.
	Studies that report on medication administration errors.

2.4.4 Data extraction

Data from each study included in the review were extracted into a modified version of the data extraction form developed by NICE (212). The data extraction form was initially piloted and subsequently modified by one reviewer (AMG). Data extraction was performed by one reviewer (AMG), and then independently verified by a second reviewer (AMC) for accuracy and completeness as per the *Centre for Reviews and Dissemination's Guidance for Undertaking Reviews in Health Care* (213). In the case of any disagreements regarding the extracted data, following discussion, a consensus was reached between both reviewers.

2.4.5 Quality appraisal

The quality of the included studies was independently assessed by two reviewers (AMG and LJS) using a modified version of the critical appraisal criteria developed by Loney *et al.* (214). This scale was developed to critically appraise studies that investigate the prevalence or incidence of a health problem and it is particularly appropriate for evaluating cross-sectional studies (215). Any disagreement between reviewers regarding quality was resolved by discussion and consensus was reached. The results of the quality appraisal were used to moderate the findings of the review but were not used for inclusion or exclusion of studies.

2.4.6 Data synthesis

Due to the heterogeneity of study settings, methodologies and outcomes reported, it was not possible to undertake a meta-analysis of the results. A narrative analysis was conducted.

2.4.7 Reporting

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (216). These guidelines were primarily developed for use for reviews of healthcare interventions. Due to the nature of this review, not all of the PRISMA guidelines were relevant, however, in so far as practical; the PRISMA guidelines were followed (Appendix 2).

2.5 Results

2.5.1 Study selection

A total of 5,490 records were identified from the initial database search. The process of study selection is outlined in Figure 2.1.

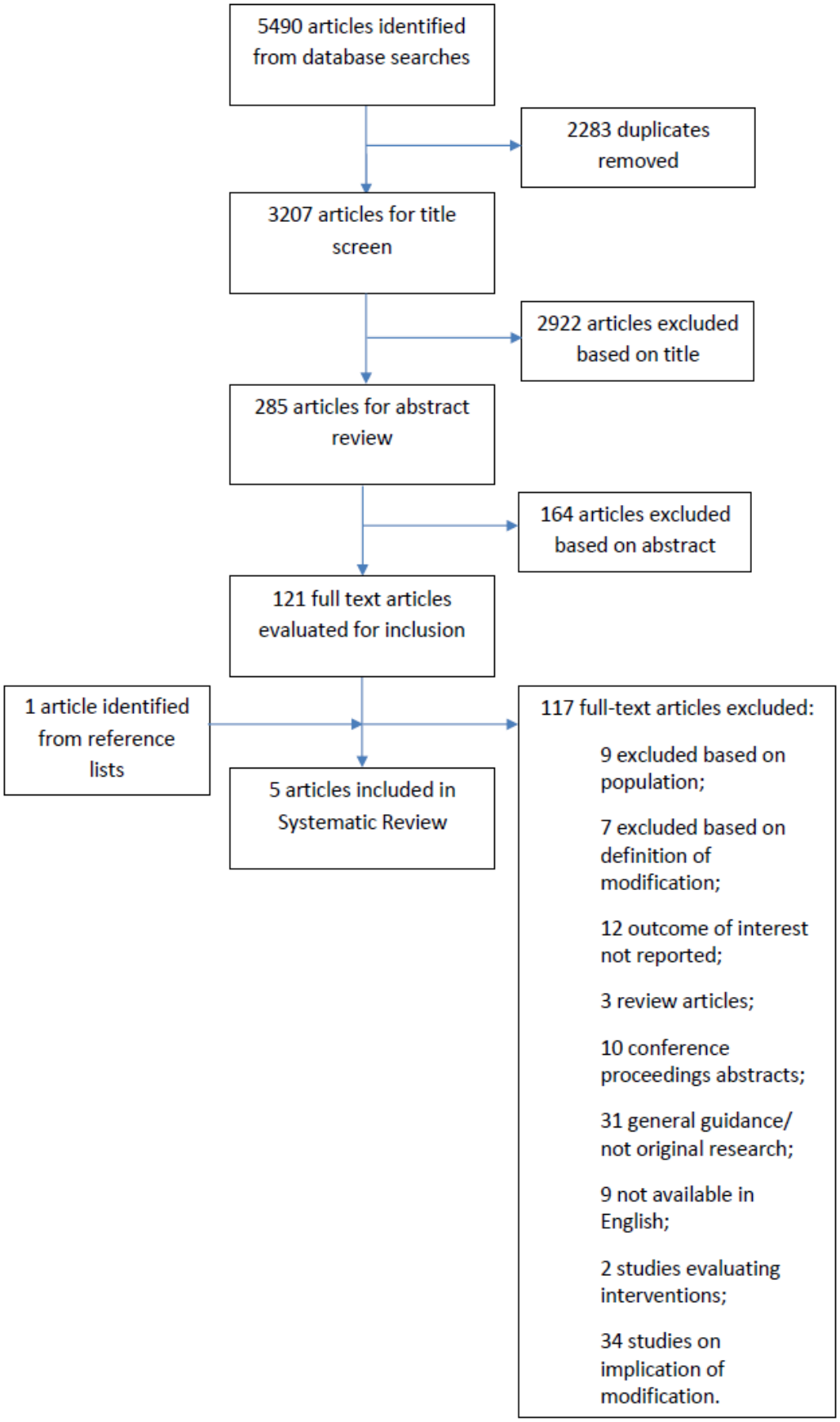

Figure 2.1 Flow diagram of study selection process

2.5.2 Study characteristics

The characteristics of the studies included in the review are summarised in Table 2.2. All five studies used cross-sectional observational designs (102, 217-220). Two studies investigated the medicine taking practices of community-dwelling older patients (217, 218) and three studies investigated medication administration to older patients in care facilities (102, 219, 220).

Table 2.2 Characteristics of included studies

Author (year); Country	Description of study settings	Inclusion Criteria	Outcomes of Interest	Method of Data Collection	n	Age categories (%)	Gender (%)
Mehuys *et al.* (2012) (217); **Belgium**	86 Randomly selected community pharmacies	(i) Aged ≥70 yrs, (ii) Using at least one chronic medicine, (iii) Home-dwelling, (iv) Ambulatory, (v) Regular client of the pharmacy	Drug use: Types of drugs used and drug-drug interactions. Drug Adherence. Drug Knowledge. Practical Drug Management Capacity.	Mixed methods: Data from electronic pharmacy database, Interview, Questionnaire.	338	70-80 yrs: 69.2% 81-90 yrs: 29.6% >90 yrs: 1.2%	M: 46.4% F: 53.6%
Mercovich *et al.* (2014) (102); **Australia**	Convenience sample of 2 ACFs with a dementia unit and HDU at each ACF	3 Medication administration rounds at each ACF over a two week period	Extent of solid dosage form modifications. Commonly modified medications and methods of modification and administration.	Direct observation of medication rounds.	160	nr [a]	nr[b]

Author (year); Country	Description of study settings	Inclusion Criteria	Outcomes of Interest	Method of Data Collection	n	Age categories (%)	Gender (%)
Paradiso *et al.* (2002) (219); **Australia**	Stratified sample of 10 ACFs: 4 high-care; 3 low-care; 3 co-located care	4 Medication rounds observed at four times during the day for four days over a one-week period at each ACF	Extent of solid ODF modification, and extent of modification of medications which should not be altered. Methods used to alter and administer solid ODFs.	Direct observation of medication rounds.	586	nr [a]	nr[b]
Stubbs *et al.* (2008) (220); **United Kingdom**	Two long-stay wards for older mentally ill inpatients in a large psychiatric hospital	Inpatients admitted to Ward A or Ward B (two long-stay wards for older mentally ill inpatients)	Extent of solid dose form modification. Drugs modified and the reasons for modifying. Frequency of inappropriate modifications.	Direct observation of medication rounds.	32	Median age 74yrs (range 60-100 yrs)	nr[b]

Author (year); Country	Description of study settings	Inclusion Criteria	Outcomes of Interest	Method of Data Collection	n	Age categories (%)	Gender (%)
Tordoff *et al.* (2010) (218); **New Zealand**	Community setting; random sample from electoral roll	(i) Community dwelling people, (ii) aged ≥75 yrs, (iii) taking one or more prescription medicine	Participant's medications, knowledge of medications purpose, problems taking medications, adherence.	Interview using a structured questionnaire.	316	75-79 yrs: 34.8% 80-84 yrs: 39.6% ≥85 yrs: 25.6%	M: 54% F: 46%

Legend: ACF = Aged Care Facility; yrs = Years; M = Male; F = Female; HDU = High Dependency Unit; nr[a] = Not reported but authors were contacted regarding age of patients. Demographic details not recorded but stated that residents of ACFs would generally be >65 years; nr[b] = Not reported.

2.5.3 Quality appraisal

A summary of the results of the quality appraisal for the included studies is provided in Table 2.3. The overall scores ranged from 3 to 6. The scores were not used to rank studies as low, medium and high quality as it is not recommended to rely on a numerical score for judging quality as this can be misleading (213).

Issues identified included the lack of an objective assessment tool to identify the prevalence of difficulty swallowing medicines or the frequency of medication modification (217, 218). There is currently no validated screening tool available to investigate these outcomes. Of the three studies that investigated patients who were resident in care facilities (102, 219, 220), none provided adequate demographic details about the study settings or subjects. Two of the studies used convenience sampling and the sample sizes were small (102, 220).

Table 2.3 Quality appraisal of included studies using criteria developed by Loney *et al.*(214)

Quality Appraisal Criteria	Mehuys *et al.* (2012) (217)	Mercovich *et al.* (2014) (102)	Paradiso *et al.* (2002) (219)	Stubbs *et al.* (2008) (220)	Tordoff *et al.* (2010) (218)
Is the study design appropriate for the research question?	Y	Y	Y	Y	Y
Is the sampling frame appropriate?	Y	N	Y	U	Y
Is the sample size adequate?	Y	N	Y	N	Y
Are objective, suitable and standard criteria used for measurement of the health problem?	N	Y	Y	Y	N
Is the health outcome measured in an unbiased fashion?	U	Y	Y	Y	Y
Is the response rate adequate?	Y	N	N	U	U
Are the estimates of prevalence given with confidence intervals and in detail by subgroup, if appropriate?	U	Y	N	N	Y
Are the study subjects and the setting described in detail and similar to those of interest?	Y	U	U	U	Y
Overall Score	5	4	5	3	6

Legend: Y = Yes; N = No; U = Unclear.

2.5.4 Difficulty swallowing oral dosage forms

Two studies reported on the prevalence of difficulty swallowing ODFs (217, 218). Both of these studies were undertaken in community settings. The observed prevalence in both studies was similar at 14% (218) and 14.8% (217). These studies relied on patient self-reported difficulty swallowing solid medications with the study by Tordoff *et al.* (218) enquiring about difficulty swallowing tablets or capsules and the study by Mehuys *et al.* (217) investigating difficulty swallowing tablets. The generalizability of these studies is limited by the age of the cohorts studied with no patients under 70 years of age being included. The voluntary nature of participation and inclusion of ambulatory patients only may also affect the generalizability of the results, as a more unwell cohort of patients may have been excluded, which may result in an underestimation of the prevalence. Both studies investigated a range of medication issues and neither was specifically designed to assess difficulty swallowing medication. Recall and reporting bias are also significant issues for both studies due to the use of patient self-report.

2.5.5 Frequency of modifying oral dosage forms

Three of the studies reported on the frequency of modifying ODFs (102, 219, 220). All three studies involved the direct observation of medication administration. The studies differ in how the frequency of modification was reported which does not allow for direct comparison of the results.

Mercovich *et al.* (102) found that 18% of residents (n=29) required at least one medication to be altered prior to administration and that in 59% of these cases, two or more medications were modified for the resident. The other studies did not report the number of patients requiring modified medications but rather reported the results as the prevalence of medicine modification as a proportion of the total number of solid ODFs administered (220) or occasions of medication administration observed (219). Paradiso *et al.* (219) found that 34% of the 1,207 occasions of medication administration observed involved the modification of one or more medicines. The prevalence was substantially higher in high-care facilities (46%) compared to low-care facilities (2%). Stubbs *et al.* (220) found that 25.5% of solid oral doses administered to older patients in long stay psychiatric wards were altered prior to administration. In both studies, residents may have been observed more than once. Therefore, it was not possible to determine the proportion of patients requiring medication modification. The generalizability of the findings of the studies was limited by the small sample size of the studies (102, 220) and the use of convenience rather than random sampling by two studies (102, 220). The method of data collection was appropriate in all studies as direct observation provides more reliable and complete data than chart review. The study conducted by Stubbs *et al.* (220) was undertaken in a psychiatric hospital and therefore the results may not be generalizable to the general older population.

All of the studies investigated the modification of solid ODFs. Modifications of liquid dosage forms were not considered. Modified medications may be mixed with

various food vehicles to facilitate administration following alteration. The frequency of addition of modified medicines to food vehicles ranged from 54.9% to 100% of administered modified medications (219, 220). Vehicles described included sprinkling on meals or toast, mixing with jam, blended fruit, custard, yoghurt, honey, chocolate milk and thickened pear juice.

2.5.6 Methods of modifying oral dosage forms

Three studies reported on the methods used to modify ODFs (102, 219, 220). Two of the studies reported that the modifications observed were tablet crushing or capsule opening (102, 220), while the study by Paradiso *et al.* (219) only reported on tablet crushing. All of the studies reported the use of a mortar and pestle (102, 219, 220), the use of pill crushing devices was observed in two studies (219, 220) while Mercovich *et al.* (102) reported the use of individual items e.g. glass cups or crushing medication between two spoons. None of the studies reported the frequency with which each method of modification was used.

When multiple medications were to be modified prior to administration to patients it was found that all the medicines were crushed together in the same vessel (102, 219). Sharing of crushing equipment between different residents was common, with Mercovich *et al.* (102) reporting that in all instances equipment was shared while Paradiso *et al.* (219) reported that for 77% of cases of medicine modification observed, the equipment was shared. Inadequate cleaning of shared equipment,

leading to potential cross-contamination, was witnessed, as was spillage or loss of medication from the crushing vessel (102, 219, 220). Mercovich *et al.* (102) reported that in all instances observed, equipment was not cleaned and spillage or loss occurred. This was higher than that seen by Paradiso *et al.* (219) at 59% for inadequate cleaning and 70% for spillage or loss. Stubbs *et al.* (220) did not report the frequency of such issues but did report concerns about inadequate cleanliness and spillage and loss from the crushing vessel.

2.5.7 Other issues identified

The proportion of altered medications that were classified as being unsuitable for modification ranged from 4.5% (220) to 17% (219) to 32% (102). The criteria used for determining whether the modification was appropriate varied between the studies: Stubbs *et al.* (220) used the manufacturer's information on contra-indications; Mercovich *et al.* (102) used the *Australian Don't Rush to Crush Handbook* (161); while Paradiso *et al.* (219) used a list of medications that an expert panel determined were unsuitable for alteration.

Stubbs *et al.* (220) also found that in 44% of cases the modification was not authorised by the prescriber. Neither of the other studies reported on the frequency with which the modification was authorised by the prescriber.

2.6 Discussion

2.6.1 Summary of evidence

This systematic review investigated difficulty swallowing ODFs amongst older patients and the modifications undertaken to overcome such difficulties. Reports and guidance documents for healthcare professionals advise that difficulty swallowing medications is a common issue amongst the older cohort and detail the clinical, professional and legal implications of modifying medicines (104, 146, 205, 209). Ultimately, this review aimed to provide an evidence base for these guidelines. There was a dearth of evidence regarding this practice in older patients and the heterogeneity of the methodologies used and outcomes reported limited the comparability of the results.

The results of the studies suggested that the prevalence of difficulty swallowing ODFs was approximately 14% amongst community-dwelling older patients. Studies investigating this outcome in other settings or in patients aged between 60 and 70 years were not identified. Difficulty swallowing oral medicines was not the primary focus of either study and both studies relied on patient self-reported difficulties. These results may underestimate prevalence due to: the voluntary nature of participation (217, 218); the use of patient self-reported data (217, 218) and; only including ambulatory patients (217). This may mean that a potentially more unwell cohort, who may be more likely to suffer with swallowing difficulties, was excluded. The use of carers as a data source may help to overcome this limitation. A number of studies have previously investigated difficulty swallowing oral medicines in a

primary care setting as their primary outcome of interest (86, 87, 221). These studies were not eligible for inclusion in this review due to the age range of patients studied. The prevalence of difficulty swallowing oral medicines ranged from 11% of a general practice population with at least one risk factor for dysphagia (221) to 37.4% of a general practice population taking at least one solid ODF for 4 weeks or more (86), to a high of 60% in a study by Strachan *et al.* (87). Reasons for the substantially higher prevalence in these studies may be due to the inclusion criteria used, as subjects were enrolled if they were suspected of having dysphagia (87) or if they experienced one or more risk factors for dysphagia e.g. stroke (221).

The method used to assess the prevalence of difficulty swallowing was a major issue. The high prevalence in these studies (86, 87, 221) may stem from the phrasing of the questionnaire which effectively assessed lifetime prevalence of difficulty swallowing any tablet or capsule, whereas Mehuys *et al.* (217) and Tordoff *et al.* (218) focused on the difficulties patients experienced with their current medication regimen. All methods used in primary care settings relied on patient self-reported difficulties, which introduced the risk of recall and reporting bias. The ideal method of assessment would be direct observation of medication administration. However, this is impractical and unfeasible in a primary care setting. There is a need for the development of a validated, sensitive and specific tool for screening for difficulty swallowing oral medicines both for research purposes and for use in clinical practice. Subjective measures of swallowing difficulties have shown similar effectiveness to objective methods when screening for dysphagia in a

nursing home population (79) which suggests that a subjective tool could be used to identify patients with difficulty swallowing medicines. Lack of communication between patients and their healthcare provider is a serious concern in this area as patients consistently report that they do not inform their healthcare provider about difficulties swallowing medication (86, 87, 222) and healthcare professionals do not enquire about difficulty swallowing oral medicines prior to prescribing or dispensing (86, 87, 222). In fact, lack of communication between healthcare professionals has also been reported to be a major issue that hinders the provision of optimum care to patients with difficulty swallowing oral medicines (156, 157, 223). Routine use of a validated screening tool in daily practice would help to overcome the communication deficit evident at present, thereby identifying patients experiencing difficulty with their oral medication regimen.

Three studies reported on the alteration of ODFs to facilitate the administration of medication to patients with difficulty swallowing. The alteration was the outcome of interest in these studies. Between one quarter and one third of medication administrations observed involved the modification of ODFs. Only one of the studies reported the proportion of patients who were administered modified medicines (220), which is a valuable term to quantify. Further research is required to establish the prevalence of ODF modifications for older adults in care settings. This research is vital to determine the extent of this practice, but in addition, to elucidate patient characteristics, medications and formulations that are associated with medicine modification. Addressing this knowledge gap is a crucial first step

that will facilitate the development of formulations and targeting of interventions that will be of most benefit to older patients who require modified medicines. All three studies were conducted in settings where a healthcare professional was responsible for the decision regarding medicine alteration. No eligible study evaluated the prevalence of medication modification in a community setting. Research in general populations suggests that 60% of people with difficulty swallowing medications resort to modifications to facilitate intake (86, 87). The lack of available data on the prevalence of this practice in the older community-dwelling cohort is of concern given that patients or their carers may be inappropriately modifying medications without involving their healthcare professionals in the decision making process (224).

This review has highlighted concerns about the methods used to modify medicines and how the modified medicines are subsequently administered. Modifying medications may affect the physical and chemical stability of the drug, the clinical performance of the drug may be affected through an increase or decrease in bioavailability, which may lead to increased adverse effects or toxicity or decreased efficacy (110, 206, 225, 226). These changes could potentially affect clinical outcomes for patients. In addition, the altered medicine is frequently administered in food vehicles (227). The interaction of medicine and vehicle should be considered as the vehicle chosen may not be considered an inert excipient in all cases. Previous research has shown that administration of medication in food vehicles can alter the stability, potency, dissolution and bioavailability of the medication (107, 108, 228).

The effect is dependent on the physical and chemical properties of the drug and the food vehicle and therefore, any guidance issued regarding compatibility with food is both drug and food specific.

All of the studies investigated the modification of solid ODFs (102, 217-220). Studies on the modification of oral liquid dosage forms were not found. Liquid dosage forms are frequently recommended for patients with difficulty swallowing (104, 229). However, liquids can be problematic in patients with dysphagia due to the risk of aspiration (230). To overcome this, liquids are frequently modified by using thickening agents (72), with an average of 8.3% of residents (range 0% to 28%) in skilled nursing facilities receiving thickened liquids (231). However, there is a paucity of data on whether liquid ODFs are routinely thickened for patients with dysphagia. Thickened liquids can significantly impair drug dissolution and bioavailability (115, 232), which could potentially have clinical implications due to sub-therapeutic drug levels. The magnitude of the effect is both thickener and drug specific with a number of factors including the physicochemical characteristics of the drug and thickening agent and the viscosity of the resultant liquid contributing to the effect on drug dissolution and hence bioavailability *in-vivo*. Therefore, general guidance on the use of thickening agents when administering liquid dosage forms cannot be issued. Further investigations are necessary to identify how frequently oral liquid medications are thickened, what medications are thickened and what thickeners are used. In tandem with this, research on the consequences of such modifications is necessary to clarify the potential impact that thickeners

may have on the therapeutic response and to assist healthcare professionals in making informed decisions about the most appropriate form of the medication to administer.

2.6.2 Implications for practice

Adherence to medication regimens is associated with improved health outcomes, with the risk of mortality amongst patient with good adherence approximately half that of poorly adherent patients (233). The majority (69%) of patients with difficulty swallowing solid ODFs in a general population admitted to not taking a tablet or capsule due to difficulty swallowing the dosage form (87). Therefore, difficulty swallowing oral medicines can result in poor adherence to prescribed treatments which can negatively impact on health outcomes.

Patients with dysphagia are more likely to experience a medication administration error than those without (234). The rate of medication administration errors in four hospitals in the UK was found to be 21.1% amongst patients with dysphagia compared to 5.9% in patients without dysphagia; with incorrect preparation of medicines being the most common error observed for patients with dysphagia (234). Therefore, there is a clear need to optimise the administration of medicines to older patients with swallowing difficulties to minimise the occurrence of errors that could potentially lead to patient harm and poor outcomes for patients. This review serves as a starting point from which further research can be undertaken.

2.6.3 Limitations

There are a number of limitations associated with this systematic review. Firstly, only a small number of relevant studies were eligible for inclusion. The characteristics, methodologies, assessment measures and reported outcomes varied significantly between eligible studies which hindered efforts to compare results across the studies. Finally, the review only included full text articles in English, and different medication administration practices may be evident in countries where English is not the first language.

2.7 Conclusions

Difficulty swallowing ODFs and ODF modifications are reported as being commonplace amongst older patients. Despite this generally accepted reality, the evidence to support such contentions is negligible. Anecdotally, and from the limited evidence available, this is an issue that needs to be addressed. Guidance to healthcare professionals on the administration of medicines to patients with difficulty swallowing advises that healthcare professionals should consider using alternative medications or alternative routes of administration. It is acknowledged that if no alternative exists, the ODF may need to be altered however, this *"should be reserved as a last-resort"* (104). Other commentators advise that the practice of manipulating medicines should not be accepted but rather patient-centred formulations should be developed (63). However, in the interim, healthcare professionals, patients and carers are tasked with ensuring that older patients receive necessary medication which often necessitates the modification of ODFs

due to a lack of suitable alternatives or due to cost considerations. It is evident that research is needed to determine: the prevalence of ODF modification; what medicines are commonly being modified and; what are the methods of modification that are used. The information obtained can be used to alert the pharmaceutical industry to develop new products that will meet the needs of older patients with swallowing difficulties, as recommended by Stegemann *et al.* (63). In addition, this research will facilitate the targeting of appropriate interventions to ensure that the administration of medicines to older patients is optimised and to provide healthcare professionals with evidence based recommendations.

2.8 Acknowledgements

We would like to thank Mr. Joe Murphy, Medical Librarian, for his assistance with the search strategy for this systematic review.

Chapter 3: Knowledge, attitudes and beliefs of patients, healthcare professionals and carers around oral dosage form modification: a systematic review of the qualitative literature

Publication two:

Mc Gillicuddy A, Kelly M, Crean AM, Sahm LJ. The knowledge, attitudes and beliefs of patients and their healthcare professionals around oral dosage form modification: A systematic review of the qualitative literature. Research in Social and Administrative Pharmacy. 2017;13(4):717-26. doi:https://doi.org/10.1016/j.sapharm.2016.09.004

Systematic review registration:

Mc Gillicuddy A, Kelly M, Crean AM, Sahm LJ. The knowledge, attitudes and beliefs of patients and their carers (healthcare practitioners and informal carers) around oral dosage form modification: a systematic review of the qualitative literature. PROSPERO: International prospective register of systematic reviews. 2015: CRD42015023494

www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015023494

3.1 Abstract

3.1.1 Background

The modification of ODFs can potentially alter drug safety and efficacy *in vivo* and can have significant legal implications for healthcare professionals in the event of any adverse events. Despite this, modifications are undertaken to facilitate the administration of prescribed doses and to overcome challenges administering medication to patients with difficulty swallowing intact dosage forms.

3.1.2 Aim

The aim of this systematic review was to synthesize the available qualitative evidence on the knowledge, attitudes and beliefs of adult patients, healthcare professionals and carers about ODF modifications.

3.1.3 Methods

A systematic search of PubMed, Medline (EBSCO), EMBASE, CINAHL, PsycINFO, Web of Science, ProQuest Databases, Scopus, Turning Research Into Practice (TRIP), Cochrane Central Register of Controlled Trials (CENTRAL) and the Cochrane Database of Systematic Reviews (CDSR) was conducted from database inception to September 2015. Citation tracking and searching the references lists of included studies was also undertaken. Grey literature was searched using the OpenGrey database, internet searching and personal knowledge. An updated search was undertaken in June 2016. Studies meeting the following criteria were eligible for inclusion: (i) qualitative data collection and analysis methods; (ii) full-text available in English; (iii) included adult patients who require ODFs to be modified to meet their needs or; (iv) carers or healthcare professionals of patients who require ODFs

to be modified. Two reviewers independently appraised the quality of the included studies using the Critical Appraisal Skills Programme (CASP) Checklist. A thematic synthesis was conducted and analytical themes were generated.

3.1.4 Results

Of 5,455 records screened, seven studies were eligible for inclusion; three involved healthcare professionals and the remaining four studies involved patients. Four analytical themes emerged from the thematic synthesis: (i) patient-centred individuality and variability; (ii) communication; (iii) knowledge and uncertainty and; (iv) complexity. The variability of individual patient's requirements, poor communication practices and lack of knowledge about ODF modification, when combined with the complex and multi-faceted healthcare environment, complicated decision-making regarding ODF modification and administration.

3.1.5 Conclusions

This systematic review has highlighted the key factors influencing the knowledge, attitudes and beliefs of patients and healthcare professionals about ODF modifications. The findings suggest that in order to optimise ODF modification practices, the needs of individual patients should be routinely and systematically assessed and decision-making should be supported by evidence-based recommendations with multidisciplinary input. Further research is needed to optimise ODF modification practices and the factors identified in this review should be considered in the development of future interventions.

3.2 Introduction

Medication represents one of the most common and most important therapeutic interventions of modern medicine. However, the key to optimising drug therapy is ensuring that the right patient receives the right drug at the right dose by the right route at the right time (235). Although ODFs, such as tablets and capsules, are preferred by both healthcare professionals and patients, modifications may be necessary to facilitate administration of the right dose or to allow administration via the oral route. ODF modifications can be defined as, *"any alteration of an oral dosage form that can be performed at the point of administration"* (66). These modifications are undertaken to facilitate medicine administration to patients with difficulty swallowing the intact dosage form (e.g. crushing tablets or opening capsules) or to facilitate fractional dosing (administration of part of an ODF to allow administration of a lower dose e.g. splitting tablets). Studies have shown that between 24.1% and 31.0% of all tablets prescribed for adult patients in primary care are split prior to administration (96, 97), with data from LTC facilities indicating that 35.4% of older adults receive at least one split medication (100). ODF modifications to overcome swallowing difficulties are also prevalent, with up to one third of all instances of medicine administration, to older patients in LTC facilities, involving ODF modification (236). Data from primary care suggest that between 9.0% and 37.4% of adult patients experience difficulty swallowing tablets and capsules, with the majority of those affected modifying the dosage form to overcome these difficulties (85, 86).

There are a number of safety and efficacy concerns around modified medicines such as reduced dose accuracy, reduced drug stability and the potential to affect the pharmacokinetic and pharmacodynamic profile of the drug *in vivo* (106, 126, 225, 237-239). Both UK and Irish guidelines advise that modifications should only be undertaken as a "*last resort*" (104) when "*other methods have been considered*" (150). In addition, there is growing concern amongst regulatory agencies about fractional dosing (178, 179). However, despite this, evidence shows that ODF modifications are a routine part of clinical practice (96, 102, 240). While modifications may be necessary due to a lack of appropriate licensed formulations (97, 100, 240), it is clear from the literature that modifications occur even in situations where alternative formulations are available (96, 97, 219) and/or in situations where the modification is expressly prohibited by the manufacturer's guidelines (96, 97, 102, 219).

Whilst quantitative studies have provided useful evidence and highlighted concerns about the practice of ODF modification, they have not elucidated the factors that influence the decision to modify. Healthcare professionals prescribe, dispense and administer modified ODFs (97, 141) and patients modify medicines, often without the knowledge of their healthcare providers (87, 97, 141). These quantitative studies suggest that both healthcare professionals and patients: experience difficulty when modifying medicines; display significant knowledge deficits about ODF modification and; have concerns about the appropriateness of modification (97, 102, 141, 241). Qualitative research methods can provide further insights into

the knowledge, attitudes and beliefs of those who modify to gain a deeper understanding of the factors that influence behaviour and practice. Qualitative studies have been undertaken to investigate ODF modifications, but to date, no systematic review of this literature has been conducted.

3.3 Aim of the systematic review

The aim of this systematic review was to synthesize the available qualitative research on the knowledge, attitudes and beliefs of adult patients, healthcare professionals and carers about ODF modification.

3.4 Methods

Details of the protocol for this systematic review were registered on the International Prospective Register of Systematic Reviews (PROSPERO) and can be accessed at:

www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015023494.

3.4.1 Search strategy

A systematic literature search of the following databases, from inception to September 2015, was undertaken: PubMed, Medline (EBSCO), EMBASE, CINAHL, PsycINFO, Web of Science, ProQuest Databases, Scopus, TRIP, CENTRAL and CDSR. No language or date restrictions were placed on the initial search. A comprehensive

search strategy was devised, using index and free-text terms related to (i) patients, healthcare professionals or carers, (ii) medicine modification, (iii) knowledge and (iv) qualitative research. The search strategy was initially developed by the primary author (AMG) and subsequently approved by a qualified medical librarian prior to undertaking the searches. The search strategy is provided in Appendix 3. The reference lists of included studies were hand-searched to identify additional relevant studies. Citation tracking of included studies was also undertaken. A search for grey literature was completed by searching the OpenGrey database, internet searching and using personal knowledge to identify further potentially relevant sources. The initial search was undertaken in September 2015 and an updated search was undertaken in June 2016.

3.4.2 Study selection

Titles were screened by one reviewer (AMG) to remove studies that did not meet the eligibility criteria. Each abstract was independently screened by two reviewers (AMG-full set and LJS or AMC). The full-text of articles identified as potentially eligible based on the abstract were obtained and assessed independently by two reviewers for inclusion (AMG and; LJS or AMC) according to *a priori* inclusion and exclusion criteria. In the case of any discrepancies between reviewers at any stage, a third reviewer independently examined the study and following discussion, a consensus on inclusion was reached by all three reviewers.

3.4.3 Eligibility criteria

Studies were eligible for inclusion if they met the following criteria: (i) qualitative data collection and analysis methods; (ii) full-text available in English; (iii) included adult patients (aged 18 years or older) who required ODF to be modified to meet their individual needs or; (iv) included carers or healthcare professionals (doctors, nurses, pharmacists, speech and language therapists) of patients who require ODFs to be modified. Whilst this thesis, as outlined in Chapter 1, is primarily concerned with ODF modifications for older adults, it was decided *a priori* that, for this review, qualitative studies that investigated knowledge, attitudes and beliefs about ODF modifications for adult patients in general would be included. The review team felt that perceptions and beliefs about modifications for adults were likely to be similar to, or at least inform, those for older adults. Therefore, particularly as this is a qualitative review, it was felt that use of an arbitrary age cut-off may be unnecessarily restrictive and result in useful concepts and insights being missed. To ensure the relevance of the findings to the older cohort, it was decided *a priori,* that if there was any evidence that the prominent themes differed based on the age of patients, the results would be presented separately. For studies undertaken using mixed methods, only the qualitative component was included. Debate exists as to whether survey data is considered qualitative or quantitative, which has posed an issue in previous qualitative systematic reviews (242). It was decided *a priori* that surveys would be excluded if the results were purely quantitative in nature, as these data lack the necessary "*conceptual depth and richness*" (243). This approach has been used previously (244). Quantitative studies, systematic reviews, meta-analyses, meta-syntheses, editorials, commentaries, letters and conference

abstracts were excluded. The primary outcomes of interest were patients', healthcare professionals' and carers' knowledge, attitudes and beliefs about the modification of ODF.

3.4.4 Data extraction

The data extraction form developed by NICE (212) was modified by AMG to meet the requirements of the systematic review. Data from the included studies were extracted by AMG. A second reviewer (AMC) independently verified the extracted data. Any disagreements were resolved by discussion and a consensus was reached by both reviewers.

3.4.5 Quality appraisal

The quality of the included papers was independently assessed by LJS and AMG using the CASP tool for qualitative research (245). The CASP tool was chosen as it allows for assessment of the rigour, credibility and relevance of qualitative research (213). In the case of disagreements between reviewers regarding study quality, AMC independently assessed study quality and following discussion a consensus was reached by all three reviewers. There is debate about the value of undertaking a formal quality assessment for qualitative studies (246). Therefore, for this review, assessment of study quality was not used to guide inclusion or exclusion of studies but rather to moderate the findings of the review based on the quality of the studies contributing to the final analytical themes.

3.4.6 Data synthesis

The thematic synthesis approach, as described by Thomas and Harden (2008) (247), was used to synthesise the findings of the eligible studies. This approach was chosen as it offers the advantage of *"staying 'close' to the results of the primary studies, synthesising them in a transparent way, and facilitating the explicit production of new concepts and hypotheses"* (247). Through this process, analytical themes are generated that offer new interpretations that "go beyond" the results of the primary studies (248). The thematic synthesis approach involves three stages: (i) free line-by-line coding of the findings of the primary studies; (ii) organisation of "free codes" into descriptive themes; (iii) development of analytical themes (247). QSR International's NVivo 10 Qualitative Data Analysis Software was used as an aid to the synthesis process (249). Initial line-by-line coding of all text labelled "Results" or "Findings" in eligible studies was performed independently by two reviewers (LJS and AMG). The coded text was compared to ensure that coding was assigned correctly and consistently. The generation of the descriptive themes was undertaken by two reviewers (LJS and AMG) during a group discussion. A third reviewer (AMC) independently examined and verified the descriptive themes generated and consensus was reached by all three reviewers. Finally, the descriptive themes were used to generate analytical themes. Analytical themes were initially generated by two reviewers (AMG and LJS) independently, following this a number of group discussions were undertaken to consolidate the analytical themes identified.

3.4.7 Reporting

This systematic review is reported in accordance with the Enhanced Transparency in Reporting the Synthesis of Qualitative Research (ENTREQ) guidelines (248) (Appendix 4).

3.5 Results

3.5.1 Study selection

In total, 6,911 articles were identified from the database search. Following the removal of 1,456 duplicates, 5,455 articles remained. Following the title screen, 5,290 records were excluded. Of the 165 articles that were examined for eligibility based on the abstract, 129 were excluded. The remaining 36 full-text articles were reviewed to identify those that met the inclusion criteria for the review. During this stage, 31 articles were excluded. Two additional studies were identified through citation tracking of the included articles; no additional records were identified from hand-searching the reference lists. Therefore, seven articles were included in the systematic review. No additional studies were identified in the updated search in June 2016. Figure 3.1 outlines the process of study selection.

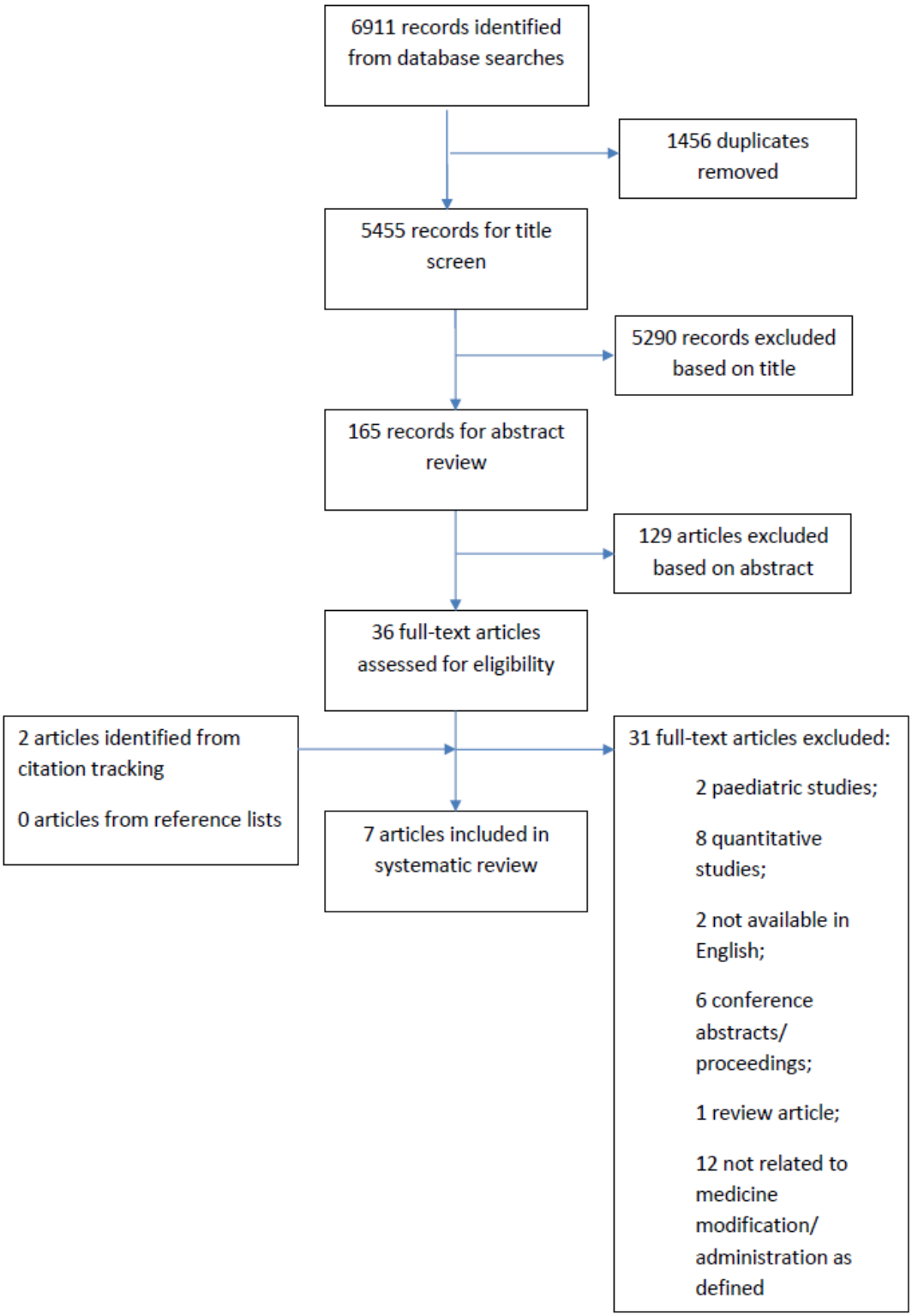

Figure 3.1 Flow diagram of study selection process

3.5.2 Study characteristics

The characteristics of the included studies are summarised in Table 3.1. The views of healthcare professionals were examined in three of the studies: one study included nurses (156); one included physicians (250) and; one included a mixed sample of healthcare professionals (157). The remaining four studies investigated the views of patients (251-254). All of the studies involving healthcare professionals were directly related to the topic of this review (156, 157, 250). For the studies involving patients, one study directly addressed the topic of interest (252). Of the remaining three studies undertaken in patient cohorts, two investigated the problems experienced by patients in managing their medication (253, 254) while one examined factors related to adherence (251). For these three articles, a number of the findings addressed the topic of interest and these findings were included in the synthesis for the review. Modifications to facilitate fractional dosing were discussed in three of the studies (251, 253, 254), while modifications for swallowing difficulties were the topic under consideration for four of the studies (156, 157, 250, 252). The majority of included studies focused on medications for older adults (156, 157, 252-254). Of the remaining studies, one included patients between 52 and 92 years of age (251), while the final study investigated the views of physicians about medications for adults with chronic pain and dysphagia (250). Therefore, the findings of the review are mainly pertinent to the older cohort and no variation in ideas or concepts were evident based on age.

Table 3.1 Characteristics of included studies (listed alphabetically according to first author)

Reference (Year)	Location	Participants (n)	Method	Analysis	Aim	Analytical Themes
Barnes *et al.* (2006) (156)	South Australia	Registered Nurses (n=11)	Semi-structured interviews	Thematic analysis broadly following Ekman and Segesten	To explore issues concerning the nursing practice of altering medication dose forms prior to administration of medicines to residents in homes for older people	Patient-centred individuality and variability; Communication; Knowledge and uncertainty; Complexity.
Borgsteede *et al.* (2011) (251)	The Netherlands	Patients with type 2 diabetes mellitus (T2DM) (n=20)	Semi-structured interviews	Content analysis and constant comparison	To explore both factors related to high and lower levels of adherence that patients experienced in their medication use and to reflect upon the findings in the context of patient education and shared decision-making.	Patient-centred individuality and variability; Knowledge and uncertainty; Complexity.

Reference (Year)	Location	Participants (n)	Method	Analysis	Aim	Analytical Themes
Kelly *et al.* (2009) (157)	United Kingdom	Consultant physicians; nurses; pharmacists; dietician; speech and language therapist and; a senior lecturer in pharmacy practice (n=10)	Focus group	Content analysis using Colaizzi's method	To identify the problems experienced by healthcare professionals related to administering medicines to patients with dysphagia and the solutions they use to overcome them	Patient-centred individuality and variability; Communication; Knowledge and uncertainty; Complexity.
Kelly *et al.* (2010) (252)	United Kingdom	Patients (n=11)	Semi-structured interviews	Content analysis using Colaizzi's method	To understand the experiences of taking medication for older people with dysphagia	Patient-centred individuality and variability; Communication; Knowledge and uncertainty; Complexity.

Reference (Year)	Location	Participants (n)	Method	Analysis	Aim	Analytical Themes
Notenboom *et al.* (2014) (253)	The Netherlands	Patients aged ≥70 years (n=59)	Semi-structured interviews	Coded according to a coding scheme; Framework type analysis	To identify the practical problems that older people experience with the daily use of their medicines and their management strategies to address these problems and to determine the potential clinical relevance of thereof	Patient-centred individuality and variability; Knowledge and uncertainty; Complexity.
Pergolizzi Jr *et al.* (2014) (250)	United States of America	Physicians (n=34)	Semi-structured phone interviews	Content analysis	To understand the knowledge, attitudes, and practices of physicians and the beliefs of patients regarding the treatment of chronic pain in the presence of dysphagia	Patient-centred individuality and variability; Communication.

Reference (Year)	Location	Participants (n)	Method	Analysis	Aim	Analytical Themes
Tordoff *et al.* (2010) (254)	New Zealand	Patients ≥65 years (n=20)	Semi-structured interviews	Grounded theory and constant comparison	To explore how people aged 65 years and older in New Zealand manage their medicines in their own homes and the problems and concerns they might have with taking them	Patient-centred individuality and variability; Communication; Knowledge and uncertainty; Complexity.

3.5.3 Quality appraisal

A summary of the results of the quality appraisal for the included studies is shown in Table 3.2. All of the studies provided a clear statement of the aims of the research, used qualitative methodology appropriately, used an appropriate research design and an appropriate recruitment strategy. Three of the studies did not provide sufficient detail about data collection (157, 250, 253); with two of the studies not discussing data saturation (157, 250) and one not providing detail about the use of a topic guide (253). Four of the studies did not address reflexivity which relates to the researcher considering their role and potential bias (156, 157, 250, 253). Two of the studies did not provide sufficient detail about the data analysis process, particularly in relation to the number of researchers who performed the analysis (157, 250). Finally, one study did not state whether ethical approval had been obtained, did not provide participant quotations to substantiate findings nor discuss in detail the findings in light of existing evidence or the implications for practice (250).

Table 3.2 Quality appraisal of included studies using the Critical Appraisal Skills Programme (CASP) Qualitative Research Checklist (245)

Quality Appraisal Criteria	Barnes *et al.* (2006) (156)	Borgsteede *et al.* (2011) (251)	Kelly *et al.* (2009) (157)	Kelly *et al.* (2010) (252)	Notenboom *et al.* (2014) (253)	Pergolizzi Jr *et al.* (2014) (250)	Tordoff *et al.* (2010) (254)
Clearly stated aim(s)?	√	√	√	√	√	√	√
Qualitative methodology appropriate?	√	√	√	√	√	√	√
Appropriate research design?	√	√	√	√	√	√	√
Appropriate recruitment strategy?	√	√	√	√	√	√	√
Data collection?	√	√	U	√	U	X	√
Reflexivity?	U	√	U	√	U	X	√
Ethical issues considered?	√	√	√	√	√	X	√
Rigorous data analysis?	√	√	U	√	√	X	√
Clear statement of findings?	√	√	√	√	√	U	√
Value?	√	√	√	√	√	√	√

Legend: √ = Yes; X = No; U = Unclear

3.5.4 Analytical themes

Four themes emerged from the synthesis: (i) patient-centred individuality and variability; (ii) communication; (iii) knowledge and uncertainty and; (iv) complexity.

3.5.4.1 Patient-centred individuality and variability

The central role of the patient and the importance of recognising the inherent inter- and intra-patient variability emerged as a strong theme in all studies (156, 157, 250-254). Individuality is key and variability of individual patient's needs and requirements has an important role in ODF modification. Although Tordoff *et al.* (254) reported that, "Most people had no difficulty swallowing tablets", it was clear from all the studies that many patients experience difficulty with medication administration and modification. A number of factors contribute to this variability including: medical conditions (156, 157, 250, 252); patient-related factors (156, 157, 251-254); and medication-related factors (156, 157, 250-254) which can be further complicated by family and institutional influences on decision-making (156, 157).

Many medical conditions can lead to dysphagia/ difficulty swallowing medicines thereby complicating medicine administration (156, 157, 250, 252) including: stroke (156, 252); cognitive impairment/dementia (156, 157); cancer (250); Parkinson's Disease (156, 157) and; epilepsy (157). However, the variable nature of these medical conditions further complicates ODF administration (157, 252), as individual patients, despite having similar diagnoses, may have very different medication formulation requirements, "The first major theme is the broad spectrum of

dysphagia… *'There are three different categories of patient we've got here which give us problems with dysphagia'*…… each variation of dysphagia brings its own problems in relation to medicine administration" (157). In addition, the natural progression of these medical conditions means that a progressive decline in function is observed (157, 250, 252) or conversely, an improvement in swallowing capability can occur, "In the case of participants who were stroke survivors, swallowing could gradually improve" (252). Therefore, continuity of medication can be problematic with disease progression (157, 250, 252). It is clear that formulation choice and decisions regarding modification for individual patients are complicated by inherent variability; due to disease stage and severity.

Individual patient-related factors were reported in all studies as being important regulators of how medicines are administered. These included: patient decision-making for example choosing not to take medicines due to difficulty swallowing (156, 157, 251, 252) or chewing medicines (253, 254); patient medication preferences such as wanting to continue previous administration practices (156, 252, 254) or preferring to modify medicines despite an intact swallow (156, 252). In addition, administration practices varied, not only from patient to patient, but also for an individual patient from administration-to-administration and from day-to-day (156, 252) depending on additional factors including their mood at the time of administration, time of day and the number of medicines being administered.

Medication related factors including the size (156, 251-254), texture (252), shape (252), taste (156, 157, 252, 253), number of medicines (156, 250-252) and viscosity of oral liquids (157) were reported by patients and healthcare professionals as impacting on medication suitability and patient acceptability. However, the importance of medication characteristics varied from person to person (156, 157, 252, 254), "Small tablets were generally easier to swallow than large ones although one participant found small round ones the hardest to swallow. Three participants found large tablets difficult and two said that size and shape were irrelevant" (252). Therefore, the preferred formulation characteristics vary from patient to patient, which is a crucial factor complicating medicine administration.

The reasons that patients receive modified medicines may not be solely related to the individual patient's needs, requirements or preferences. Family members' influence on healthcare professional's decision-making was discussed in two studies (156, 157). This influence may result in healthcare professionals making decisions based on family member's priorities rather than patient's preferences, "… *[some] families tend to pill count and cost monitor and many of them prefer us to press on with the tablets and crush them rather than the [liquid] alternative which they prefer not to pay for … [t]here have been occasions where we've disregarded the resident's request and favoured the family's insistence in relation to the crushing of medication"* (156). Institutional and professional issues were also discussed as important factors influencing medicine administration practices. Barnes *et al*. (156) highlighted the pressure placed upon nurses to ensure prescribed medicines are

administered, “All but one nurse presented the need to ensure that prescribed medications were administered as the dominant imperative”, along with the pressure to complete medicine administration in a timely manner, “Thus, the overall organizational requirements, including completion of the medication round, often took precedence over attending to individual needs of particular residents” (156).

Numerous options were discussed to overcome difficulties with formulations including: changing the formulation, for example to oral liquids (156, 157, 250, 252); discontinuing unnecessary medications (157, 254); using various coping strategies e.g. the chin-tuck position, or using food or various liquids to facilitate intake (252-254) or; modifying ODFs (156, 157, 250-254). It was noted that alternative formulations were often not available (156, 250) or there was a lack of knowledge about the availability of alternatives (156, 252). However, even in situations where alternative formulations were available, other problems arose including: cost (156, 157, 250); unsatisfactory formulation characteristics (157) and; poor patient acceptability (157, 252). Therefore, these issues can result in alternatives not being fit for purpose and modifications of ODFs are preferable or necessary.

3.5.4.2 Communication

The importance of communication was a recurring theme in the majority of included papers (156, 157, 250, 252, 254). While communication plays an important role in the optimisation of medicine administration and modification practices, poor communication and lack of communication presents a significant barrier that may negatively influence medicine administration. Two distinct lines of communication were seen; communication between patients and their healthcare professionals and communication between healthcare professionals.

Communication between patients and their healthcare professionals

Communication between patients and their healthcare professionals also influenced modification practices and the selection of appropriate alternatives that avoided the need for modification. In general, patients had a positive view of their healthcare professionals (157, 252). However, there were examples of poor communication between patients and healthcare professionals, which negatively impacted upon medication adherence; "One man, finding it hard to break his aspirin tablets into quarters as prescribed, asked his GP [General Practitioner] to change them to the type he'd had in hospital. *'I've told him but he don't take any notice'* " (254). Good communication and continuity of care were important to patients, with locums unpopular as they are unfamiliar with the patient and their needs and preferences, "Key points were the need for GP continuity and the recognition that locums…are a drawback…So I thought, 'Don't call the locum!'" (252), "Variability of pharmacist was also identified as a problem, even when the

patient went to the same pharmacy: 'Also, where we go it always seems to be a different pharmacist. You never see the same ones. There doesn't seem to be a consistent one there'" (252).

One of the barriers to effective communication seems to focus on the healthcare professional's reactive, rather than proactive, approach to patient's difficulties or preferences (157, 250, 252). This is compounded by the observation by Barnes *et al.* (156) that individual patient's medication formulation requirements are not routinely or systematically assessed. As a result, healthcare professionals are unaware of patient's requirements and make decisions about medicines for their patients without fully appreciating their needs. This was particularly true in the case of pharmacists with patients reporting that different formulations were dispensed without the patient's views being sought, "Participant 3's pharmacist had changed the formulation of one of his medicines from a smooth-coated, torpedo-shaped tablet to a chalky form that he found difficult to take, and he put the change down to the tablets being cheaper" (252). However, communication should ideally be a two-way process and patients admitted that they often neglected to inform their healthcare professionals about the difficulties they experience with medications (157, 252). This may be due to many reasons: (i) aphasia (157); (ii) carers collecting medicines (252); (iii) patient's lack of knowledge that alternative formulations may be available (252) or; (iv) patients being unwilling to question healthcare professional's decisions (157, 252).

Communication between healthcare professionals

Extensive inter-professional communication to discuss individual patient's needs was reported in two studies (156, 157), "*We speak to the pharmacist for him to have a look at what medications they're on to see if those can actually be crushed before we actually give them crushed… [t]he (pharmacist) will… give us a suggestion as to what tablet, what alternatives we can use…and then we discuss it with the medical officer…*" (156). However, this inter-professional communication often takes place on an informal basis rather than being a routine and systematic process, "Nurses were concerned that they were working in an information vacuum, due to limited information resources and informal communication with other healthcare professionals" (156). While on the whole, communication and information sharing between healthcare professionals was noted as an aid to decision-making, a key issue, highlighted by Kelly *et al.* (157), centred on 'data flow' with necessary information not being available to the appropriate individual in a timely fashion. Data flow problems arose due to deficits in communication practices, for example, prescriptions tended not to specify the necessary formulation or that a patient had dysphagia (157) and communication between specialists and primary care was problematic (252). The varying expertise of the different members of the multidisciplinary team (MDT) further compounded these communication deficits, "Even if medicine charts do contain information on dysphagia there are problems identifying a common language… Thus, as identified by the speech and language therapist: *'We are not always sure what we should say...'* " (157). Therefore, the input of many different healthcare professionals was often necessary to make the

most appropriate decision, but the lack of a formal communication process hinders this. A formal, systematic process of communication between healthcare professionals would ensure that all the necessary information is available for decision-making and would facilitate information and expertise sharing on a routine basis.

3.5.4.3 Knowledge and uncertainty

Knowledge about medicine modification and administration was an important theme that emerged from the synthesis. Although confidence in one's knowledge and abilities was reported by one nurse, "*...I rely on my own knowledge of medication, which has always been quite comprehensive because I've always dispensed medication and I'm quite experienced*" (156), it was clear that overall there was a significant knowledge deficit and uncertainty about medicine modification and administration amongst both healthcare professionals (156, 157), "*… you're participating in a practice that you're really not totally au fait with*" (156) and patients (251, 252), "One of the issues that participants identified was their own lack of knowledge" (252). This knowledge deficit arose due to a lack of information and guidance related to medicine modification, particularly for healthcare professionals (156, 157). It was noted by Kelly *et al*. (157) that the availability of formal guidance or information from the manufacturers is limited as modifications generally represent an off-licensed use of the formulation, "…absence of information because medicine formulations are frequently altered in order to administer them to dysphagic patients and so are given outside licence" (157). This

was reiterated by Barnes *et al*. (156) who highlighted the deficits of commonly used resources, "*We have a series of medication resources, but not necessarily associated with the crushing of tablets, more associated with what the tablets are for*" (156).

Consequently, the lack of explicit information resources results in a reliance on informal information provided by healthcare professionals or continuation of previous medication modification and administration practices. For healthcare professionals, seeking the advice and recommendations of other members of the MDT was commonly undertaken (156, 157), "…the nurses reported discussing individual resident's medication needs with pharmacists and doctors" (156). However, although generally helpful, it was noted that different healthcare professionals have different priorities with the result that nurses reported receiving conflicting advice which complicated decision-making, "When the nurses sought advice about how to decide between the various options with which they were faced, they were sometimes given varying and contradictory advice. Different professional disciplines (nursing, medicine and pharmacy) that are involved in the provision of residential care had conflicting views about what should be done" (156). However, it was acknowledged that no one healthcare professional has all the knowledge and expertise necessary to make an informed decision for individual patients, "*… the knowledge related to dysphagia and medication that falls within each professional's sphere of* expertise" (157). Therefore, MDT involvement is vital to ensure that all necessary expertise is available. Healthcare professionals also relied on their previous experience and practice to guide decision-making, "*Nurses*

tend to put their own interpretation on how things are done – governed by perhaps their social background in nursing, by their experience in nursing, by their academic experience in nursing" (156). The lack of a standard knowledge base, reliance on previous practice and varying interpretation of guidance, led to varying and inconsistent practices.

Patients were very reliant on information provided by healthcare professionals (251, 252), "*...you follow his [the doctor's] advice... The pharmacy provides those big information sheets, with everything written clearly. Well you read everything*" (251). Therefore, healthcare professionals have an important role in providing information, knowledge and skills to patients, formally through the provision of verbal and written instructions but also informally, through observation of healthcare professional's practice (157, 252). However, both healthcare professionals (157) and patients (252) acknowledged that inconsistent practice by healthcare professionals led to patient confusion regarding best practice, "*… each time a different nurse gave it [the medicine] they gave it in a different form… so how the patient was meant to learn which form they should do when they go home … it would very confusing I would imagine*" (157). Similarly to healthcare professionals, patients also relied on their previous experience and reported the use of various coping mechanisms to overcome difficulties with their medications including using food, warm fluids or the chin tuck position to facilitate swallowing and using tablet devices or learned techniques to facilitate fractional dosing (251-254).

Due to this knowledge deficit, patients and healthcare professionals expressed concerns, fears and worries about modifying medicines, including concerns about the accuracy of fractional dosing (251, 253), the effect of the modification on the pharmacological action of the drug including absorption, the pharmacokinetic profile and adverse effects (156, 157, 252). There were also concerns about the methods used to modify medicines including the potential for cross-contamination (157). Conversely, some healthcare professionals expressed apprehension about not modifying medicines as this may lead to medicine discontinuation or choking (156, 157).

3.5.4.4 Complexity

Complexity was a key theme that emerged from the synthesis. Although complexity was a factor associated with the themes discussed previously, the overall complexity associated with nearly every aspect of decision-making for ODF modification ensured its importance as an analytical theme. This complexity was particularly related to the need to balance the advantages and disadvantages associated with modification and the complexity of the healthcare structure. Medicine modification was seen to be both necessary and advantageous as it: (i) facilitated administration of vital medicines (156, 252); (ii) promoted adherence (157, 252) and; (iii) overcame some of the concerns regarding choking (156) or medicine discontinuation due to difficulty swallowing (157). It also facilitated the administration of the correct dose for individual patients (253). However, there was a conflict between these advantages and the accepted disadvantages of

modification (including the lack of information (156, 157), difficulty modifying medicines (251, 253, 254), the unlicensed nature of administration (157), the impact on nursing workload and time management (156), the taste of modified medicines (156, 157, 252) and concerns around the efficacy and safety of modified medicines (156, 157, 252, 253)). This conflict must be negotiated by healthcare professionals and patients. Decision-making was complicated, as shown by the observation by Kelly *et al*., "Although both problems and solutions were discussed by the group, they were not separate issues because a solution in one area could be a problem in another" (157), which highlights the dilemma faced when trying to balance the conflicting aspects of medicine administration and modification. This leads to professional, therapeutic and ethical dilemmas.

This "complex" environment contributes significantly to the challenge of optimising ODF administration practices. Barnes *et al.* (156) summed up the situation, "This complex and 'messy' environment meant that the implementation and evaluation of the process of alteration of medications, rather than being systematic and orderly, was often *ad hoc*". This complexity arises due to a number of inter-related factors: the lack of a systematic, proactive assessment of patient's needs; the absence of clear, explicit evidence-based guidance for staff and patients; the informal communication structures and; the hierarchical structure of the healthcare system.

3.6 Discussion

This systematic review synthesised the available qualitative research evidence on the knowledge, attitudes and beliefs of patients and healthcare professionals about the modification of ODFs. Key challenges include; the variability of individual patient's requirements, poor communication practices and lack of knowledge which when combined with the multi-faceted healthcare environment complicate decision-making regarding ODF modification and administration. Although there were a limited number of eligible studies, particularly involving patients, the strength of this review lies in the fact that the synthesis included studies investigating the perspectives of both healthcare professionals and patients. This provides a deeper understanding of the challenges encountered from prescribing right through to medication-taking behaviour. In addition, the diverse nature of patients in the included studies is a strength of the systematic review as it highlights the range of experiences encountered. The similarity of findings between studies adds to the validity of the findings and highlights key areas that need to be addressed. However, it also served to elucidate differences in the knowledge, beliefs and priorities of patients and healthcare professionals which may give rise to misunderstandings and conflict in practice.

This review highlights that ODF selection for patients is complicated by the variable nature of patient's needs and preferences, which is influenced by the interplay between patient's medical conditions, patient's preferences, formulation characteristics as well as external influences including family input. Whilst it is

widely accepted and recommended that healthcare providers treat the patient as an individual and *"for services to be tailored to respond to the needs, preferences and values of the patient"* (255), the continual move towards clinical guidelines, protocols and treatment algorithms has raised concerns about the standardization of medical care at the expense of individualised patient-centred care (256). While there are on-going efforts to ensure that patient's preferences are considered in the implementation of evidence-based guidelines, it is clear from this synthesis that variability of patient disease state and preference is a major factor that must be considered when choosing appropriate formulations. Therefore, communication, between patients and healthcare professionals and between different healthcare professionals, is vital. This review has also illustrated however, that poor communication between patients and their healthcare professionals is widespread and results in poor awareness of patient's needs. This finding is consistent with previous studies that report that patients do not discuss their difficulties with medication with their healthcare professionals and healthcare professionals do not routinely enquire about these difficulties (86, 87). There is a clear need for the routine evaluation of patient's ODF requirements prior to the prescribing, dispensing and administration of medication. This echoes the findings of the quantitative systematic review in Chapter 2, which called for the development and routine use of a validated screening tool to identify patients with difficulty swallowing medication (236). Use of such a tool may help to overcome the current communication deficit and informal, *ad-hoc* assessment process. Communication between members of the MDT, particularly at transitions of care, was also shown to be suboptimal, which is in-line with previous literature (223). Continuity of

healthcare at transitions of care is a major challenge facing the healthcare system (257). Again, a formal, systematic process of communication may help to address this, as structured communication has been shown to improve the effectiveness of information transfer and communication between healthcare professionals (258).

In order to make appropriate decisions for individual patients, healthcare professionals require timely access to evidence-based information. A clear issue that emerged from the synthesis is the lack of information about the appropriateness of ODF modifications which created a knowledge deficit and subsequent concern amongst healthcare professionals. Given that patients rely on their healthcare professionals to provide advice about medication use, this invariably results in a lack of knowledge amongst patients about ODF modifications. Previous research has shown an absence of explicit information to support clinician decision-making regarding modifications (96). The absence of accurate, evidence-based information contributes to the concerns of patients and healthcare professionals and the complexity of decision-making. Improved education regarding ODF modification may be one method of improving knowledge; however this needs to be supplemented by increased availability of information about the potential consequences of modification of medicines.

This review has highlighted the complexity associated with ODF modifications and the challenges of optimising ODF administration. Interventions to reduce

inappropriate tablet splitting have focused on the prescriber (259, 260). Both studies reported that the implementation of a computerised decision support and warning system reduced the frequency of inappropriate splitting, with Hsu *et al*. (260) reporting a substantial effect on prescribing behaviour. However, Quinzler *et al.* (259) reported that half of all alerts were not acted on by the physician despite a more suitable formulation being available in 82% of cases. Bourdenet *et al.* (261) investigated if recommendations on crushing tablets could lead to an improvement in crushing practices. Following the implementation of these recommendations, significant reductions in medicine crushing and inappropriate crushing were seen. A study by Hanssens *et al.*(262) found that a two-day training program improved nurses' knowledge about medicine administration for patients with swallowing problems and feeding tubes, however, the impact of this improvement in knowledge on practice was not assessed. The results of this synthesis suggest that a complex, multi-faceted intervention will be required to optimise ODF modification practices and future interventions should be cognisant of the findings of this review. Any intervention or quality improvement initiative must consider all the factors and challenges encountered by patients and healthcare professionals in daily practice. This review has served to highlight some of the prominent influencing factors. A gap in the literature is the absence of qualitative research investigating carers' perceptions of ODF modification. Further research investigating the views of healthcare professionals and patients is also necessary given the limited evidence available. In particular, given the observation that many patients without any clinical evidence of dysphagia are modifying ODF without the knowledge of their healthcare professionals, further research directly focusing on

ODF modification from the perspective of patients is required. Only one such study has been reported to date.

The results of the synthesis suggest that to optimise ODF modification and administration practices, input is needed from patients and all members of the MDT. The needs of patients should be routinely and systematically assessed when medications are prescribed and dispensed. Decision-making should take into consideration the individual needs of the patient but reliable and pertinent information from drug manufacturers, guidelines and recommendations from healthcare colleagues are needed to support this.

There were a number of limitations associated with this review. For three of the studies involving patients the review topic was not the sole focus of the studies, therefore, not all the findings were relevant for inclusion in the synthesis. The inclusion of English language articles only, may hinder the generalizability of the findings.

3.7 Conclusions

Through the synthesis of the existing qualitative literature, the findings of this systematic review have highlighted that the key factors influencing the knowledge, attitudes and beliefs of patients and their healthcare professionals about ODF modifications are: patient-centred individuality and variability; communication;

knowledge and uncertainty and; complexity. These factors can act as both barriers and facilitators to medicine administration and modification. It is evident from the synthesis that the individual needs of patients should be routinely and systematically assessed and that decision-making should be based on evidence-based recommendations with multidisciplinary input. Further research is needed to optimise ODF modification practices and the findings of this synthesis should inform the development of future interventions.

3.8 Acknowledgements

We would like to acknowledge Mr. Joe Murphy, Medical Librarian, for his assistance with the search strategy.

Chapter 4: The modification of oral dosage forms for older adults: a retrospective audit of practices in an Irish aged care facility

Publication three:

Mc Gillicuddy A, Kelly M, Sweeney C, Carmichael A, Crean AM, Sahm LJ. Modification of oral dosage forms for the older adult: An Irish prevalence study. International Journal of Pharmaceutics. 2016;510(1):386-93. doi:http://dx.doi.org/10.1016/j.ijpharm.2016.06.056

4.1 Abstract

4.1.1 Background

Administering ODFs to older patients can be complicated by age-related changes in the swallowing mechanism and pharmacokinetic and pharmacodynamic changes that alter drug sensitivity. These age-related changes may result in the modification of ODFs to facilitate administration or to individualise dosing e.g. crushing or splitting tablets or opening capsules. These physical alterations may invalidate the product licence and can potentially affect drug quality, safety and efficacy.

4.1.2 Aim

The aim of this study was to investigate the appropriateness of ODFs for older adults by determining the prevalence of ODF modifications in an aged care facility (ACF) in the Munster region of Ireland. Secondary aims included identifying the most commonly modified medicines and the evidence-base for these modifications.

4.1.3 Methods

Ethical approval was granted for this retrospective, descriptive study by the Clinical Research Ethics Committee of the Cork Teaching Hospitals. The study was conducted in a 63 bed ACF in the Munster region of Ireland between April and August 2015. Patients were eligible for inclusion in the study if they were: (i) aged ≥65 years and (ii) were resident in continuing care (CC) on the 31st of December 2014 or were admitted for respite care (RC) between October and December 2014. Drug charts and medical notes for eligible patients were obtained. Details of all medications administered to patients were recorded. ODF modifications were

examined to determine if they were evidence-based: defined as complying with the terms of the Product Licence or one of two best practice guidelines (BPGs).

4.1.4 Results

In total, 111 patients were included in the study (mean age (standard deviation (SD)) 83.0 years (7.8); 66.7% female). Of the study cohort, 35.1% of patients (n=39) received at least one modified medicine. Medicines were most commonly modified to facilitate fractional dosing (82.0%) followed by to overcome swallowing difficulties (10.3%). Sixty-eight instances of medicine modification were undertaken for 32 medicines. Of these 68 modifications, 35.3% were authorised in the product licence. Of the 44 unlicensed modifications, 14 complied with BPGs. Therefore, 44.1% of modifications were not evidence-based.

4.1.5 Conclusions

This study highlights that clinicians routinely have to tailor commercial ODFs to meet older patients' needs despite the lack of an evidence-base for almost half of these modifications. The main factor contributing to the need to modify these medications appears to be the lack of appropriate, licensed dosage forms. However, reimbursement policies may also play a role. Research is needed to optimise medicine administration and to provide clinicians with much needed evidence to support their daily practice.

4.2 Introduction

Despite accounting for between 12 and 18% of the population of developed countries, people aged 60 years and over, consume approximately 50% of all prescribed medicines and are responsible for 60% of medication-related costs (49). Given the projected growth in the older population (199), healthcare systems are tasked with optimising medication use in an environment of increasing demand and expense. Provision of optimum medical care to older patients involves the consideration of a number of specific age-related challenges including pharmacokinetic and pharmacodynamic changes and increased susceptibility to adverse effects (8, 94). Pharmacists' involvement in strategies to increase the appropriateness of medicine use for older patients have shown favourable results (263-265), but as the healthcare system moves towards a more multidisciplinary approach, pharmacists need to continue to add value to MDTs. Pharmacists are recognised experts in medicine and have a unique understanding of all aspects of medication use, from formulation to use in a clinical setting. One area where pharmacists' specialised knowledge could be used is in the optimisation of medication administration by aiding the selection of appropriate dosage forms for the individualised needs of patients.

The oral route of drug administration is preferred as it is the simplest, most convenient and safest route of administration (65). Solid ODFs are favoured as they facilitate accurate drug dosing, in a manner that ensures the chemical and physical stability of the drug (65). However, for certain patients with individualised needs,

ODFs may prove problematic (266). Solid ODFs (e.g. tablets and capsules) may need to be modified for fractional dosing or to overcome actual or perceived swallowing difficulties. ODF modification appears to be quite prevalent in the community setting with between 59% (86) and 68% (87) of patients with difficulty swallowing medication modifying the ODF to facilitate administration. Tablet splitting is also common, with just under one in four tablets prescribed in a German study being split prior to administration (96). However, as identified in Chapter 2, there is a dearth of specific studies investigating medicine modification for older adults (236). Given that the prevalence of dysphagia increases with increasing age (72) and is higher in nursing home residents (63), difficulty swallowing oral medicines is likely to complicate ODF administration to older adults in ACFs. Older patients represent a heterogeneous cohort with a diverse range of pharmacokinetic and pharmacodynamic changes that may further complicate dosing. Therefore, ODF modifications may be required to meet the individual needs of older patients: to facilitate fractional dosing and /or to overcome difficulty swallowing medication. There is a clear need, as discussed in Chapter 2, to investigate the proportion of older adults receiving modified ODFs and to determine which medications are most frequently modified. This chapter aims to address this literature deficit using preliminary evidence from an Irish setting.

As previously discussed, ODFs are becoming increasingly complex as dosage forms control factors including the: (i) rate; (ii) extent; (iii) site of drug release and; (iv) drug stability, both in the dosage form and the gastrointestinal tract (65). If these

ODFs are modified to facilitate fractional dosing, the administered dose may not be accurate (128) and the method of modification may affect dosing accuracy (237). Modifications for fractional dosing or swallowing difficulties may affect the physical and chemical stability of the drug or the clinical performance of the drug through an increase or decrease in bioavailability, which may lead to adverse effects or toxicity or decreased efficacy (106, 110, 225, 226). These changes could potentially affect clinical outcomes for patients. In addition, the taste of the modified medicine may be an issue, which could impact on patient acceptability and adherence (156, 157, 252). In Chapter 3, it was evident that a lack of information resources about ODF modification resulted in a knowledge deficit about the practice which gave rise to uncertainty and concern amongst healthcare professionals. In addition to examining current ODF modification practices, it is vital that the evidence-base for these modifications is investigated to determine if clinicians are supported in their decision-making.

There is a growing acceptance that the needs of the older patient must be considered in the design, formulation and evaluation of medicines (64). The EMA have highlighted the importance of investigating if the specific needs of the older patient are being met and identifying the issues that should be addressed to ensure that medicines that are developed are suitable for older patients (267). By investigating the use of oral medicines in routine clinical practice, the needs of the older adult can be elucidated and drug development adapted to meet these needs.

4.3 Aim and objectives

The overall aim of this study is to investigate if practice-based evidence shows that there is a deficit of patient appropriate and patient-centred drug formulations for older patients. To achieve this goal, the primary objective of this study was to determine the prevalence of ODF modifications for older patients in an ACF, by pharmacist-led drug chart review. The secondary objectives were to identify the most commonly modified medicines, along with the accompanying rationale and the presence or absence of an evidence-base for these modifications.

4.4 Methods

4.4.1 Ethical approval

Ethical approval for the study was obtained from the Clinical Research Ethics Committee of the Cork Teaching Hospitals, Cork, Ireland (Appendix 5).

4.4.2 Study design and setting

This retrospective, descriptive study was undertaken in an ACF in the Munster region of Ireland between April and August 2015. The ACF comprises a 63-bed unit with two distinct patient cohorts: CC patients and RC patients. CC patients are long-term residents and generally have high dependence levels. RC patients are admitted for one or two weeks respite care and are generally reflective of a less dependent, community-dwelling population. A research pharmacist (AMG), not employed at the ACF, was responsible for data collection.

4.4.3 Inclusion criteria

Patients were eligible for inclusion if they met the following criteria:

- Aged ≥ 65 years
- Resident in a CC bed on the 31st of December 2014 or
- Admitted to a RC bed in the last quarter of 2014 (October to December 2014).

4.4.4 Data collection

For all eligible patients, drug charts and medical notes were obtained. Using a standardised data collection form, the researcher recorded demographic details for each patient (age, gender, category of admission and details of previous swallowing assessments).

Details of all drugs administered during 2014 (for CC patients) and in the last quarter of 2014 (for RC patients) were recorded. Medicines charted for "when required" (PRN) use were only included if the medication was administered. The following medication details were recorded: (i) name; (ii) dose; (iii) formulation; (iv) strength; (v) route of administration; (vi) instructions for ODF modifications on the drug chart and; (vii) initiation and discontinuation dates. In addition, AMG used her professional judgement to decide whether a modification would have been necessary, based on the dose prescribed, e.g. 12.5mg quetiapine necessitates halving of a 25mg tablet. A second pharmacist (MK), experienced in working in a

medication dispensing role in Ireland, analysed 20% of patient records to make an independent judgement as to whether a modification would have taken place and to allow determination of the inter-rater agreement. Any discrepancies were discussed and a consensus was reached about the likelihood of ODF modification.

Medications were categorized using the Anatomical Therapeutic Chemical (ATC) classification system. Analysis included recording the number of medications administered to patients. For changes in strength or brand of a medication, the medication was counted once only. If the formulation changed e.g. from immediate release to sustained release, this was recorded as two different medications. For non-chronic medications e.g. antibiotics, each non-consecutive administration was counted separately.

The evidence-base for the modification was assessed by determining whether the modification complied with the terms of the product licence, using the SPC or "Patient Information Leaflet" for each formulation. If the modification complied with the product licence it was considered to be a "Licensed Modification". If the modification was not authorised using these sources, the modification was checked against two BPGs: "The NEWT Guidelines for Administration of Medication to Patients with Enteral Feeding Tubes or Swallowing Difficulties" (159) and; the "Handbook of Drug Administration via Enteral Feeding Tubes" (160). The modification was considered to be evidence-based if it was recommended in at

least one of these guidelines. Figure 4.1 details the process of determining whether the modification was evidence-based.

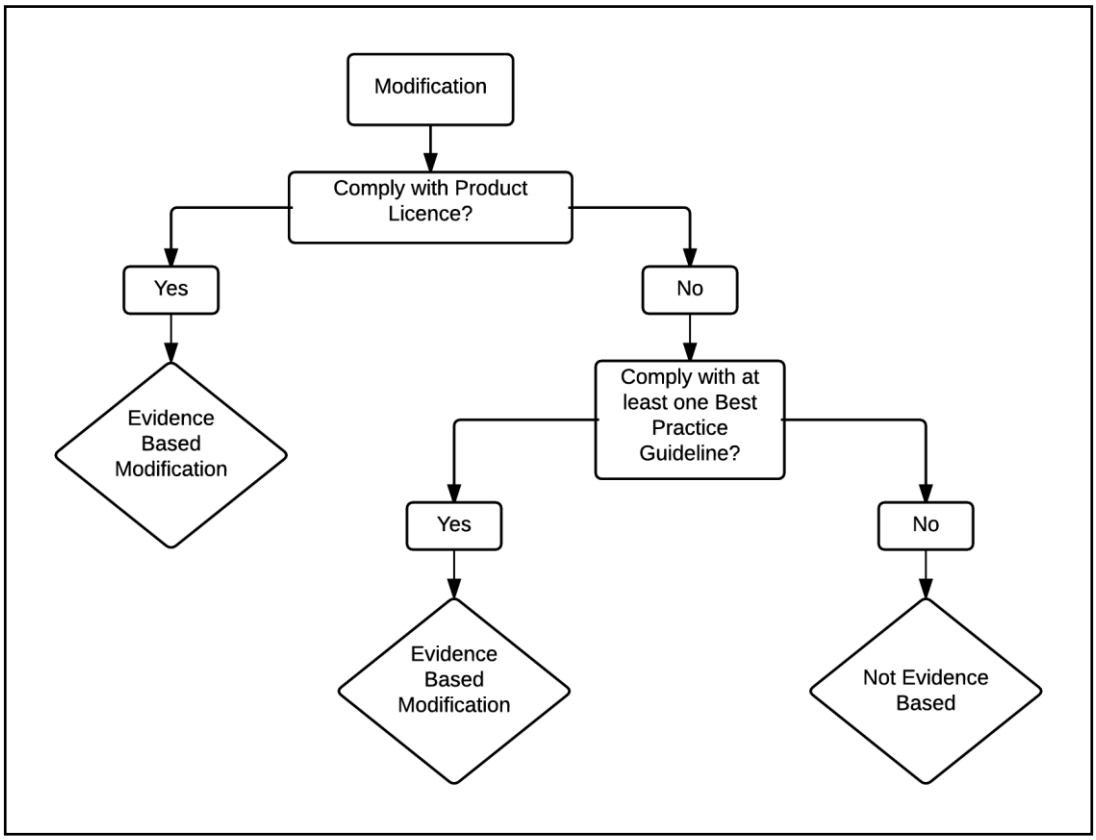

Figure 4.1 Decision process for determining if a modification was evidence-based

4.4.5 Statistical analyses

Data were analysed using IBM's Statistical Package for the Social Sciences (SPSS) for Windows, Version 22.0 (IBM Corp., Armonk, NY). Descriptive analysis was undertaken for categorical variables and reported as percentages. Mean and SD were recorded for normally distributed numeric variables, and median and interquartile range (IQR) were reported for non-parametric data.

Associations between categorical variables were assessed using Pearson's Chi-square test, Yates continuity corrected Chi-square test or Fisher's Exact test as appropriate. The inter-rater agreement between pharmacists for the need for ODF modification was measured using Cohen's Kappa statistic. The guidelines proposed by Landis and Koch (268) were used to interpret the strength of agreement between raters. P values <0.05 were considered to be statistically significant.

4.4.6 Reporting

This study is reported in accordance with the "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) guidelines (269) (Appendix 6).

4.5 Results

4.5.1 Patient demographics

In total, 111 patients met the inclusion criteria for the study: 41 in CC and 70 in RC. Initially, 117 patients were identified based on the admission criteria; 5 were excluded as they were aged <65 years and one was excluded as no drug charts were available. Available drug charts were sourced for the 111 included patients. For five CC patients, not all drug charts were available. The available charts were treated as the full record for these patients. The mean age of study participants (SD) was 83.0 (7.8) years. The demographic details of the study cohort are summarised in Table 4.1.

Table 4.1 Demographic details of study cohort

		CC (n=41)	RC (n=70)	Total (n=111)
Gender	Male	26.8%	37.1%	33.3%
	Female	73.2%	62.9%	66.7%
Age	65-75 years	19.5%	14.3%	16.2%
	76-85 years	43.9%	51.4%	48.6%
	86-95 years	29.3%	31.4%	30.6%
	≥ 96 years	7.3%	2.9%	4.5%
Evidence of Swallowing Assessment[a]	Yes	26.8%	20.0%	22.5%
	No	73.2%	80.0%	77.5%

Legend: CC = Continuing Care; RC = Respite Care; [a] = Evidence from patient's notes that they previously had their swallow assessed/ had a recommendation for altered consistency food/ fluid

There were no statistically significant differences between the CC and RC groups based on gender (χ^2_{yates} (1) = 0.817, p=0.366), age range (χ^2 (3) = 1.918, p=0.590) nor evidence of previous swallowing assessment (χ^2_{yates} (1) = 0.355, p=0.551).

To assess the inter-rater reliability, records for 20% of patients (n=23) were examined by a second pharmacist who made a judgement regarding the requirement for medicine modification. There was very strong agreement between raters for the need for modification (k = 0.893, p<0.005). The kappa statistic of 0.893 indicates "almost perfect" agreement (268).

4.5.2 Medication use in the study cohort

The median number of medicines administered to the study cohort during their admission was 13 (IQR 9-19). The median number of oral medicines administered was 11 (IQR 7-13). There was no statistically significant difference in the likelihood of medicine modification for those receiving less than five medicines during their admission compared to those who received five or more medicines (p=0.551, Fisher's Exact Test).

4.5.3 Modification of medicines

Of the 111 patients, 35.1% (n=39) received at least one modified medicine. Medicines were significantly more likely to be modified for CC residents than for RC patients (χ^2_{yates} (1) = 8.542, $p<0.05$). The proportion of patients receiving at least one modified medicine based upon category of admission is shown in Table 4.2.

Table 4.2 Proportion of patients receiving at least one modified medicine according to category of admission

Oral Medicines Modified	CC (n=41)	RC (n=70)	Total (n=111)
Yes	53.7%	24.3%	35.1%
No	46.3%	75.7%	64.9%

Legend: CC = Continuing Care; RC = Respite Care

No significant associations were observed between medicine modification and age (χ^2 (3) = 1.942, p=0.585), gender (χ^2_{yates} (1) = 0.044, p=0.833) nor evidence of previous swallowing assessment (χ^2_{yates} (1) = 0.667, p=0.414).

Of the 39 patients who received modified medicines, the majority (69.2%) received one modified medicine, 17.9% received two, 7.7% received four, 2.6% received five and the remaining 2.6% received 10 modified medicines. The most common reason for modifying medicines for patients in the study cohort was to facilitate fractional dosing (82.0%). Other reasons included swallowing difficulties (10.3%) and percutaneous endoscopic gastrostomy (PEG) administration (5.1%). A low percentage of patients (2.6%) had medicines modified to facilitate both fractional dosing and to overcome swallowing difficulties.

Table 4.3 provides a breakdown of the most commonly modified medications according to ATC classification system. Medicines affecting the CNS were most frequently modified. Quetiapine; an atypical antipsychotic, was the most commonly modified medication accounting for 23.5% of all incidences of modification.

Table 4.3 Most commonly modified medicines according to ATC classification

ATC Code Classification	No. of modified medicines	No. of instances of modification	%
Alimentary Tract and Metabolism	4	8	11.8%
Blood and Blood Forming Organs	2	2	2.9%
Cardiovascular System (CVS)	11	15	22.1%
Central Nervous System (CNS)	14	41	60.3%
Anti-infectives for Systemic Use	1	2	2.9%
Total	32	68	100%

4.5.4 Evidence-base for modifications

Of the 68 instances of ODF modification, 35.3% of modifications complied with the terms of the product licence. Therefore, almost two thirds (64.7%) of all modifications were outside the terms of the product licence. Figure 4.2 details the proportion of modifications that were licensed according to the reason for undertaking the modification.

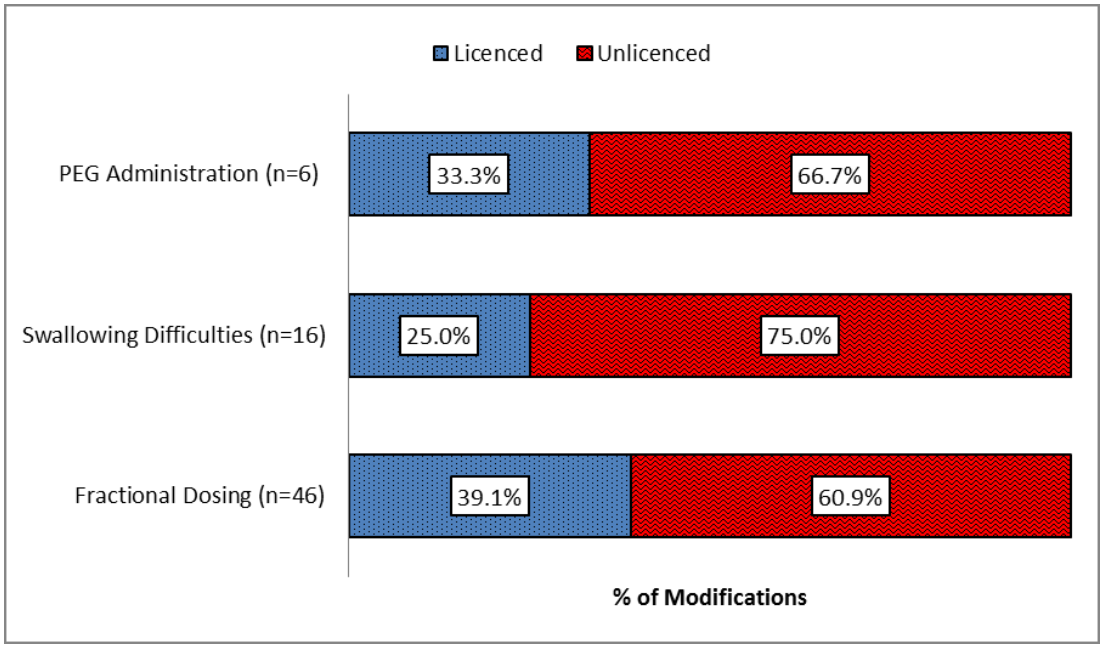

Figure 4.2 Licensing status of modifications categorised by reason for modification (n=68)

Of the 68 instances of medicine modification, 44 did not comply with the terms of the product licence. Of these 44, there were 14 that were permitted in at least one of the two BPGs. Therefore, 44.1% (n=30) were outside the terms of the product licence and were not recommended in either BPG. Table 4.4 details the unlicensed modifications and the evidence-base for these modifications.

Table 4.4 Evidence-base for unlicensed modifications

Medication	Modification	Incidence (n=44)	Comply with BPG	Reason for BPG non-compliance	Available solid ODF strengths	Alternative Formulation (Licensing Status)*
Quetiapine	Administer 12.5mg (halve a 25mg tablet)	14 (20.6%)	X	1	25mg, 100mg, 200mg and 300mg tablets	Oral Solution or Suspension (Unlicensed)
Quetiapine	Crush 25mg tablet	2 (2.9%)	√	N/A	25mg, 100mg, 200mg and 300mg tablets	Oral Solution or Suspension (Unlicensed)
Trazodone	Open 100mg capsule	1 (1.5%)	√	N/A	50mg and 100mg capsules 150mg tablet	Oral Solution (Licensed but not marketed)
Diazepam	Administer 1mg (halve a 2mg tablet)	1 (1.5%)	X	2	2mg, 5mg and 10mg tablet	Rectal Solution (Licensed); Oral Solution or Suspension (Unlicensed)

Medication	Modification	Incidence (n=44)	Comply with BPG	Reason for BPG non-compliance	Available solid ODF strengths	Alternative Formulation (Licensing Status)*
Alprazolam	Administer 125mcg (halve a 250mcg tablet)	4 (5.9%)	X	2	0.25mg, 0.5mg and 1mg tablets	Oral Suspension (Unlicensed)
Amitriptyline	Crush 25mg tablet	1 (1.5%)	√	N/A	10mg and 25mg tablets	Oral Solution (Unlicensed)
Escitalopram	Crush 10mg tablet	1 (1.5%)	X	3	5mg, 10mg, 15mg, and 20mg tablets	Oral Drops (Licensed but not marketed)
Venlafaxine	Crush 75mg tablet	1 (1.5%)	√	N/A	37.5mg and 75mg (immediate release) tablets	Oral Solution (Unlicensed)
Riluzole	Crush 50mg tablet	1 (1.5%)	√	N/A	50mg tablet	No Alternative
Warfarin	Crush 1mg or 5mg tablet	1 (1.5%)	√	N/A	1mg, 3mg and 5mg tablets	Oral Suspension (Unlicensed)

Medication	Modification	Incidence (n=44)	Comply with BPG	Reason for BPG non-compliance	Available solid ODF strengths	Alternative Formulation (Licensing Status)*
Spironolactone	Administer 12.5mg (halve a 25mg tablet)	1 (1.5%)	X	1	25mg, 50mg and 100mg tablets	Oral Suspension (Unlicensed)
Pravastatin	Crush 20mg tablet	1 (1.5%)	√	N/A	10mg, 20mg and 40mg tablets	No Alternative
Bumetanide	Administer 0.5mg (halve a 1mg tablet)	3 (4.4%)	X	2	1mg and 5mg tablets	Oral Liquid or Injection (Licensed but not marketed)
Amlodipine	Crush 10mg tablet	1 (1.5%)	√	N/A	5mg and 10mg tablets	Oral Solution or Oral Suspension (Unlicensed)
Rosuvastatin	Crush 5mg tablet	1 (1.5%)	√	N/A	5mg, 10mg, 20mg and 40mg tablets	No alternative
Midodrine	Administer 1.25mg (halve a 2.5mg tablet)	1 (1.5%)	X	2	2.5mg and 5mg tablets	No alternative

Medication	Modification	Incidence (n=44)	Comply with BPG	Reason for BPG non-compliance	Available solid ODF strengths	Alternative Formulation (Licensing Status)*
Bisoprolol	Administer 0.625mg (halve a 1.25mg tablet)	1 (1.5%)	X	1	1.25mg, 2.5mg, 3.75mg, 5mg, 7.5mg and 10mg tablets	Oral solution (Unlicensed)
Timolol and bendroflumethiazide	Administer 5/1.25mg (halve a 10/2.5mg tablet)	1 (1.5%)	X	1	10/2.5mg tablet	No alternative
Slow Sodium	Administer in Yoghurt	1 (1.5%)	X	4	600mg tablet	No alternative
Macrogol	Administer half a sachet	2 (2.9%)	X	1	13.8 gram adult sachet 6.9 gram paediatric sachet	No alternative
Nitrofurantoin	Open 50mg capsule	2 (2.9%)	√	N/A	50mg and 100mg tablets 50mg and 100mg capsules	Oral Suspension (Unlicensed)

Medication	Modification	Incidence (n=44)	Comply with BPG	Reason for BPG non-compliance	Available solid ODF strengths	Alternative Formulation (Licensing Status)*
Donepezil	Crush tablet	2 (2.9%)	√	N/A	5mg and 10mg tablets	Orodispersible Tablet (Licensed but not marketed); Oral Solution (Unlicensed)

Legend: BPG = Best Practice Guideline; 1 = Fractional dosing not recommended; 2 = Score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses, therefore, dose cannot be guaranteed; 3 = Disperse do not crush; 4 = Swallow whole with water; N/A = Not applicable as the modification was recommended in BPG; X= Did not comply with BPG; √ = Complied with at least one BPG; * = Refers to the marketing/licensing status in the Republic of Ireland; Unlicensed= Product licensed outside the Republic of Ireland or a product manufactured in a "specials" laboratory (270)

4.6 Discussion

The aim of this study was to determine the prevalence of ODF modifications for older patients in an ACF. ODF modifications were frequently undertaken, with over one third of residents receiving at least one modified medication. Almost half of all necessary modifications were not detailed in current evidence-based guidelines. In accordance with previous literature (220, 261), medicines affecting the CNS were modified most frequently, followed by drugs acting on the CVS, which indicates that these commonly prescribed medication classes, do not meet the needs of older patients and further research investigating this is necessary.

There is a lack of comparable evidence on the prevalence of ODF modifications for older adults. Previously, an Australian study reported that 18% of older patients received crushed tablets (102), while 32.3% of patients in a French study received crushed tablets or opened capsules (103). In contrast, in this study, any physical alteration of a dosage form, including fractional dosing, was included. Therefore, the prevalence of capsule opening and tablet crushing in this study setting is lower, but the overall prevalence of ODF modification is higher (35.1%) due to the inclusion of fractional dosing. Paradiso *et al.* (219) found that medicine modification was significantly more likely in high-care facilities compared to low-care facilities which concurs with the finding that the more dependent CC population were more likely to receive modified medicines than the RC cohort.

Studies and guidelines (63, 102, 271) have recommended that ODF modifications are best avoided due to the clinical and legal risks they pose and research has repeatedly called for further staff education and training to improve knowledge about the practice (102, 156, 272). However, in order to reduce the prevalence of ODF modifications, as observed in this and previous studies (102, 219, 220, 234), it is important to firstly consider and address the key factors that give rise to ODF modification.

The most common reason for modifying medication in this study was to facilitate fractional dosing. Previous research only considered crushing tablets or opening capsules (102, 103, 219, 220), with studies investigating tablet splitting considering this in isolation (96, 97). Fractional dosing has not been addressed extensively in the literature. However, age-related pharmacokinetic and pharmacodynamic changes may alter dosing requirements (89, 92, 93), leading physicians to “start low and go slow” (273), which may necessitate fractional dosing. Fractional dosing has also been proposed as a cost containment measure (274). This study represents a novel investigation as any alteration of an ODF was included. The majority of modifications for fractional dosing were unlicensed. Modifications for fractional dosing could affect dosing accuracy (237) and/or the pharmacological action of the drug *in vivo*. This would depend on factors including the therapeutic index of the drug and the characteristics of the formulation. However, to administer the appropriate dose for individual older patients, clinicians often need to prescribe fractional doses of ODFs (273). This highlights that the dosing requirements of older

adults are not being fully met by commercially available ODFs. Regulatory agencies are increasingly considering the issue of tablet splitting, with both the FDA and the EMA issuing guidelines related to the splitting of scored tablets to facilitate fractional dosing (178, 179). However, these guidelines are nonbinding recommendations, and in the case of the European guidelines relate to paediatric medicines. Therefore, a consensus effort is required to evaluate fractional dosing and how it relates to older patients.

In this study the most frequent ODF modification was the halving of 25 mg quetiapine tablets. This is a commonly reported modification for older adults (101, 275) and this modification arises due to a clear and unmet need. Unique patient factors undoubtedly contribute to this and have been discussed; i.e. pharmacokinetic and pharmacodynamic changes (8, 63, 236). Other studies have found that modifications may also arise due to the culture within the institution including prescribing, dispensing and administration practices and communication and MDT engagement (261, 262, 276). Alternatives to ODF modification recommended in the BPGs include unlicensed formulations or alternative medicines (104). However, the cost of alternatives can be prohibitive (157). The unlicensed formulation alternative for 12.5 mg quetiapine is an oral suspension. This product is over 10 times the cost of the halved tablet for 30 doses. Decisions regarding medicine use are increasingly dependent on budgetary considerations. Unlike quetiapine tablets, quetiapine suspension in the Irish setting is not funded under the GMS scheme, which entitles the patient to receive the drug at a substantially

reduced price, presenting a significant barrier to the use of this alternative. In addition to the cost/reimbursement challenges of these alternative formulations, many of these formulations are unlicensed with consequent implications for the prescriber (277) and the formulations may be difficult to source (156, 278).

However, direct and indirect costs need to be considered when evaluating the cost-effectiveness of expensive alternatives compared to modifying ODFs. It has been shown that administering a modified medication takes twice as much time as a non-manipulated drug (279), with consequent implications for nursing workload. Additionally, the cost of any deleterious consequences of inappropriate modifications must also be considered. In tandem with this, the potentially increased risk of medication errors also needs to be evaluated given the observation by Kelly *et al.* (234) that patients with dysphagia experience a significantly higher risk of errors compared to patients without dysphagia. Further research is needed to assess the cost-effectiveness of the various options.

In addition to the patient factors and budgetary factors discussed, other environmental/cultural factors can also contribute to ODF modification. Other studies have suggested that a lack of communication between the various healthcare professionals providing care for patients (156, 280), and between patients and their healthcare professionals (86, 87, 157), may present a barrier to optimisation of ODF administration for individual patients. This study site is unique

due to the presence of an on-site medical team and pharmacy, which is unusual in an ACF setting. Strict policies regarding the modification of ODFs for swallowing difficulties are in place, with a pharmacist reviewing all potential administration options. Decisions regarding modification are then made following consultation between the medical, pharmacy and nursing teams. The clinical implications of the modifications were not formally investigated in this study as it is beyond the scope. However, the observed modifications are considered by the authors to be unlikely to affect patient outcomes. In contrast, previous studies have reported that ODF modifications that could potentially affect patient outcomes/ lead to adverse reactions were observed (102, 219). This suggests that MDT involvement and detailed policies, as are in place in this study site, can help to ensure that ODF modification practices are optimised in so far as possible in situations where there is a lack of an evidence-base to support these modifications.

This study highlights that clinicians have no choice but to routinely tailor commercial ODFs to meet the needs of older patients. The lack of an evidence-base to support the modifications necessary to meet older patient's needs was of concern: over two-thirds of all modifications were unlicensed placing a substantial legal burden on the healthcare professionals involved (146, 208). Medication use involves balancing the risks associated with the medication and the benefits to be gained from treatment. Clinicians may determine that the need for treatment outweighs concerns regarding the unlicensed use of the medicine. However, given the lack of an evidence-base for 68% of the unlicensed modifications, further

research investigating common ODF modifications is required to provide clinicians with this evidence-base to support their decision-making. Ideally, clinicians would have access to data on the pharmacokinetic profile of modified medicines to allow evaluation of the potential clinical consequences of modification. The NEWT guidelines are, “a compilation of theoretical, practical and anecdotal information from a variety of sources” (159). In some, but not all, cases it may be supported by pharmacokinetic data possessed by the pharmaceutical marketing authorisation holder. Pharmaceutical companies are only required to provide information on the licensed use of medicines. If available, this pharmacological information would facilitate clinician decision making, however, issues around legal responsibility for any harms would need to be addressed.

A key issue also highlighted from this study is that commercially available, licensed ODFs are not meeting the needs of older adults from dosing or swallowing perspectives. These ODFs are routinely marketed based on the results of clinical trials that exclude older patients (95, 170, 281). There is a clear need for researchers, regulators and the pharmaceutical industry to prioritise engaging with older patients to facilitate the development of ODFs that meet the needs of this expanding patient cohort. A regulatory approach akin to that previously implemented to facilitate the development and accessibility of medicinal products for use in the paediatric population (282) may be required to achieve this aim. To ensure that the needs of older adults can be met, a key step will involve engaging with relevant stakeholders including older patients, their carers and healthcare

professionals in order to ascertain their needs, priorities and preferences around oral medicines.

The generalisability of the study results to other ACFs in Ireland and internationally is limited by inclusion of one site. In addition, the CC patients at this site are a highly dependent, frail population. However, the respite patients are more representative of a community-dwelling older population. There are limited data available on ODF modifications for older adults, and this is the first study in an Irish setting. This study represents a pilot study. The study was undertaken as a retrospective review, with the advantage that a large amount of data was obtained. However, there are limitations with this method: modifications may have occurred that were not recorded on the drug chart, there is no information about how the modifications were performed or how the modified medication was administered. Therefore, the prevalence of ODF modifications may be underestimated. Using the results generated in this study, a prospective study of medicine administration will be undertaken to detail how medicines are modified and subsequently administered.

4.7 Conclusions

This study provides practice-based evidence that ODF modifications are frequently necessary to meet the needs of older patients. Almost half of these modifications are not supported by a recommendation in BPGs. Modifications were most commonly undertaken to facilitate fractional dosing, followed by to facilitate

administration. The factors contributing to the necessity to modify ODFs for older adults are multifaceted. While the lack of availability of appropriate, licensed dosage forms is a major factor, other factors also play a role such as prevailing budgetary and reimbursement policies. To address the needs of older patients', further research is warranted; to identify problematic medications and any clinical implications of modifying medicines but also to address the factors contributing to this practice.

4.8 Acknowledgements

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Chapter 5: Nurses' knowledge, attitudes and beliefs about oral dosage form modification for older adults: a qualitative interview study

Publication four:

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5.1 Abstract

5.1.1 Background

Oral medicines are frequently modified to meet the needs of older adults. However, these modifications can have clinical, legal and/or ethical implications. Nurses, in acute and long-term care settings, bear responsibility for medicine administration and hence, perform these modifications.

5.1.2 Aim

The aim of this study was to investigate the knowledge, attitudes and beliefs of nurses about ODF modification for older adults.

5.1.3 Methods

A qualitative study was conducted using semi-structured, face-to-face interviews with nurses providing care to older adults in 16 purposively selected care settings in the Munster region of Ireland; 4 acute care (AC) and 12 long-term care (LTC) settings. Nurses were recruited by convenience sampling at these sites. Interviews were conducted between March 2016 and February 2017. Interviews were audio-recorded and transcribed verbatim. Data were analysed thematically. Interviews were conducted until no new themes emerged using the Francis method.

5.1.4 Results

Eighteen nurses participated (83% female, 67% LTC, 33% AC, median age 38.0 years (IQR 32.5-52.0)). Three major themes: modifying – *a necessary evil*; nurses' role as patient advocate and; modifying – *we are working very much as a team;* and two minor themes: fractional dosing; and covert administration; emerged from the data. Nurses viewed ODF modifications as being a routine and necessary

occurrence in older patient care due to limitations of available formulations and the presence of age-related challenges in drug administration. Nurses' knowledge of residents' requirements ensured that they advocate for those with individualised formulation needs, however nurses rely on pharmacists for information about modifications. Nurses expressed a desire for supports including increased education and ward-specific, pharmacist-developed recommendations on common modifications.

5.1.5 Conclusions

This study has provided useful insights into the views of nurses regarding ODF modification for older adults. The unique and varied formulation requirements of older adults must be acknowledged. Increased engagement by healthcare professionals, the pharmaceutical industry, regulatory agencies and policy-makers is required to facilitate the development of age-appropriate formulations. In the interim, practical interventions, informed by the findings of this study, are required.

5.2 Introduction

Medication administration is guided by a number of principles, with the ultimate aim of ensuring that the right medication is administered to the right patient at the right dosage, in the right form and at the right time (150, 283). Given the global trend towards an aging population (199, 284, 285), combined with the high rates of medication use amongst the older cohort (49, 201), there is widespread recognition of the need to optimise medication use for older adults (8, 286). However, various age-related changes, including dysphagia (67, 74, 80) and altered pharmacokinetics and pharmacodynamics (89, 92), can complicate the administration of the right form or the right dose of oral medication, resulting in ODFs being modified to meet the needs of older adults. Modifications of ODFs are of concern for healthcare professionals as they can potentially affect therapeutic outcomes for patients and adverse events have been reported as a consequence of medicine modification (106, 206).

Data from international literature has demonstrated that ODF modifications are undertaken to overcome difficulty swallowing (102, 103, 219, 287) and to facilitate fractional dosing (100) for older adults. The retrospective review of drug charts in an Irish ACF, described in Chapter 4, found that 35% of residents received at least one modified ODF during their admission (240). Whilst many of the factors that influence the need to modify will be similar across different countries, healthcare structures and settings, there may be nuanced, context-specific variables that influence the requirement to modify ODFs. Based on the modifications documented

in Chapter 4, various factors contributing to the need to modify medications in an Irish setting were postulated including supply and reimbursement issues (240). However, there is a limit to the insight that can be gained using quantitative research methods alone and other factors may play a substantial role in influencing daily practice.

Qualitative study methodologies can be used to gain a deeper understanding of the factors that influence this practice in healthcare (288). A number of qualitative studies have investigated medicine modification (156, 157, 252), however, as discussed in the systematic review of qualitative literature described in Chapter 3, there is a need for further research in this area given the limited number of studies (289). Whilst, "*The activities associated with medication management involve the nursing, midwifery, medicine and pharmacy professions and the patient/service user*" (150), ultimately nurses bear responsibility for medicine administration and therefore, perform modifications and administer modified medicines, in acute and long-term care settings. Despite this, only two previous qualitative studies investigated nurses views about medicine modification: an interview study conducted with nurses working in nursing homes in Australia (156) and; a focus group study from the UK, which investigated the experiences of ten healthcare professionals (including five nurses) of the challenges encountered in administering medication to patients with dysphagia (157). Neither study considered ODF modifications to facilitate fractional dosing. Investigation of the views and experiences of nurses about ODF modification will provide an insight into the

factors influencing this practice and the challenges encountered by nurses and patients on a daily basis. Increased understanding of these factors will aid the identification of potential areas for prioritisation for intervention and further research. Factors unique to the Irish healthcare setting may also be elucidated. This study will contribute to, and further develop, the evidence base in this area, given the inclusion of nurses working in acute and long-term care and investigation of all types of ODF modifications, including fractional dosing.

5.3 Aim of the study

The aim of this study was to examine the knowledge, attitudes and beliefs of nurses about the modification of ODFs for older adults (aged ≥65 years).

5.4 Methods

5.4.1 Ethical approval

Ethical approval for this study was granted by the Clinical Research Ethics Committee of the Cork Teaching Hospitals, Cork, Ireland (Appendix 7).

5.4.2 Study design

Semi-structured interviews were conducted with nurses who provide care for, and administer medicines to, older adults (aged ≥65 years) within the Munster province in the south of the Republic of Ireland (290). Semi-structured interviews were

chosen as rich, in-depth, detailed accounts of participant's experiences, perspectives and opinions can be generated and one-to-one interviews are particularly suited for discussing sensitive issues, such as individual nurse's medicine administration practices (288).

5.4.3 Study setting and sampling

Purposive sampling, which involves actively selecting the most productive sample to answer the research questions (291), was utilised for site identification. A sampling matrix of important variables was developed to ensure that the range of sites providing care for older patients were included. LTC settings from each category (public, private and voluntary (publicly funded but governed by a religious or charitable organisation)) (25); both with and without specialist dementia units (SDUs) were actively sampled (292). Previous research has shown that ODF modifications are more common in high dependency units (219). According to the Department of Health, the public nursing home sector in Ireland has the highest proportion of maximum dependent older people at just over 60%, compared to private nursing homes where almost 35% of residents are maximally dependent (293). Therefore, the funding category of the LTC site was used as a surrogate descriptor for dependency. In addition, ODF modifications have been shown to be more common in dementia care units (102), providing the rationale for this variable. In the AC setting, both acute geriatric hospital wards and acute stroke wards were sought as previous studies have demonstrated that modifications are commonly undertaken in wards of these types (261, 287). Interview participants

were identified by convenience sampling of nurses within the purposively selected sites. Where possible, two of each type of care site, and at least one nurse from each site were sought for inclusion in the study. For one category of LTC site, only one such facility was available in the geographical area in which the study was conducted.

The Medical Director or Director of Nursing at each of the purposively identified sites was contacted by telephone or e-mail and provided with details of the study. The person in charge approached individual nurses to identify potential participants. The inclusion criterion for interview participants was any nurse who provides care for, and administers medicines to, older adults (aged ≥65 years) at the purposively selected sites. Whilst healthcare assistants are also commonly employed in acute and long-term care settings in Ireland, their responsibilities centre on personal care and do not usually extend to medication administration. Therefore, in an Irish setting, nurses are responsible for medicine administration, providing the rationale for choosing nurses as the interview participants for this study. It was highlighted to nurses that participation was voluntary and no incentive for participation was offered. When a nurse expressed an interest in participating, the primary researcher (AMG) followed up with a telephone call to arrange a convenient time for the interview.

5.4.4 Data collection

The topic guide was developed by the authors based on a review of the literature (289), observations from a prevalence study (240) and the authors' practical knowledge of the research area. The topic guide was modified following piloting with an experienced geriatric nurse who provided feedback on the content and language. This pilot interview was not included in the analysis. The topic guide underwent iterative revision throughout the study, to ensure that emerging themes were captured in subsequent interviews. Table 5.1 provides a summary of the topic guide.

Table 5.1 Summary of topic guide for interviews

Medicine administration to older adults
Experience of medicine modification and medicine administration to older adults
Knowledge about ODF modification
Attitudes and beliefs regarding ODF modification
Factors influencing practice
Decision-making
Information sources/ resources used
Healthcare professionals and their involvement
Desire for any further resources/ supports

All semi-structured interviews were conducted by AMG, a research pharmacist with training in qualitative research methods and qualitative interviewing techniques. No relationship was established between the interviewer and the participants prior to study commencement. The interviews were conducted in a private area at the

participant's workplace between March 2016 and February 2017. Only the interviewer and participant were present during the interview. All participants provided written informed consent for participation. Prior to initiating the interview, participants completed a demographic data collection form which recorded details including: participant's gender; age; qualifications; length of time working with older patients and; details of any specific training undertaken in medicine administration. The interviews were audio-taped and transcribed verbatim by AMG. Transcripts were not returned to participants for comment and repeat interviews were not conducted. The interviewer recorded any relevant field notes after conducting the interview.

The method used by Francis *et al.* (294) was used to determine when data saturation had been reached. An initial analysis sample of fifteen and a stopping criterion of three were specified *a priori*. The initial analysis sample was determined based on the pre-specified stratification factors in the sampling matrix, which sought to recruit at least one nurse from each purposively selected study site. The stopping criterion of three required that a further three consecutive interviews were conducted, in which no new concepts emerged, to confirm that data saturation had been achieved.

5.4.5 Analysis

The "Thematic Analysis" approach, as described by Braun and Clarke (295), was used to analyse the data. The data (transcripts) were inputted into QSR International's NVivo 10 Qualitative Data Analysis Software to facilitate analysis (249). Thematic analysis involves six phases: (i) familiarisation with the data, (ii) generation of initial codes, (iii) searching for themes, (iv) reviewing themes, (v) defining and naming themes and (vi) producing the report (295). Data familiarisation began at an early stage with data transcription, reading and re-reading of the data. Open coding (phase 2) was undertaken by one author (AMG) to generate initial, non-hierarchical codes. These initial codes were then categorised and re-ordered to generate potential themes. The next step involved reviewing and refining the themes generated in phase 3. The fifth stage involved further analysis to refine the themes and to generate clear definitions and names for each theme. The final stage involved drafting of the report. Participants were not asked to provide feedback on the study findings.

To ensure that codes were applied consistently, a co-author (MK) independently coded a random sample of three interview transcripts. The inter-rater reliability between coders was determined by calculating the Kappa Coefficient for interviews coded by AMG and MK. The Kappa Coefficient measures the level of agreement, and ranges from 0 to 1; with 1 indicating perfect agreement and 0 indicating no agreement (268). In addition, each of the co-authors (LJS, AMC and MK) read six

interview transcripts to assess if the themes were reflective of the interview content, to further ensure the confirmability of the findings.

5.4.6 Reflexivity

The research team sought to address reflexivity during the design of the study. All four authors are pharmacists, and all are female. Two are academic staff members (one in Clinical Pharmacy Practice and one in Pharmaceutics) and at the time of the study, the other two researchers were PhD students (both in Clinical Pharmacy Practice). None of the researchers were employed at any of the study sites and they had no prior relationship with any of the nurses who participated in the study. All members of the research team have been involved in research investigating ODF modifications for older adults. The research team discussed their preconceptions and thoughts about the research area and all felt, based on their previous experience, that medicine modification was likely to be encountered by nurses in older patient care. However, all members of the research team acknowledged that they were unaware of the challenges encountered when physically performing medicine administration and modification as none had any previous practical experience in this area. Therefore, the views of nurses were given primacy and an inductive approach was seen to be most appropriate.

5.4.7 Reporting

This study is reported in accordance with the "Consolidated Criteria for Reporting Qualitative Research" (COREQ) guidelines (296) (Appendix 8).

5.5 Results

5.5.1 Characteristics of interview participants

Eighteen interviews were conducted. The interviews ranged in length from 7 minutes 19 seconds to 31 minutes 41 seconds, with a mean interview duration (SD) of 16 minutes 29 seconds (6 minutes 21 seconds). Twelve of the interviewed nurses worked in LTC and six worked in AC. Of the nurses who participated in the study, 83% were female. The median age of participants was 38.0 years (IQR 32.5-52.0). Seventeen nurses provided details about their experience caring for older people and the median length of experience in geriatric nursing was 8.0 years (IQR 5.0-11.5). Table 5.2 describes the characteristics of the interview participants.

Table 5.2 Characteristics of interview participants (n=18)

Characteristic		n (%)
Gender	Male	3 (17%)
	Female	15 (83%)
Age groups	20-29 years	1 (6%)
	30-39 years	10 (56%)
	40-49 years	2 (11%)
	50-59 years	4 (22%)
	60-69 years	1 (6%)
Nurse profession	Staff nurse	4(22%)
	CNM 1	1 (6%)
	CNM 2	5 (28%)
	Assistant Director of Nursing	1 (6%)
	Nurse (not specified)	7 (39%)
Care Setting (n=16)	Public LTCF with SDU (n=2)	2 (11%)
	Public LTCF without SDU (n=2)	2 (11%)
	Voluntary LTCF with SDU (n=1)	1 (6%)
	Voluntary LTCF without SDU (n=2)	2 (11%)
	Private LTCF with SDU (n=3)	3 (17%)
	Private LTCF without SDU (n=2)	2 (11%)
	Geriatric Ward in Acute Hospital (n=2)	4 (22%)
	Stroke Ward in Acute Hospital (n=2)	2 (11%)
Medicine administration training completed	Yes	17 (94%)
	No	1 (6%)
Medication administration training mentioned included: on-site medication management training courses, refresher courses, on-line training, undergraduate training, pharmacy-provided training		

Legend: CNM = Clinical Nurse Manager; LTCF = Long Term Care Facility; SDU = Specialist Dementia Unit

5.5.2 Inter-coder reliability

A Cohen's Kappa score of 0.924 was obtained which demonstrated aligned thinking between coders. In addition, following review of the themes in relation to interview content, all authors agreed that the themes generated were representative of the content of the interviews.

5.5.3 Themes

Three major themes emerged from the data: modifying - *a necessary evil*; nurses' role as patient advocate; modifying- *we are working very much as a team*. In addition, two minor themes emerged: covert administration and; fractional dosing. In order to comprehensively discuss nurses' views on the topic of medicine modification, these two minor themes will be briefly addressed.

5.5.3.1 Major themes

Modifying - *a necessary evil*

Modifications of ODFs were viewed by participants as being a routine and necessary part of clinical practice and were undertaken on a daily basis as part of drug rounds, "*That would be a daily basis*" (Nurse 12, AC). It was strongly felt that the older cohort in particular require modified medicines more frequently, *"To be honest I think that modifying medicines is a necessity, especially in elderly patients"* (Nurse 2, LTC), *"It would be very common here in the unit. It's a geriatric ward... it would be very common I suppose here because of our patient group"* (Nurse 10, AC).

Participants discussed a number of different types of modifications that they encountered, including tablet crushing, capsule opening, tablet splitting, dispersing or dissolving tablets and mixing medications with food. However, the modification that was reported as being most common was tablet crushing, *"In 95% of cases when we are talking about modifying medicines we are talking about crushing"* (Nurse 5, LTC). The necessity to modify medications was seen to be an inevitable part of older patient care and participants highlighted common reasons for this including: swallowing difficulties or dysphagia, medical conditions with dysphagia as a sequela, patient preference or difficulty with large dosage forms, family input and formulation characteristics. Overall, age-related swallowing difficulties and dementia were the most commonly implicated reasons for ODF modification. It was clear from the interviews that formulation suitability is extremely individualised, *"all patients are so different… so you'd be looking at lots of different types of medications… whatever fits in with the individual patient"* (Nurse 9, AC) and it is vital that each patient's needs are assessed on a regular basis due to the potential for fluctuations in formulation suitability, "…*you can see progressively the swallow or the level of cognition fluctuates, that affects the swallow and it's something that you are looking at and thinking, oh my god* [sic]*, this patient actually was taking oral tablets a matter of weeks ago and now it's a case of that we're dispersing them and giving them different suspensions… we are just keeping an eye out for ourselves* [nurses watch for changes in patient's ability to take different medication formulations]*"* (Nurse 9, AC).

Participants reported that alternative formulation options are investigated when patients experience difficulty with solid ODFs. Options discussed included changing the route of administration or the formulation of the medication e.g. liquid formulations, transdermal patches, dispersible tablets etc. The availability of appropriate alternative formulations was satisfactory for certain classes of medications e.g. antibiotics and anti-dementia medications; and participants expressed that in many instances the use of these alternatives was preferable to modifying solid ODFs. However, there was an almost universal acknowledgement that there were significant limitations associated with alternatives that often resulted in modifications of ODFs being required or even preferred including: lack of availability or difficulty sourcing alternatives; cost; alternatives not being covered on reimbursement schemes; difficulties administering large or small volumes; and issues with the viscosity of the liquids that may increase the risk of aspiration, *"…then we have liquid forms, again it's hard to give liquid form medications to people with swallowing difficulties because of aspiration"* (Nurse 13, LTC).

Participants expressed a wide variety of attitudes and beliefs about ODF modifications. As stated, it was clear that the majority of participants felt that modifications were a routine part of practice. Participants highlighted a number of benefits of modifying ODFs including ensuring that vital medications are administered and overcoming concerns about not modifying medications e.g. the risk of choking or discontinuation of necessary medication, *"Your choice is … crush the medicine which is what we do… or give the medication in its uncrushed form and*

run the risk of the person choking on it or not give the medicine at all and then, you know, the risk of the illness that's treating" (Nurse 5, LTC). However, notwithstanding the general acceptance of modifications as a routine occurrence, participants reported numerous concerns about modifications including: inaccurate dosing, altered drug absorption or effectiveness, potential interactions with food vehicles used for administration, possible cross-contamination issues, occupational hazards for nurses due to exposure to powdered drugs and the unlicensed nature of the modified medicines, *"Sometimes I question it because… you crush all the tablets, they are all kind of going into one, you know, one dust…so are you modifying you know… the chemistry or what the tablet actually does because each tablet is made up individually… Plus, I don't know are they getting the full dose of what they should be getting, because obviously there is going to be residue inside in the crush pouch that you can't ever get out, and also… some in the yoghurt, or in the yoghurt tin or whatever you mix it in. So am, I'd say they probably don't always get the right dose"* (Nurse 13, LTC). An additional issue identified by nurses was the time-consuming nature of modifications, which impacted on nurses' time and work-load, on the patient receiving the modified medicine and on other patients in the ward, "*It definitely affects nurse's time…we have a resident here … it takes twenty minutes to finish only that patient because everything needs to be crushed individually and you have to give everything individually. So it takes a good bit of time from you… that will affect the other patients as well… time is everything"* (Nurse 1, LTC).

Overall, it is clear that nurses' view modifying ODFs as being a key part of their medication administration role. Whilst nurses were aware that modifications may not be appropriate and did express concerns about the effect of modifications on drug action, it is accepted that to meet the many individualised and varied needs of older patients, ODF modifications are a necessity, *"Look it's essential….it's a necessary evil… I'm all for modifications because it's necessary"* (Nurse 4, LTC)

Nurses' role as patient advocate

Medicine administration was acknowledged by participants as being a key aspect of their role and nurses viewed medicine administration as their area of expertise. However, from the interviews, it was clear that the responsibilities of nurses extend far beyond simply modifying and administering the medication. Nurses are at the frontline of healthcare provision and play a central role in every aspect of patient care related to ODF modification. Nurses: identify when patients are experiencing difficulty swallowing medications; arrange review by appropriate healthcare professionals; highlight patient's requirements and needs to other healthcare professionals, especially doctors and pharmacists when prescribing and dispensing and; communicate and liaise both with and between members of the MDT. Therefore, the input of nursing staff is crucial in the area of medicine modification, *"Very much nurse led…"* (Nurse 6, LTC). The importance of nurses knowing their patients was central to this, *"…one of the huge advantages of working in care of the older person in long-term settings is that you really get to know the patient…"* (Nurse 7, LTC). Nurses, particularly in LTC, know the patients, and therefore their

preferences and requirements, extremely well, *"The most important thing is to know the person, know each individual"* (Nurse 8, LTC). Nurses are also alert to subtle changes in the patient that may suggest that the patient is experiencing difficulty, *"… as their medical condition changes… they've become unwell and we know that, you know, they're coughing a lot or that their swallow has changed or that they're not able for their big medications, it's because we know our patients so well I suppose"* (Nurse 17, LTC). Participants did acknowledge that although some healthcare professionals do consider patient's formulation requirements, particularly those who know the patient or geriatric specialists, overall there was a reliance on nurses to communicate patient's formulation requirements. Nurses were cognisant of this responsibility and were particularly aware of highlighting this to out-of-hours doctors, "*Especially* [out-of-hours GP service] *you have to be there on top of them saying no, this person is liquid, this person is, you know, suspension or whatever"* (Nurse 6, LTC) and locum nursing staff. Nurses also shoulder responsibility for liaising between the various members of the MDT and communicating various recommendations within the team as often the MDT members communicate through the nursing staff rather than directly, *"The pharmacist will do a review, the pharmacist leaves instructions, I communicate them to the GP"* (Nurse 17, LTC).

It was evident that care provision in the area of medicine modification is very much nurse-led and nurses play a central role in this area. Nurses appeared to be confident in exercising these responsibilities and at the centre of this was their

acknowledgement that knowing the patient and developing a good relationship with them is a key component of their role. This allows nurses to act as an advocate for their patients. For nurses, acting as an advocate for their patients is an intrinsic component of their professional responsibility and identity *"…none of them can speak for themselves, so you have to have somebody that knows them to be able to..."* (Nurse 8, LTC).

Modifying – we are working very much as a team

Nurses believed that decision-making around medicine modification requires the input and expertise of many different members of the MDT. Nurses repeatedly highlighted the importance of ensuring that modifications are safe and appropriate *"So we'd always make sure that if we're crushing tablets that it's safe to do so"* (Nurse 18, AC). Nurses, throughout the interviews, demonstrated knowledge that certain formulations should never be modified e.g. sustained-release and enteric coated preparations, which was based on their previous experience with such medications, *"We'd know as well… the slow release, long acting, enteric coated or retard medicines… that we couldn't be crushing them"* (Nurse 14, LTC). Ultimately however, nurses acknowledged that drug formulations and modification appropriateness was not their area of expertise, *"We would always seek external advice for that because that's not our area of expertise"* (Nurse 7, LTC), and that they always sought information and advice prior to modifying oral medicines, *"I always say it, I'm not a pharmacist and I'm not a doctor and I think it's something*

that, I'm very cautious by nature anyways, am, so it's something I always double and triple check" (Nurse 9, AC).

The main information source for nurses about ODF modification and the availability of alternative formulations was the pharmacist, *"It is always the pharmacy"* (Nurse 7, LTC). Nurses reported relying on information provided by the pharmacist, *"If I have any concerns I always ring the pharmacist and I always go by their directions… but always check with the pharmacist"* (Nurse 2, LTC), *"That would be a rule that we just don't go off modifying the tablets ourselves, we have to do it in liaison with the pharmacy department so that we know… the patient is getting the benefit of the medication, it is not altering the effectiveness of the drug and that it's safe for the patient"* (Nurse 10, AC). In general, nurses had very positive views of pharmacists, *"Our pharmacists are excellent. They are very accommodating to us"* (Nurse 3, LTC) and pharmacists were seen to be the most knowledgeable member of the MDT in relation to modifications, *"On a Sunday or a bank holiday, you could discuss it with the medical team on call but often... regs* [registrars] *will tell you really to refer to the pharmacy department as soon as possible because I suppose, they've the most knowledge in relation to medication, the altering and modifying of them"* (Nurse 10, AC). One nurse did express dissatisfaction with the support provided by a pharmacy in the past, "*There was one pharmacy alright that were a bit slack that I worked with*" (Nurse 6, LTC). However, this reliance on pharmacists did present challenges in the AC settings when the pharmacy department is closed, *"We don't have any 24*

hour pharmacy… you know so it may not be appropriate forms, it could be whatever you can get" (Nurse 15, AC).

Nurses did mention a number of reference sources e.g. the British National Formulary (BNF), the Monthly Index of Medical Specialities (MIMS) and SPCs, however, these resources did not provide information related to medicine modification *"And it's not really in the MIMS either… it doesn't say whether you can crush it or not"* (Nurse 16, LTC). In one AC setting, a ward-specific guideline on medicine modification was developed by the pharmacy department which was mentioned as a useful resource available at the moment of medication administration, *"Just definitely, that do-not-crush book, that's like our bible here"* (Nurse 12, AC).

The attitudes of interview participants differed regarding the need for more resources and supports. Many of the participants expressed satisfaction with the supports and systems in place in their workplace. The majority of participants reported that they had very good working relationships with other members of the MDT and they valued a collaborative approach to decision making in which their opinions were listened to and accepted, *"We have a very good working relationship but generally they don't question, they accept, you know, our judgement on it I suppose"* (Nurse 5, LTC). Notwithstanding this finding, some participants did discuss a number of potential methods of improving multidisciplinary collaboration

including: the MDT meeting to review and discuss patient's needs and greater consideration being given to patient's formulation requirements by doctors and pharmacists when prescribing or dispensing, *"I suppose, as a multidisciplinary, sitting down as a nurse, GP and pharmacist together… there isn't enough constructive reviewing of that, it's very much the GP does the monthly round, the script goes to the pharmacist, the pharmacist sends it up and the follow up really is the nurse"* (Nurse 7, LTC). Some participants also expressed a desire for auditing of their medication administration practices, *"I suppose observing how we are doing it because again, you can't constructively say right, that's the correct procedure unless you actually observe it yourself"* (Nurse 7, LTC). A number of other suggestions were mentioned including: more education and training from pharmacists and availability of a pharmacy-developed, site-specific formulary or online database on commonly encountered modifications, *"I think all nurses should be given extra pharmacy education, especially in specialist areas where we are doing a lot of modifications"* (Nurse 9, AC), *"A pharmacy-led manual on the ward where, whatever amount of medications they can go through, whether they state whether this medication could be crushed or halved or dissolved in water or whether, you know, it is readily available in that particular hospital in liquid form"* (Nurse 10, AC). Nurses also stated that increased availability of alternative formulations and increased recognition by the pharmaceutical industry of the formulation challenges encountered by older patients on a daily basis would be welcome, "*…older people are the greatest consumers of medicines but many of these medicines are tested on people... they are young and they are fit and they are not people who normally consume those medicines… so you are effectively trialling the drugs on a cohort of*

people who are very different physiologically and in other regards from the people who are going to be consuming them. So that's another area for researchers... to give some consideration to" (Nurse 5, LTC).

5.5.3.2 Minor Themes

Fractional dosing

Fractional dosing involves the administration of part of a dosage form e.g. half a tablet, to facilitate the administration of a lower dose. Whilst score-lines are often present on tablets, in many instances these score-lines do not divide the tablet into equal doses but rather allow tablets to be split to facilitate swallowing. When participants were asked to discuss the common modifications they encountered in practice and the reasons for undertaking modifications, none of the participants volunteered fractional dosing. While splitting tablets was commonly mentioned, this was to overcome difficulty swallowing large tablets rather than for fractional dosing. However, when participants were specifically asked about modifications for fractional dosing, it was viewed as being frequently undertaken for older patients, *"Yeah, daily … some of the medication that we give out on a daily basis doesn't come in a dose that's prescribed"* (Nurse 11, AC). Fractional dosing was felt to be necessary for older adults due to a combination of increased sensitivity to higher doses and a corresponding lack of commercial formulations that meet these dosing requirements, *"I see a lot more of it here* [fractional dosing on a geriatric ward]*…you would find that they're constantly altering doses because some of them might be too severe, patients don't react well and it's always finding the fine balance to keep*

some of the patients on an even keel" (Nurse 9, AC), *"…splitting the tablet because the form, the dosage wouldn't be available, especially with the anti-hypertensive tablet, we always split it or quarter it"* (Nurse 1, LTC). Drugs acting on the CNS, especially quetiapine (an atypical antipsychotic), and the CVS were the most commonly implicated medications, *"Seroquel … comes in a 25 mg tablet. That has to be split for 12.5. Yet 12.5 is the most common dose… but there is no 12.5 available"* (Nurse 6, LTC). Fractionally dosed medications were often supplied pre-split by the pharmacy which seemed to account for nurses not considering this a modification as they did not physically perform the modification themselves, *"The pharmacy will do the alteration if they are required, we don't do it at floor level no"* (Nurse 17, LTC). In addition, there was a general belief that scored tablets are designed to be split in two for fractional dosing, *"I mean many tablets as you know are scored to be divided in two"* (Nurse 5, LTC). However, some nurses did report checking with pharmacy colleagues if fractional dosing was appropriate, even for scored tablets. While overall, participants did not have many concerns about administering fractionally dosed medications, particularly if the pharmacy had split the tablets in advance or the tablets were scored, a number of concerns were raised including inaccurate dosing, wastage and difficulties splitting tablets, *"How accurate is the dose?… like, as somebody said to me 'I gave him the big half'. Yeah, that says everything"* (Nurse 6, LTC). Overall, participants' attitudes to the modification of ODFs for fractional dosing were distinct from attitudes to modifications due to swallowing difficulties or patient preference. This appeared to be related to lack of knowledge about the purpose of score lines on tablets and

different attitudes towards modifications when tablets are pre-split by the pharmacy.

Covert administration

The modification of ODFs to facilitate covert administration was mentioned by a number of participants and it would be remiss not to address this as a separate theme. A number of participants acknowledged that covert administration was commonly undertaken in the past, particularly for patients with dementia or agitated patients, *"Now I would admit, I'm a long time in the profession, certainly that has happened in the past"* (Nurse 5, LTC). The majority of participants who discussed covert administration stated that it was not undertaken at their site of employment, *"Now, it's not actually done in this hospital"* (Nurse 6, LTC) and that it is no longer commonly encountered. The ethical implications of covert administration and the importance of respecting patient's wishes was a major factor influencing this, *"Oh no, no, we would never… if a patient refuses that's it… the law as you may know, says no means no. And no even means no from somebody who is cognitively impaired"* (Nurse 5, LTC). There was an acknowledgement that very occasionally, covert administration occurs but that this is undertaken in strict adherence to detailed policies and guidelines on covert administration, following discussion with all members of the MDT and the patient's family and taking the importance of the medication into consideration, *"We have a policy around it and I suppose it would have to be in the person's best interest whether they need the tablet or not"* (Nurse 16, LTC). The main challenge discussed by nurses relating to

covert administration was the ethical dilemma that arose when trying to balance respecting patient's wishes and providing optimal medical and pharmacological care to individual patients.

5.6 Discussion

This study has identified the knowledge, attitudes and beliefs of nurses about the modification of ODFs for older adults using qualitative, semi-structured interviews. Three major themes emerged from the data: modifying – *a necessary evil*; nurses' role as patient advocate; modifying – *we are working very much as a team*. The findings of this study provide important insights that will enable us to better understand ODF modification practices and the challenges that need to be addressed to optimise formulation suitability for older adults.

From the results of this study, it is clear that nurses view ODF modifications as being a necessity in the care of older patients. Whilst a myriad of factors contributed to this, one of the most important influences was the belief that formulation suitability is extremely individualised and varies significantly between patients due to e.g. medical conditions, patient preference, severity of dysphagia and the clinical status of the patient. This finding concurs with the qualitative systematic review on the views of healthcare professionals and patients about ODF modification which found that patient-centred individuality and variability was a key driver of ODF modification (289). Whilst it was noted that alternatives to solid

ODFs are often simply not available, it was also highlighted that modifications are often preferred due to unsatisfactory properties of available alternative oral liquid formulations such as: viscosity and the consequent risk of aspiration; expense; difficulties sourcing and; difficulties administering the necessary volume. These reported challenging properties of alternative formulations echo the findings of previous qualitative studies (156, 157). This study further develops the evidence base through the inclusion of nurses working in both acute and long-term care settings and also by investigating modifications to facilitate fractional dosing which have been neglected in qualitative literature thus far. Data from quantitative studies have demonstrated that modifications are prevalent (102, 219, 240, 297), and alternative formulations are often unavailable or unsatisfactory (240, 278) which confirms the beliefs expressed by nurses about modifications. However, despite this reality, guidance provided to healthcare professionals generally advises that modifications should be avoided (104, 150). It is clear that this advice can be difficult for healthcare professionals to adhere to given limitations of currently marketed ODFs.

The nurses' role as patient advocate was a strong theme present throughout the data. Familiarity with, and knowledge of, the patient ensures that nurses have a vital role in identifying patients' difficulties with oral formulations and liaising with other healthcare professionals to address any issues. Previous studies have found that inadequate communication practices result in lack of awareness of patient's formulation requirements (236, 289). This study has found that for patients in LTC

and AC settings, nurses' knowledge of the patient allows them to act as an advocate on the patient's behalf which helps to overcome this communication deficit. This is particularly true in LTC given the length of stay. On acute geriatric wards, nurses spend more time on direct nursing care compared to many other ward types (298) and have more direct patient contact than any other healthcare professional, facilitating the development of the nurse-patient relationship. A key tenet of nursing care and the subject of much nursing literature is the concept of "knowing the patient" (299, 300). The importance of the nurse-patient relationship has been suggested as being an important contributor to the individualisation of care provision and potentially improved patient outcomes (300, 301). This finding has important implications for other members of the MDT who should be encouraged to consult with nurses as they "know" the patient prior to prescribing and dispensing medications for this cohort. A more formal, proactive review of patients, in the presence of all necessary members of the MDT, was also mentioned as a possible method to optimise formulation suitability for individual patients in the absence of satisfactory alternative dosage forms. An approach such as this would not only ensure that all necessary expertise was available but would also allow other healthcare professionals to benefit from the nurses knowledge of the individual and decrease the time spent by nurses in communicating recommendations from one healthcare professional to another. Administrative tasks such as these can be time-consuming for nurses which takes time away from direct patient care (302). The importance of a patient advocate needs to be recognised by healthcare professionals, which has particular implications for community-dwelling patients. Studies have previously reported that healthcare

professionals are frequently unaware of the difficulties with medication intake experienced by community-dwelling patients (86, 87, 222), which highlights the importance of enquiring about difficulties, either from the patient themselves or a suitable advocate who knows the patient e.g. a carer.

Some nurses in this study expressed a desire for resources and supports that would help them in their day-to-day practice. Nurses were reliant on pharmacists for information provision regarding the appropriateness of ODF modification and satisfaction with pharmacists' role was generally expressed. In addition, while not a major source of information, nurses also expressed satisfaction with the role of the doctor in their workplaces, who support nurses by ensuring that modifications are authorised on drug charts. Some nurses did express a desire for further education and training on the pharmacological and pharmaceutical implications of modification, and while they did acknowledge that this was not their area of expertise, some felt that increased knowledge would facilitate nurses to be more empowered in this area. There were variations in nurse knowledge displayed which may serve as starting points for educational interventions, particularly in the area of capsule opening and fractional dosing. Knowledge about the purpose of the score-line on tablets differed, with some nurses assuming that this score-line was to facilitate fractional dosing and therefore, divided the tablets into two equal halves. This has been identified as an issue previously (175) and regulatory agencies are becoming more concerned about the presence of non-functional score lines on tablets (178, 179). This may highlight a potential role for education of nurses on

relevant, fundamental aspects of pharmaceutics (dosage form design). Nurses seemed to express a preference for pharmacists to deliver such educational programmes. Another possible intervention suggested by nurses was the use of a pharmacist-developed, site-specific guidance document which would provide recommendations on commonly encountered modifications within the care setting. One study site had such a resource and the participant found this to be extremely useful in their daily practice. Bourdenet *et al.* (261) found that the implementation of good practice recommendations and the development of a list of medications that should not be modified resulted in a significant reduction in the number of patients receiving crushed medication and a significant reduction in crushing of drugs that should not be modified. Whilst practical interventions such as this should be developed and evaluated in an attempt to support nurses and patients administer medications in the short-term, ultimately there is a need to increase the availability of licensed formulations that meet the needs of the older adult. Nurses advocate for individual patients in daily practice however, the older cohort requires advocates to highlight their needs to industry, regulatory agencies and policy-makers, to encourage the development of age-appropriate formulations. Optimisation of formulation suitability for older adults will require a thorough understanding of the challenges of administering medication to older adults. The literature abounds with commentaries on the age-related challenges in medication administration (8, 63, 168). A growing body of evidence from clinical practice is required to quantify the breadth of the problems encountered. However, to truly understand the challenges encountered, the views of healthcare professionals, patients and carers need to be heard to ensure that any potential solutions

developed reflect the priorities and needs of end-users and therefore, will be of maximal benefit (194). This study adds to the existing evidence-base on the views of nurses about ODF modification (156, 157). In addition to the potential interventions discussed above, further research should investigate the views of patients and their informal carers in community settings where there may be limited healthcare professional input into decision-making around ODF modification (86, 87). This research should seek, not only to identify the main challenges encountered by this cohort, but also to determine the "ideal" formulation characteristics from the perspectives of patients, carers and healthcare professionals.

There are a number of strengths associated with this study. The use of semi-structured interviews allowed for in-depth, detailed accounts of participants' experiences and perceptions to be elucidated (288). The data were analysed thematically (295), using an inductive approach to coding which produced rich findings that were firmly rooted in the data. The timeframe of the study also facilitated an iterative approach to data collection and analysis which allowed a thorough interrogation of the data. The transferability of the study findings may be questioned given that the interviews were conducted in one geographical area in Ireland. However, the use of the sampling matrix helped to ensure that the views of nurses working in a variety of care settings were elucidated which helped to overcome this limitation. In addition, the findings cohered with the limited evidence from other qualitative and quantitative studies which further confirms the

transferability of findings. Social desirability is another potential limitation of the study. Participants were aware that the interviewer was a pharmacist and that the research team were all based at a School of Pharmacy. Therefore, participants may have given socially desirable answers. Whilst it is difficult to eliminate this bias, the research team had discussed this prior to undertaking the study and felt that it would be unethical not to disclose the research team's background. However, this was balanced by highlighting to participants that the research team were interested in hearing, and gaining a greater understanding of, the views and experiences of nurses. Social desirability did not appear to emerge as a significant issue given the honest, forthcoming nature of the interviews, with both positive and negative experiences with pharmacy colleagues being reported and discussed. In addition, nurses were asked to describe the procedure followed in their institution when medications were required to be modified for patients. Nurses, in different institutions, all described the input of pharmacists and the role they played. The role of the pharmacist was similar across all institutions included in the study, so it is likely that this reflects the true role that pharmacists play in an Irish setting. The length of the interviews ranged from 7 minutes to 31 minutes. The shortest interview was conducted on an extremely busy ward in an acute hospital, which is likely to have contributed to the brevity of this interview. However, useful insights were still gained in this interview. The interviews focused on ODF modification, which was clear to participants from the information leaflet for the study. Therefore, from the outset, the interviews focused on medicine administration and modification for older adults. Therefore, very detailed insights into this topic were gained from what could be considered to be relatively short interviews. The authors

feel that the interviews provided comprehensive coverage of the topic and therefore the length of the interviews has not impacted on the quality or depth of findings of the study. It was not possible from the detail provided in the completed data collection forms to ascertain the primary nursing qualification of all participants due to variability in how nurses completed the data collection form. Regardless of qualification, all of the interview participants would be required to demonstrate their competency to, and register with, the Nursing and Midwifery Board of Ireland and adhere to the relevant national guidelines on medicine administration. In addition, the number of years working in care of older patients was recorded but not the total number of years since qualification, as the former was of more interest for the purposes of this study. No variation in ideas or responses was observed between participants based on age, qualification type or length of experience in older patient care. However, previous research has investigated how nursing competence relates to length of clinical experience (303). Whilst in this study, similar themes and insights were gained irrespective of length of experience in older patient care, future research should consider qualification type and time since qualification to investigate whether this affects practice.

5.7 Conclusions

This study has provided a useful insight into the knowledge, attitudes and beliefs of nurses on the modification of ODFs for older adults. Modifications of ODFs are viewed as unavoidable in care of the older person, due to limitations of available formulations. Nurses had a number of concerns about modifications and valued

input from other healthcare professionals, particularly pharmacists. Nurses' knowledge of individual patients ensures that nurses have a vital role to play in identifying and assessing patients experiencing difficulty with oral medicines and in communicating with other healthcare professionals. The unique and varied formulation requirements of older adults must be acknowledged by healthcare professionals, academics, regulatory agencies, the pharmaceutical industry and policy makers to promote the development of more age-appropriate formulations. Further research will be central to the development of these formulations, both to ascertain the prevalence of the practice and the most problematic drugs/ formulations and to identify the priorities and needs of end-users. In the interim, practical interventions and guidance should be developed, taking into consideration the themes that were identified in this study.

5.8 Acknowledgements

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Chapter 6: Oral dosage form modification and administration in an Irish aged care setting: a direct observation of practice

Publication five (under preparation):

Mc Gillicuddy A, Sahm LJ, Crean AM. Oral dosage form modification and administration in an Irish aged-care setting: a direct observation of practice. Propose to submit to the International Journal of Pharmaceutics.

6.1 Abstract

6.1.1 Background

ODF modifications can potentially affect drug safety and efficacy; however, this is dependent on factors including the medication, the dosage form, the method of modification and the subsequent method of administration. There are a lack of data describing ODF modifications, particularly the methods of modification and administration, in an Irish setting. In order to identify priority areas for intervention, there is a requirement for a thorough investigation of current ODF modification and administration practices in ACFs in Ireland.

6.1.2 Aim

The aim of this study was to elucidate ODF modification and administration practices in ACFs in Ireland using undisguised, direct observation of drug rounds.

6.1.3 Methods

Undisguised, direct observations of medication administration to older patients on 13 wards in 5 ACFs in Ireland was undertaken between May 2017 and August 2018. Patients who met the following criteria were eligible to be included in the study: (i) resident in the ACF; (ii) aged ≥65 years; (iii) received medication from nurses during drug rounds and; (iv) written, informed consent for inclusion was provided (by the patient or their next-of-kin if the patient lacked the capacity to consent). Demographic and medical details about included patients were recorded from the patients' medical records. The drug round observations were undertaken by one researcher who recorded details including: the name, dose, dosage form, route and

method of administration of medication, as well as details of any ODF modifications.

6.1.4 Results

Medicine administration to 141 patients (63.8% female, mean age (SD) 83.96 years (7.26)) was observed. In total, 44.7% of patients received at least one modified solid ODF during the observed drug rounds. Amongst patients who received modified medicines (n=63), 46.0% had medicines modified to overcome swallowing difficulties, 41.3% to facilitate fractional dosing and 12.7% required medicines to be modified for both reasons. There were 178 modifications observed for 71 different medications, with drugs acting on the CNS the most commonly modified. Of these 178 modifications; 81.5% were unlicensed, and just under half of these unlicensed modifications were authorised in the BPGs. Modified medicines were most frequently administered using food vehicles or thickened fluids, while almost one-fifth of non-modified solid ODFs and liquid ODFs were administered with thickened fluids or in food vehicles.

6.1.5 Conclusions

This study has provided insights into ODF modification and administration practices in ACFs in Ireland. ODF modifications are commonly required to tailor oral medicines to meet the swallowing capabilities and dosing requirements of older adults. Whilst many of the modifications were neither authorised in the product licence nor BPGs, the majority of administration practices were optimised within the limitations of currently marketed formulations. Further research is needed to improve medication formulation suitability for older adults and the findings of this

study, by describing the current reality of medication administration, should inform the direction of this research.

6.2 Introduction

This thesis investigates ODF modifications for older adults, particularly as they relate to the Irish setting. Following the systematic review of the quantitative literature described in Chapter Two, it was found that there are limited data on ODF modifications for older adults, with none from an Irish setting (236). To address this gap, a retrospective review of drug charts in an ACF was undertaken (Chapter Four), which suggested that ODF modifications are common in Ireland (240). However, there were limits to the depth of information that could be gained from this study given the retrospective nature of data collection. In addition, as highlighted in Chapter Two, there are a number of limitations of the published literature investigating ODF modifications, particularly relating to how data collection was performed and how the study findings were presented (102, 219, 220, 236).

In Chapter Three, the qualitative literature on ODF modifications was systematically reviewed (289). Following on from this systematic review, and informed by the findings of the retrospective review of drug charts, the views and opinions of nurses responsible for administering medicines to older adults in Ireland were sought. It was clear that modifications were viewed by nurses as being both common and necessary for older patients, and there was a perception that there was often no alternative to modifying ODFs. In addition, a number of nurses suggested that observations of drug rounds would be useful, both to audit practice and to gain an understanding of the challenges encountered by nurses, *"I think really it should be audited… observing how we are doing it because again, you can constructively say*

'right that's the correct procedure'" (Nurse 7), *"With respect I would say pharmacists maybe need to be aware of the challenges at ground level… I mean if you were to have been able to come in earlier this morning and come on a drug round with me and see, and be physically beside me and see why it is that I had to crush so and so's medicines. And come in and see that individual and see for yourself that this is why"* (Nurse 5).

Internationally, a number of quality improvement studies have sought to optimise ODF modification practices (260, 261, 280, 304-306). These studies were predicated on the assumption that the modifications that were being undertaken were inappropriate and arose due to poor prescribing, dispensing and/or administration. However, whether similar interventions would be warranted or useful in an Irish setting could not be determined without gaining a greater understanding of ODF administration practices. Therefore, following consideration of the findings of Chapters Two, Three, Four and Five, this study was designed in an attempt to provide more detailed information on ODF modification practices in an Irish setting, in order to address the identified gaps in the literature and to inform the direction of future research and potentially, interventions.

6.3 Aim and objectives

The primary aim of this study was to elucidate ODF modification and administration practices in ACFs in Ireland using undisguised, direct observation of drug rounds. To

achieve this aim the following objectives were defined: to determine the prevalence of ODF modifications for older adults in a sample of ACFs in Ireland; to identify the most commonly modified medicines; to determine the methods of modification used; to describe the methods of administration of medicines and; to determine if there is an evidence-base to support decision-making around ODF modification.

6.4 Methods

6.4.1 Ethical approval

Ethical approval to conduct this study was granted by the Clinical Research Ethics Committee of the Cork Teaching Hospitals, Cork, Ireland (Appendix 9). During the observation of drug rounds, nurses were observed preparing and administering medicines and patients were observed taking medications. Therefore, written informed consent for observation was obtained from nurses and patients (or the patient's next-of-kin if the patient lacked the capacity to consent). The researcher did not actively participate in the drug round, but rather was present as an observer. It was within the terms of the ethical approval however, that if the observer, a qualified pharmacist, witnessed any potential errors that represented a significant risk to the patient (e.g. wrong dose, wrong drug or wrong patient) the observer would intervene. This approach has previously been used in a number of studies involving the direct observation of medicine administration (234, 297).

6.4.2 Study design

This study was an undisguised, direct observation of drug rounds in five ACFs in the Munster region of Ireland.

6.4.3 Study setting and sampling

The study was conducted on thirteen wards in five ACFs in the Munster region of Ireland. As previously described, the aged care or "nursing home" sector in Ireland includes public, private and voluntary nursing homes, with the public nursing home sector providing care for a more highly dependent patient population (293). "Specialist Care Units for People with Dementia", also known as "Specialist Dementia Units" (SDUs), are a feature of the Irish nursing home sector and they are a model of long-term residential care established to provide specialist care to small groups of people with dementia (292). Given that previous research has suggested that ODF modifications are more common in high dependency units (219) and patients with dementia are also more likely to receive modified medicines (102), the sampling strategy for this study sought to ensure that at least one ACF from each funding category was represented. In addition, a number of SDUs were also sought for inclusion in the study.

The Director of Nursing or the Medical Director at the purposively selected ACFs was provided with an information letter or e-mail outlining the purpose of the study. A member of the research team followed up the invitation letter with a telephone call or visit to discuss, and provide further information about, the study.

Following agreement to participate, a suitable timeframe for the conduct of the study was arranged. Patients were provided with an invitation letter and information leaflet about the study and those who wished to participate provided written, informed consent. The medical/nursing team at the study site identified patients who were unable to provide informed consent, and in this instance, if possible, the patient's next-of-kin were contacted and supplied with the invitation letter and information leaflet for the study. If the patient's next-of-kin provided written, informed consent, the patient was enrolled in the study. Nurses who were observed administering medication also provided written, informed consent to be observed.

6.4.4 Inclusion criteria

Patients were eligible for inclusion in the observational study if they met the following criteria:

- Aged ≥65 years old;
- Resident in an ACF included in the study;
- Were administered medication during drug rounds;
- Provided written, informed consent for participation.

In the event that a patient lacked the capacity to provide informed consent, the patient's next-of-kin could provide informed consent for participation on their behalf. The decision as to whether a patient had capacity to consent was made by the medical/ nursing team at the ACF.

Nurses were eligible to be observed in the study if they met the following criteria:

- Administered medication to older adults in a participating ACF;
- Provided written, informed consent to be observed.

6.4.5 Data collection

Data collection and the observation of drug rounds were performed by one researcher (AMG), a qualified pharmacist. Data collection began at the first site in May 2017, and sites were recruited on a phased basis thereafter, with the final observations being completed in August 2018. Each participant in the study was assigned a unique study number. The researcher completed a standardised data collection form for each participant, using data retrieved from the participant's medical records. The following data were collected: type of ward; category of admission; gender; date of birth; medical conditions; documented diagnosis of dysphagia; any relevant recommendations regarding food texture and fluid grade and; Barthel Index Score (if available) (307). For the swallowing recommendations, wherever possible, the recommendations regarding food and fluid consistency were reported in accordance with the preferred terminology in the "Consistency Descriptors for Modified Fluids and Food Consensus Document", issued by the Irish Association of Speech and Language Therapist and the Irish Nutrition and Dietetic Institute (308). The Barthel Index Score was used as a surrogate descriptor of patient dependence; higher scores indicating greater levels of independence (307). For the drug rounds, observations were conducted over a full day (including morning, lunch, evening and night-time drug rounds) with the goal of observing a

full day of medication administration for each participating patient. However, in some instances it was not feasible to observe every administration for each patient e.g. due to patient absences from the ward for appointments, lack of access at certain drug rounds in the ACF etc. During the drug round, the observer shadowed the nurse as s/he prepared and administered medications for participating patients. A standardised data collection form was used to record details of the drug round including: the time; the names of medications administered; the dose; dosage form type and route of administration; whether the medication was modified; the method of modification; whether the modification was authorised on the drug chart and; the method of administration of both modified and non-modified medications. Only medications that were administered were included for analysis in the study, i.e. medications refused by the patient, "when required" (PRN) medications charted but not administered or medications that were administered by nurses but not witnessed by the researcher were not included in the analysis.

The approach used in Chapter Four to assess the evidence-base for the modifications (Figure 4.1) was also used for this study. Briefly; the first step involved assessing if the modification was licensed, in which case it was an evidence-based modification. Unlicensed modifications were considered to be evidence-based if they were recommended in at least one of, "The NEWT Guidelines for Administration of Medication to Patients with Enteral Feeding Tubes or Swallowing Difficulties" (159) or the "Handbook of Drug Administration via Enteral Feeding Tubes" (160).

6.4.6 Statistical analyses

Data analyses were performed using IBM's SPSS for Windows, Version 22.0 (IBM Corp., Armonk, NY) and Microsoft Excel (2010). Descriptive analysis was undertaken. Continuous variables were described by means and SDs for normally distributed data and by medians and IQRs for non-parametric data. Categorical variables were described by counts and percentages. Associations between categorical variables were investigated using Pearson's Chi-square tests, or Yates' Continuity Corrected Chi-Square tests as appropriate. Independent samples t-tests and Mann-Whitney U tests were used to investigate differences between groups for normally distributed and non-parametric continuous variables respectively. P-values <0.05 were considered to be statistically significant. The analysis was primarily conducted at the patient level. The researcher recorded details of all medicines that were observed being administered to study participants. The total number of medications administered to each individual patient, based on the active ingredient, was calculated. For the analysis, if medications were administered to one patient multiple times over the course of the day, the medication was only counted once. A similar approach was used if ODFs were administered more than once in the day, with the exception of different strengths or formulation types, which were counted separately.

6.4.7 Sample size

Assuming that the prevalence of ODF modification for older adults in ACFs is 35.1% (based on the findings of the retrospective review of drug charts reported in

Chapter 4 (240)), it was estimated that a sample size of 351 patients would be required to determine the prevalence with 95% confidence to within ± 5%.

6.4.8 Reporting

This study is reported in accordance with the "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) guidelines (269) (Appendix 10).

6.5 Results

6.5.1 Patient demographics

The Medical Director or Director of Nursing at eight ACFs were contacted, informed about the purpose of the study and invited to participate. Of these, two did not reply to the invitation to participate, while six agreed to participate. However, a suitable time for the conduct of the study could not be arranged at one of these sites, therefore, the study was conducted in five ACFs (2 public, 2 private and 1 voluntary). Of 267 patients who met the inclusion criteria in these 5 nursing homes, informed consent for participation was obtained for 141 patients (73 patients and 68 next-of-kin). Figure 6.1 provides an overview of the study recruitment process.

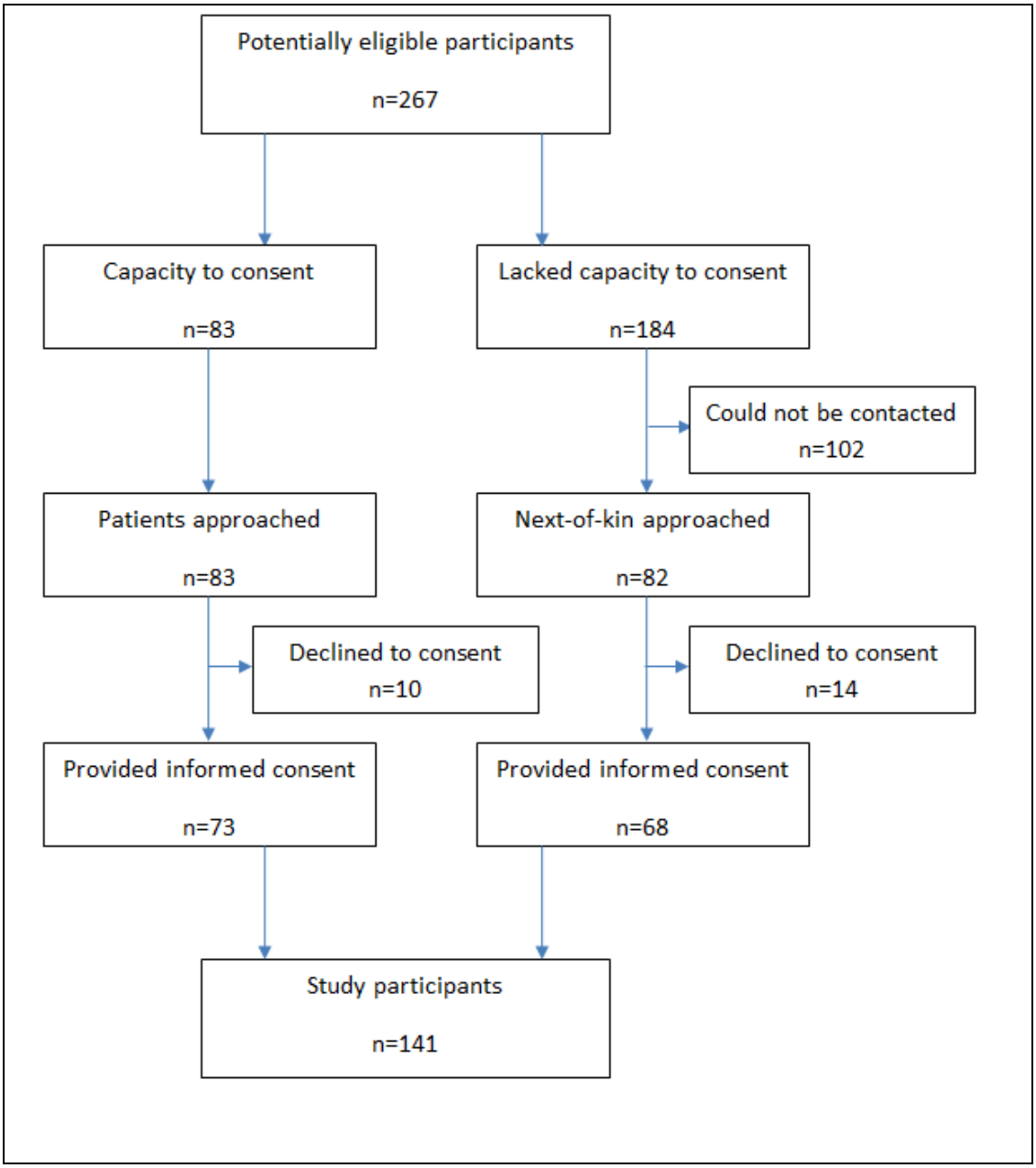

Figure 6.1 Overview of study recruitment process

The administration of medicines to 141 patients (63.8% female, mean age (SD) 83.96 years (7.26)) was observed during this study. All of the study participants were admitted for long-term care; 17 to SDUs and 124 to regular nursing home wards. Table 6.1 provides demographic details of the study cohort.

Table 6.1 Demographic details of patient cohort (n=141)

Variable		n (%)
General Demographic Details		
Gender	Male	51 (36.2%)
	Female	90 (63.8%)
Nursing Home Category	Public with SDU (n=1)	5 (3.5%)
	Public without SDU (n=1)	33 (23.4%)
	Private without SDU (n=2)	49 (34.8%)
	Voluntary with SDU (n=1)	54 (38.3%)
Nursing Home Ward Type	SDU	17 (12.1%)
	Non-SDU ward	124 (87.9%)
Age Range (n=139)	65-75 years	18 (12.9%)
	76-85 years	67 (48.2%)
	86-95 years	45 (32.4%)
	≥96 years	9 (6.5%)
Swallowing Details		
Documented Dysphagia Diagnosis	Yes	9 (6.4%)
	No	83 (58.9%)
	Unclear	49 (34.8%)
Recommendations Regarding Swallowing	Yes	56 (39.7%)
	No	83 (58.9%)
	Unclear	2 (1.4%)
Food Texture Recommendations (308)	Texture A	20 (14.2%)
	Texture B	15 (10.6%)
	Texture C	16 (11.3%)
	Texture D	1 (0.7%)
	Texture dependent on time of day	1 (0.7%)
	No food recommendation despite swallow review	5 (3.5%)
	No review of swallow	83 (58.9%)

Variable		n (%)
Fluid Grade Recommendations (308)	Grade 1	12 (8.5%)
	Grade 2	14 (9.9%)
	Grade 3	2 (1.4%)
	Normal fluids	23 (16.3%)
	Thickened fluids (not specified)	3 (2.1%)
	Use of special cup	1 (0.7%)
	No fluid recommendations despite swallow review	3 (2.1%)
	No review of swallow	83 (58.9%)
Medical Conditions		
Documented Diagnosis of Dementia	Yes	60 (42.6%)
	No	70 (9.6%)
	Cognitive impairment	11 (7.8%)
Documented Diagnosis of Stroke	Yes (in past 6 months)	1 (0.7%)
	Yes (>6 months previously)	21 (14.9%)
	Transient Ischaemic Attack	7 (5.0%)
	No	112 (79.4%)

Legend: SDU = Specialist Dementia Unit.

In a number of instances there was uncertainty in the medical notes regarding the patients' swallowing difficulties. Two patients had a diagnosis of dysphagia recorded in their medical notes however no recommendations regarding food and fluid were present. For subsequent analysis, these two individuals were categorised as having dysphagia but not having a documented swallowing recommendation. In contrast, 49 individuals had recommendations regarding food texture and/or fluid grade but dysphagia was not a documented medical condition in their medical

notes. In this case, for subsequent analyses, these 49 individuals were classified as being likely to have dysphagia. The median number of chronic medical conditions (IQR) experienced by the study cohort was 5 (3-7). A Barthel Index Score was available for 137 patients and the median score (IQR) was 9 (3-14).

6.5.2 Medication use amongst the study cohort

The median number of drug rounds observed for each patient was 2 (IQR 1.5-2.5, range 1-4). The administration of medicines to any patient was not observed on more than one occasion at any time-point i.e. each patient was only observed for one morning drug round, one lunch time drug round, one evening drug round and one night time drug round. The median number of medicines that were observed being administered to patients, based on the active ingredient, was 8 (IQR 5-11), while the median number of oral medicines was 7 (4-10). Oral dosage forms were the most commonly prescribed formulations with participants receiving a median of 7 ODFs (IQR 4.5-10), of which solid ODFs were the most common (median 6 (IQR 4-9)).

6.5.3 ODF modifications

During the drug rounds, modified ODFs were observed being administered to 44.7% (n=63) of the study cohort. Amongst the group of patients who received modified medicines, 29 patients (46.0%) had medicines modified to overcome swallowing difficulties, 26 (41.3%) received fractionally dosed medicines, while a further eight patients (12.7%) had medicines modified to facilitate fractional dosing and to

overcome swallowing difficulties. For the majority of patients (96.8%), the modifications were expressly authorised on the drug chart by the prescriber, with only two patients receiving modified medicines that were not expressly authorised. For one of these patients, although the modification was not authorised, it was licensed and consequently the nurse did not require prior authorisation from the prescriber. The other patient received multiple modified medicines but only one of these modifications had not been authorised. Therefore, only one medication in the study was modified without the expressed authorisation of the prescriber.

The median number of modified solid ODFs administered to patients was 2 (IQR 1-4). Figure 6.2 provides a breakdown of the number of modified solid ODFs administered to patients.

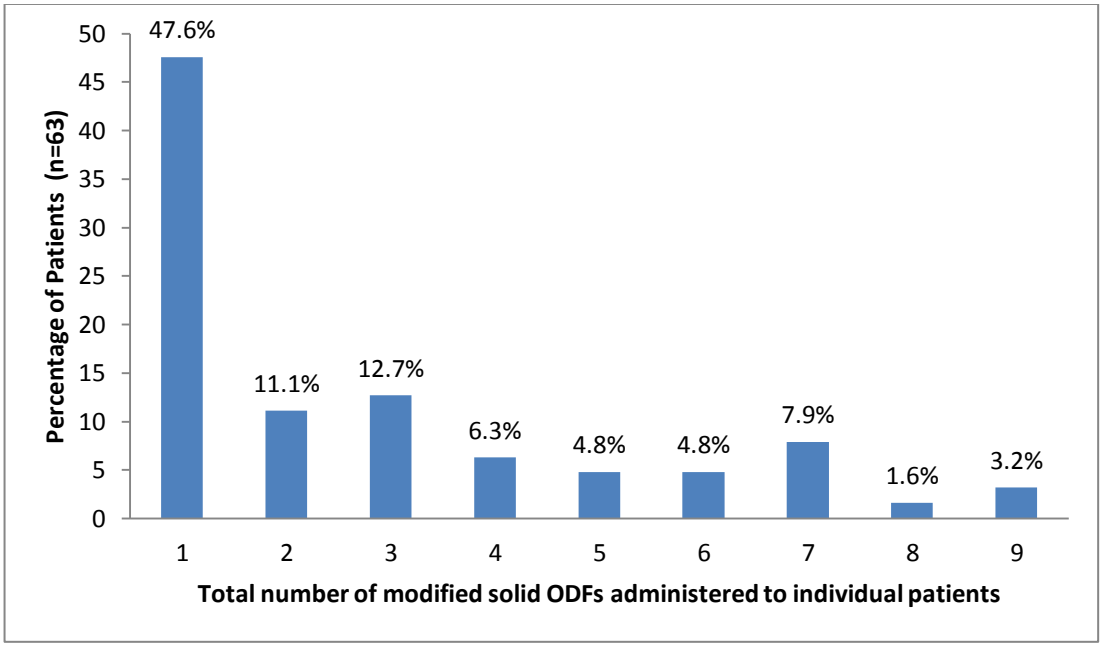

Figure 6.2 Breakdown of the number of modified medicines received by patients (n=63)

The association between medicine modification and various patient characteristics was investigated. Medications were significantly more likely to be modified for patients with dysphagia (χ^2_{yates} (1) = 5.139, $p<0.05$) and for those with a documented swallowing recommendation (χ^2_{yates} (1) = 6.703, $p<0.05$). A diagnosis of dementia or cognitive impairment was found to be potentially associated with modification (χ^2_{yates} (1) = 3.830, $p=0.05$). Neither gender (χ^2_{yates} (1) = 0.206, $p=0.650$) nor stroke (χ^2_{yates} (1) = 0.024, $p=0.878$) were found to be associated with medicine modification. Independent samples t-tests were used to compare the age of those who received modified medicines to those who did not receive modified medicines. There were no statistically significant differences between these two groups based on age (t (137) = -0.756, $p=0.451$). A Mann-Whitney U Test demonstrated a statistically significant difference in the Barthel Index Scores between those who received modified medicines (median = 5.0, n = 60) compared to those who did not (median = 11.0, n = 77), (U = 1398, z = -3.964, $p<0.001$, r = 0.34).

Analysis was undertaken to examine modifications for fractional dosing and swallowing difficulties separately. It was found that none of the above variables were associated with modifications for fractional dosing. In contrast, modifications to overcome swallowing difficulties were associated with dysphagia (χ^2_{yates} (1) = 15.992, $p<0.001$), the presence of swallowing recommendations (χ^2_{yates} (1) = 17.867, $p<0.001$) and a diagnosis of dementia or cognitive impairment (χ^2_{yates} (1) = 9.076, $p<0.01$). In addition, a statistically significant difference was seen in the Barthel Index Scores of those who required medicines to be modified to overcome

swallowing difficulties (median = 2.5, n = 34) compared to those who did not require such modifications (median = 11.0, n = 103), ($U = 872$, $z = -4.388$, $p<0.001$, $r = 0.37$).

During this study, modifications including tablet crushing, capsule opening and tablet splitting were observed. Tablet crushing was performed for 33 patients, with between 1 and 9 tablets crushed for these individuals. The Silent Knight Tablet Crusher®, which consists of an individual, disposable plastic pouch into which tablets are placed, prior to crushing using the crushing device (309), was used to crush tablets for 32 of the patients who received crushed medicines. The remaining individual had medications crushed using a commercial twist-type crushing device. Capsules were opened to overcome swallowing difficulties for 14 individuals, with these patients receiving between 1 and 3 opened capsules. Tablet splitting was also commonly observed, with split tablets administered to 36 individual patients: 31 patients had tablets split for fractional dosing; 2 to overcome swallowing difficulties and; 3 had tablets split due to the necessity to administer a fractional dose as well as to overcome swallowing difficulties. A variety of tablet-splitting techniques were employed, including the use of a commercial tablet splitter, having tablets pre-split by the pharmacy or the nurse breaking the tablets by hand. Four patients who received more than one split medication had medication split using different techniques. Figure 6.3 provides details on the methods used to split tablets for patients (n=36) in the study.

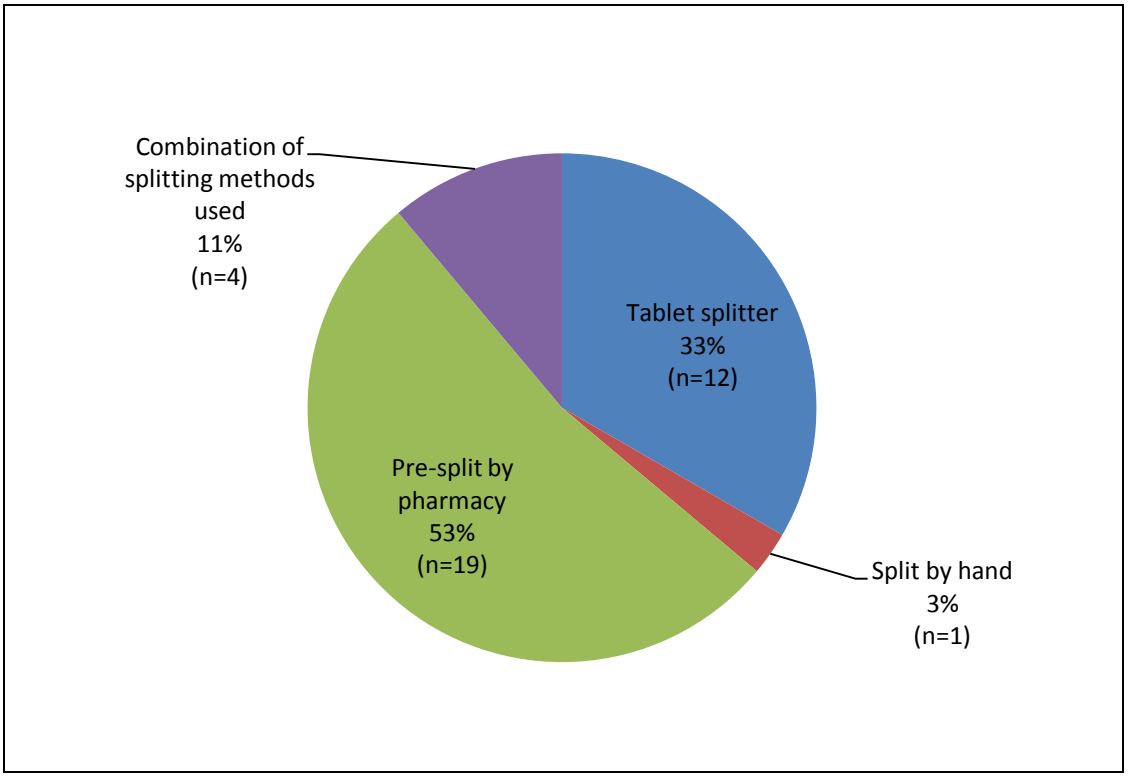

Figure 6.3 Methods used to split tablets for patients (n=36)

Seventy-one different medications were observed being modified during the study, with 178 separate instances of modification of these medications being recorded. The modified medications were classified according to the ATC code and it was found that drugs belonging to the "Nervous System" anatomical group were most frequently modified (Table 6.2). Given that analysis was conducted at the patient level, when a medication was observed being modified more than once in the day for an individual patient (e.g. at the morning and night time drug round), this was only counted as one instance of medicine modification.

Table 6.2 ATC classification of modified ODFs

ATC Code Classification (arranged alphabetically)	No. of modified medicines	No. of instances of modification	% of all instances of modification
Alimentary Tract and Metabolism	10	22	12.4%
Blood and Blood Forming Organs	10	20	11.2%
Cardiovascular System	15	33	18.5%
Central Nervous System	27	90	50.6%
Systemic Hormonal Preparations	1	5	2.8%
Anti-infectives for Systemic Use	2	2	1.1%
Genito-urinary and Sex Hormones	3	3	1.7%
Respiratory System	3	3	1.7%
Total	71	178	100%

The frequency of medicine modification was also examined at the individual medication level. Table 6.3 documents the top twelve most commonly modified medications and the reasons for these modifications.

Table 6.3 Most commonly modified medications and the reason for modification

Drug	Instances of modification	Reason for Modification		
		FD	SD	Both SD and FD
Quetiapine	16	9	5	2
Paracetamol	13	0	13	0
Memantine	9	0	8	1
Aspirin	8	0	8	0
Bisoprolol	6	0	6	0
Trazodone	5	0	5	0
Mirtazepine	5	3	2	0
Lorazepam	5	1	3	1
Senna	5	0	5	0
Nebivolol	5	4	1	0
Levothyroxine	5	0	5	0
Calcium and Vitamin D	5	0	5	0

6.5.4 Evidence-base for modifications

The 178 instances of modification that were observed during the drug rounds were examined according to the criteria described in Chapter Four for assessing the evidence-base for the modifications. Modifications were considered to be evidence-based if the modification was authorised in the product licence or alternatively if it was recommended in one of two BPGs. Figure 6.4 provides a breakdown of the evidence-base for the observed modifications.

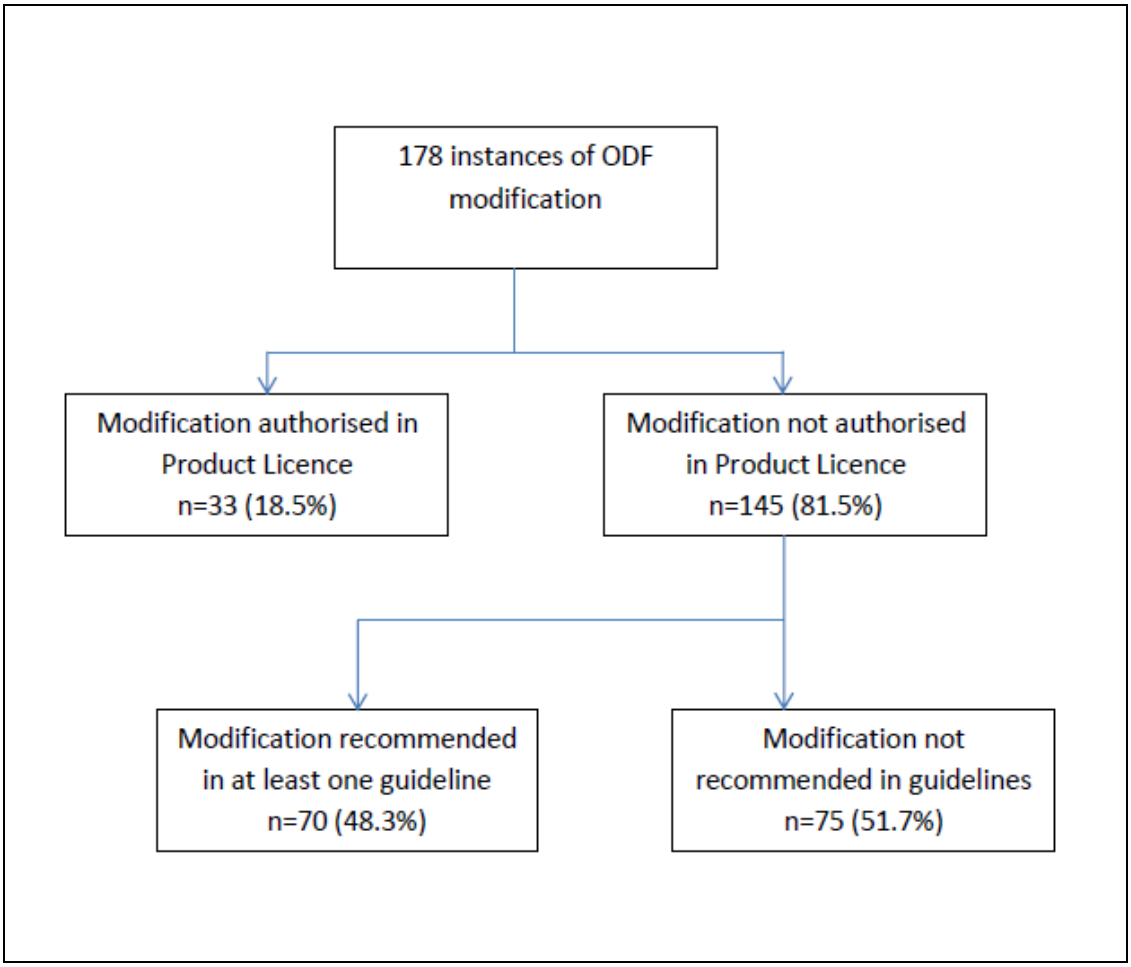

Figure 6.4 Evidence-base for observed modifications

Of the 75 modifications that were neither licensed nor recommended in best practice guidelines, the majority (70.7%) were undertaken to overcome swallowing difficulties, 25.3% were to facilitate fractional dosing and 4.0% involved an initial modification to administer a fractional dose, followed by a subsequent modification to overcome swallowing difficulties.

6.5.5 Methods of administration of medicines

Details of how modified and non-modified ODFs were administered to patients were recorded during the drug rounds. Table 6.4 provides further details on how the various ODFs were administered to individual patients.

Table 6.4 Method of administration of ODFs to individual patients

Administration vehicle	n	%
Modified ODFs (n=63 patients)		
With water or other thin liquid	23	36.5%
With custard	17	27.0%
With yoghurt/ petit filous	12	19.0%
With thickened fluids e.g. Swalloweze® and water	6	9.5%
With nutritional supplement e.g. Forticreme Complete®	2	3.2%
With very thickened flavoured water	2	3.2%
With yoghurt in morning, very thickened water at night	1	1.6%
Liquid ODFs (n=80 patients)		
Administered directly to the patient	66	82.5%
Thickened prior to administration	8	10.0%
Administered in food vehicle e.g. custard, petit filous	6	7.5%
Non-modified solid ODFs (n=118 patients)		
With water or other thin liquid	92	78.0%
In food vehicle e.g. petit filous, custard, yoghurt	14	11.9%
With thickened fluids	9	7.6%
Chewable medicines- chewed by patient	3	2.5%

Legend: petit filous = fromage frais; a smooth fresh cheese with a thick yoghurt consistency.

In all instances where a food vehicle was used to administer medication, a small quantity of the food vehicle was used, and the purpose of the vehicle was to facilitate medicine administration rather than a meal being used for administration of medication. Similarly, when a nutritional supplement was used, it was prescribed for the patients on the drug chart and a spoon of the nutritional supplement was used to administer the medication. The medication was not added to, or mixed in with, the full quantity of the nutritional product.

6.6 Discussion

Through the direct, undisguised observation of medication administration in ACFs, detailed insights into ODF modification and administration practices in an Irish setting were gained. Modifications were found to be extremely common, with 44.7% of all patients receiving at least one modified solid ODF. Both modifications to overcome swallowing difficulties and to facilitate fractional dosing were prevalent, with approximately one-quarter of patients requiring medicines to be modified for these reasons. This study contributes to the literature on ODF modifications for older adults by providing comprehensive data from an Irish perspective as well as affording greater insights into the reasons modifications are required and which medications are most commonly altered. However, particularly novel is the level of detail that was obtained regarding the methods of modification and methods of administration of both modified and non-modified medicines which aids in the comprehension of the challenges encountered in administering medicines to older adults.

The findings of this study broadly concur with previously published studies on tablet crushing and capsule opening (102, 103, 219, 220), as well as the limited reports on fractional dosing (100). Prevalence of medicine modification was found to be higher in this study than in the retrospective review of drug charts in Chapter 4, which may be due to the inclusion of less-dependent, respite patients in the retrospective study (240), whereas in the current study only long-term care patients were included. However, as was reported in Chapter 4, ODF modifications were slightly less common in Ireland compared to international reports (100, 103, 219), which may stem from differences in the study settings, the organisation of healthcare or medication formulation availability as well as differences in the methods of data collection and reporting. Collectively, the findings of these studies highlight that across different jurisdictions, in a variety of healthcare settings, ODF modifications for older adults are the norm, occurring on a daily basis in order to meet the needs of this cohort (100, 102, 103, 219, 220, 240).

An important finding, which concurs with previous studies, is that highly dependent patients and those with dementia or dysphagia are particularly likely to require modified medicines (102, 219, 310). Therefore, healthcare professionals should be vigilant of the need to consider formulation suitability for these individuals. However, a significant issue that may hinder identification and engagement with these patients, was the finding that dysphagia was often not expressly reported in patient's medical notes, with swallowing difficulties inferred from recommendations regarding food and fluid administration which were reported in

daily care notes for healthcare assistants. The inconsistent recording and reporting of dysphagia and swallowing recommendations for older patients in long-term care facilities, in agreement with the findings of this study, has previously been identified as an issue (280). Inadequate communication and information sharing have been highlighted as barriers to the optimisation of formulation suitability for older adults (156, 157, 289). The absence of clearly documented, easily accessible information about patients' swallowing capabilities is likely to complicate communication of patients' requirements as staff members may simply be unaware of the difficulties experienced by patients. Jackson *et al.* (280) identified that ineffective and inefficient communication of medication related swallowing recommendations was a major contributor to inappropriate medication administration practices in two continuing care facilities for older adults. Through the implementation of new communication processes, which involved clearly documenting speech and language therapists' recommendations on medication administration records and doctors' order sheets and creating dysphagia alerts in the pharmacy dispensing systems, compliance with medication swallowing recommendations improved and inter-disciplinary communication was optimised. A similar approach, in which swallowing recommendations, diagnoses of dysphagia as well as any relevant, patient-specific difficulties with medication formulations are documented in patient's medical notes, may help to encourage the routine consideration of formulation suitability during the prescription, dispensing and administration of medication to older adults. This would prove particularly useful for locum and agency staff. In this study, although it was clear that pharmacists were involved in providing recommendations regarding medicine modification and

doctors authorised modifications, the processes by which swallowing recommendations were communicated between nurses, doctors, pharmacists and speech and language therapists were not evaluated. Further research should investigate communication and information sharing around swallowing recommendations and medication suitability in the long-term care setting in Ireland, in order to identify if there is scope for alteration of practice to optimise communication and enhance formulation suitability for older patients.

This study was designed in an attempt to address a number of the limitations of published literature investigating ODF modifications, as described in Chapter 2; and to provide greater detail on ODF modification practices than could be gained from the retrospective review of drug charts described in Chapter 4. In particular, insights into the methods of modification and administration of modified medicines were sought. Previous studies have reported the occurrence of concerning modification and administration practices (102, 219, 220), with crushing equipment being shared between residents, inadequate cleaning of shared equipment, and administration of modified medications in food in a manner which could affect administration of the full dose e.g. adding the medication to the patient's meal. In this study, no such concerning practices were witnessed. When tablets were crushed, all bar one administration involved the use of a crushing device in which the medication was contained in a disposable plastic bag during crushing (309) which helped to overcome issues associated with cleanliness and cross-contamination. Only one instance of tablet crushing involved the use of an

alternative crushing device, however, this device was cleaned by the nurse, both before and after the administration. For fractional dosing, the majority of split medications were split in advance by the pharmacy. However, when communal, commercial tablet splitters were used, they were inspected and cleaned by the nurses prior to use. Therefore, cross contamination and inadequate cleanliness did not emerge as significant concerns in this study. In addition, although a number of vehicles were used to facilitate the administration of modified medicines e.g. yoghurt, custard etc., these vehicles were used solely for the purpose of medicine administration and only a sufficient quantity to facilitate administration was utilised. No medication was observed being administered in meals, as has been witnessed in previous studies (102, 219, 220).

As stated, the results of this study, when taken into consideration with work conducted by other research groups (102, 103, 219, 261, 280, 304, 305) as well as the findings of Chapters 2, 4 and 5, highlight the ubiquity of ODF modifications. A recent proliferation in the publication of reviews (311, 312) and intervention studies (304-306) addressing the topic of ODF modifications has been apparent. This increased engagement with the issue of ODF modifications for older adults is to be welcomed. However, the potential applicability of these recommendations and interventions in an Irish setting cannot be ascertained without understanding current practices. The value of this study is that it facilitates the assessment of the applicability, and likely benefits, of these recommendations, in light of real-world evidence from an Irish setting. Whilst the evidence from this study highlights that

modifications are prevalent in an Irish setting, there were numerous positive practices observed: the overwhelming majority of modifications were authorised by the prescriber, there was documented evidence of regular review of patients' medication with pharmacists involved in the provision of advice regarding modifications, and there were fewer concerns about modification and administration practices than have been reported in similar studies internationally. However, notwithstanding these findings, modifications were still routinely being undertaken and for many of these modifications there was a lack of evidence-based information sources to facilitate decision making. A number of recently published reviews have described approaches that could be used as an alternative to ODF modification including: the use of alternative formulations of the medication, use of different medications from the same therapeutic class, extemporaneous compounding, discontinuation of unnecessary medication, or teaching patients' strategies to overcome difficulty swallowing (311, 312). These approaches, where available, should be trialled. However, based on the findings of this study, it is clear that in many instances these options are unfeasible or simply unavailable. The use of alternative dosage forms e.g. liquids, is commonly suggested. However, liquid formulations are often expensive, can be difficult to source and may prove challenging to administer, particularly for patients with dysphagia who frequently require liquids to be thickened to minimise the risk of aspiration (231, 313). Uniquely, this study reported on the method of administration of liquid ODFs, finding that almost one in five administrations of liquid ODFs involved thickening the liquid or adding it to a food vehicle to facilitate administration. There is much uncertainty in the literature about the potential impact of thickeners on drug

dissolution and bioavailability (116, 232). For both solid and liquid ODFs, there is a lack of evidence to recommend the use of a particular food vehicle or thickening agent for administration of specific medication. In some instances, drug companies may provide some information on compatibility with certain foods e.g. Xarelto (rivaroxaban) tablets are licensed to be crushed and mixed with water or apple puree (314). Given the lack of information about the appropriateness of various food vehicles and thickening agents, despite their routine use for medication administration, there is a need for further research in this area. Recently, an inert gel, Gloup® has been marketed as an aid to tablet swallowing (315). The manufacturers state that Gloup® has no known interactions with medications. However, there was no evidence of the use of this vehicle in the sites included in the study. Further investigation of the utility of such a product in the LTC setting should also be undertaken.

In addition, many of the liquid dosage forms that were recommended as alternatives to modification in the BPGs were unlicensed formulations. Therefore, in the hierarchy of options, modifying a licensed dosage form is often preferred to using an unlicensed or extemporaneously compounded formulation. As regards the recommendation for deprescribing or withdrawal of unnecessary medication, there was evidence from the medical charts that patients' medication regimens were regularly reviewed by doctors and pharmacists. Deprescribing, particularly for older adults, has become a key focus of research in recent years and the evidence base to support the benefits of deprescribing is growing (316, 317). However, it is

commonly reported that physicians have concerns about deprescribing and can be hesitant to withdraw medications (318, 319). It is vital that necessary medications are not withheld or withdrawn from older adults inappropriately. In general, it can be difficult for healthcare professionals to make decisions on the risk-benefit profile of deprescribing. However, in the case of deprescribing due to swallowing difficulties, the absence of an evidence-base on the appropriateness of modification is likely to further complicate the decision-making process for healthcare professionals who seek to make informed decisions about the risks and benefits associated with deprescribing versus modification.

As regards intervention studies; the majority have focused on ODF modifications as a medication error, either at the prescribing or more frequently, at the administration level (261, 304-306). As a result, these studies have aimed to optimise ODF modifications by reducing the occurrence of inappropriate modifications. Various strategies have been used including: staff education (280, 304-306), the development and dissemination of guidelines or do-not-crush lists (261, 305, 306) or altering practices or processes e.g. implementing warning labels, computerised decision support systems and new protocols (280, 304, 305). However, thus far, the evidence from an Irish setting, as outlined in this and previous chapters (Chapters 4 and 5), suggests that the predominant challenges are not that inappropriate modifications are routinely being undertaken, but rather that the medications that are available are not fit for purpose and must be modified in order to meet the requirements of older patients. In addition, of the

interventions that were evaluated in these studies, many were being implemented in some form in the ACFs in Ireland e.g. the vast majority of modifications were authorised by the prescriber, with evidence of review of patients' medication and modifications by pharmacists. It is likely that the stringent regulation of the nursing home sector in Ireland contributes to optimisation of these practices.

Whilst there appears to be a growing acceptance of the need to engage with the issue of swallowing difficulties with medication intake amongst older adults, medicine modification to facilitate fractional dosing is still a neglected consideration. This study adds to the data on this issue which was first highlighted in the retrospective audit study (240). Modifications for fractional dosing were required for almost one-quarter of all patients, which is similar to the proportion requiring modifications for swallowing difficulties. Many of these modifications were not licensed. Therefore, despite a similar prevalence, there is a paucity of recommendations on modifications for fractional dosing compared to modifications for swallowing difficulties. No specific patient characteristics were found to be associated with fractional dosing, which potentially suggests that it is common across all older patients. Whilst there is debate surrounding the clinical consequences of modifications for fractional dosing, with many suggesting that it is unlikely to cause patient harm (135-137), this study clearly highlights that the dosing requirements of older adults are being neglected in the development of oral medications. Whilst the modification itself can represent an off-licence use, it should also be noted that the dose prescribed may also be off-licence if it is below

that recommended in the SPC. This was the case for many of the fractionally dosed medications administered in this study. This is an important finding for regulators and for the pharmaceutical industry as it clearly demonstrates the urgent requirement for consideration of the needs of older adults in the drug development and authorisation process, to support healthcare professionals in ensuring that patients receive necessary medication, at a dose that will provide therapeutic benefit without resulting in adverse effects.

One of the most pertinent outcomes from this study is that it provided detailed information on the reality of medication administration to older adults. It is clear that medicines are frequently being modified to meet older patients' requirements. However, even in situations where solid ODFs are being administered whole, they are often being administered with thickened fluids and in food vehicles to overcome difficulties with medication intake. In addition, liquid ODFs are also being thickened and administered in food to ensure patient safety. There needs to be an acknowledgement of the challenges associated with administering medication to the older cohort and a concerted effort must be made to take this reality into consideration when designing, developing and authorising medications. This research should serve as a starting point for acknowledging the reality faced by doctors when prescribing, pharmacists when dispensing, nurses when administering and patients when taking medications.

There are a number of limitations associated with this study. The study was conducted in five ACFs in one geographical area in Ireland. Therefore, the generalisability of the study findings to other sites may be questionable. In an attempt to overcome this limitation, ACFs from each funding category (public, private and voluntary) were included in the study. In addition, the stringent regulation of long-term care facilities in Ireland, and the requirement to meet national, prescribed standards on medicine modification and administration (151), may help ensure that the observed practices are reflective of those across Ireland. As a result, the findings should be transferable to other ACFs in Ireland. However, the generalisability of the findings internationally may be limited if different medication administration and management practices are implemented in other jurisdictions.

Undisguised, direct observation of medicine administration was undertaken in this study. Both undisguised (234, 297) and disguised observation methods (304) have been used in previous studies that involved the observation of medicine administration. It could be argued that the use of undisguised observation is a limitation of the study, as the nurses may have behaved differently during the observed drug rounds. However, it has previously been shown that observation of practice does not lead to alterations in behaviour (320) and nurses have previously reported willingness to be observed administering medication (321). For this study, the research team felt that it would be inappropriate to use disguised observation. Previous studies that used disguised observation investigated medicine

administration errors (304), which was not the purpose of this study. In order to overcome the potential for nurses to change their behaviour, the aim of the study i.e. to investigate the reality of, and challenges associated with, medicine modification and administration for older adults, was explained in detail to the nurses. Nurses were also advised that they were free to decline to participate in the study.

Given the challenges experienced with recruitment, it was not possible to reach the target sample size. Hence, the study is under-powered and this should be borne in mind when interpreting these findings. However, whilst the study did not have the desired number of participants, the size of the study still compares favourably with similar studies investigating ODF modifications (102, 219, 297). In addition, a significant strength of this study is the large number of observations that were undertaken and the inclusion of drug rounds at morning, lunch, evening and night time, as in previous studies individual patients were often only observed at one time point (102, 219, 297). Unfortunately, there were a number of challenges encountered in conducting this study including: difficulties arranging suitable times for consenting patients and next-of-kin at the ACFs; the time-consuming nature of the consent process and; difficulties arranging suitable times for data collection and the observation of drug rounds in the busy environment of an ACF. These challenges were not unique to this study and many literature reports have previously described the difficulties associated with conducting research in long-term care settings (322-325). Therefore, further research is warranted to confirm

prevalence; however, this work is unlikely to be feasible using the direct observation method. Rather, given that this study demonstrated that in the ACFs, the vast majority of modifications that were undertaken were authorised, a retrospective audit of drug charts, which is less-time consuming and would circumvent the challenges associated with obtaining consent and arranging suitable times for observations, could be used.

The findings related to the patient characteristics that are associated with medicine modification must be interpreted with caution as these were not the primary objectives of the study. However, the findings should provide direction for further research and investigations of medicine modification and formulation suitability for older adults. Whilst individuality of formulation suitability is a substantial factor that complicates the targeting of interventions, ascertainment of medication types and patient characteristics that increase the likelihood of modification may serve as a useful starting point for efforts to optimise formulation suitability.

Finally, modifications were classed as evidence-based or not evidence-based in accordance with the criteria used in Chapter 4 (240). However, the clinical significance of the modification was not assessed as this was beyond the scope of the study. Some of the “evidence-based” modifications may still have the potential to affect clinical outcomes, particularly for NTI drugs, whilst the majority of the “non-evidence-based” modifications would be unlikely to result in any significant

patient harm. The value of categorising modifications in this manner was that it facilitated examination of the resources and information sources available to healthcare professionals when they are tasked with making decisions regarding medication modification for patients. Therefore, the lack of information available highlights the uncertainty encountered by healthcare professionals when prescribing, dispensing and administering medication to older patients for whom ODFs must be modified.

6.7 Conclusions

This undisguised, direct observation study provided important insights into ODF modification and administration practices in ACFs in Ireland. It is clear that ODF modifications are commonly required to tailor oral medicines to meet the swallowing capabilities and dosing requirements of older adults. Whilst many of the modifications lacked an evidence-base to support decision-making, the majority of practices were optimised within the limitations of currently marketed formulations. A key finding related to the method of administration of medication, with modified and unmodified solid ODFs, as well as liquid ODFs, routinely being administered in food vehicles or thickened fluids. Further research and development is needed to optimise medication formulation suitability for older adults and the findings of this study, by describing the current reality of, and challenges associated with, medication administration, should inform the direction of this research.

6.8 Acknowledgements

The research team would like to sincerely thank all of the patients, their next-of-kin and the nurses who agreed to participate in this study.

We would also like to thank all of the staff at the participating ACFs, particularly the Directors of Nursing and the Medical Directors, who facilitated the conduct of this study.

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Chapter 7: The knowledge, attitudes and beliefs of community-dwelling older adults and their carers about oral dosage form modification: a qualitative interview study

Publication six:

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7.1 Abstract

7.1.1 Background

ODF modifications are commonly undertaken to adapt commercial formulations to meet the individualised needs of older adults. In the community setting, older adults and/or their carers make decisions about medicine administration, often without seeking advice or input from healthcare professionals. However, there is a dearth of research investigating the experiences and opinions of community-dwelling older adults and carers about ODF modification and administration.

7.1.2 Aim

The aim of this study was to investigate the knowledge, attitudes and beliefs of community-dwelling older adults and carers of community-dwelling older adults about ODF modifications.

7.1.3 Methods

Qualitative, semi-structured, face-to-face interviews were conducted with community-dwelling older adults and carers of community-dwelling older adults who experienced difficulty swallowing ODFs, or who required ODFs to be modified to facilitate intake or for fractional dosing. Participants were recruited using a combination of purposive, convenience and snowball sampling from purposively selected community pharmacies throughout county Cork in Ireland. Interviews were conducted between May 2017 and June 2018. All interviews were audio-recorded and transcribed verbatim. The data were analysed thematically using the Braun and Clarke methodology. Interviews continued until no new themes

emerged. The Francis method was used to determine when data saturation had been reached and hence governed sample size.

7.1.4 Results

Twenty six interviews, involving 13 patients and 13 carers, were conducted (76.9% female, median interview length 11 minutes 17 seconds (IQR 8 minutes 3 seconds to 16 minutes 23 seconds)). Four themes emerged from the data: variation in medical needs and preferences; balancing acceptance and resignation; healthcare professional engagement and; opportunities for optimising formulation suitability. The wide range of medical conditions and functional limitations experienced by community-dwelling older adults resulted in a variety of modifications being undertaken to accommodate the individual's needs and requirements. Overall, patients and carers are quite accepting of medications and formulations prescribed and dispensed. Unfortunately, in some instances, when challenges arise, patients and their carers tend to feel resigned to coping within the constraints of the current medication regimen. This resignation resulted in a lack of focused communication with healthcare professionals about their challenges and thus, healthcare professionals remained unaware of the difficulties and did not offer advice or solutions. However, carers of patients with significant difficulties appeared to be more likely to engage with healthcare professionals about modifications and formulation suitability.

7.1.5 Conclusions

From this study, the views of community-dwelling older adults and their carers about ODFs have been elucidated. There is a clear need for healthcare professionals

to engage proactively with this group by advising on the availability of different formulations and the appropriateness of modifications. Pharmacists should offer workshops and supplemental training on medicines administration to those who care for the older adult. In addition, it would be useful to have a list of triggers that prompt the pharmacist to ask about ODF modifications, including both patient and formulation factors likely to influence acceptability. Whilst it is clear that a holistic approach to medication management is ideal, the disadvantage is that no single healthcare professional may identify this as their responsibility, therefore, as medication experts, it is up to the pharmacy profession to take ownership and become the champion of, and for, the patient.

7.2 Introduction

Due to age-related pharmacokinetic, pharmacodynamic and physiological changes (63, 67, 89, 92, 273), ODF modifications are a reality in older patient care with previous research, including research conducted as part of this doctoral research (Chapters 2 and 4), highlighting that in older patient care settings, approximately one-third of all patients receive modified medicines (219, 236, 240, 261, 287). Despite the routine occurrence of ODF modifications, there are concerns about the potential effect on dosing accuracy, drug absorption and release profiles and therefore therapeutic outcomes or adverse events (106, 126, 127, 209). As a result, various interventions have sought to reduce the prevalence of ODF modifications (259-261, 304). However, it is clear that in many instances, there are simply no alternatives to modification due to an absence of suitable formulations coupled with a clinical need for the medication (63, 96, 97, 240). Consequently, guidance to healthcare professionals routinely advocates the use of alternative formulations or routes of administration, with the alteration of solid ODFs being "*reserved as last-resort and practised only after appropriate advice has been sought from a pharmacist and/or Medicines Information Centre*" (104).

Research investigating the views of healthcare professionals about ODF modifications for older adults has shown that the practice is regarded as being routine and necessary (156, 157, 289, 326). Reports have suggested that healthcare professionals' lack knowledge about the appropriateness of ODF modifications (157, 158, 262). Qualitative research has provided further insights, highlighting that

whilst healthcare professionals were often cognisant of the potential for therapeutic consequences when modifying ODFs, they expressed concerns and uncertainty about decision-making in this area (156, 157, 289, 326). However, they negotiated this uncertainty through the involvement of other members of the MDT (156, 157, 289, 326). Therefore, when modifications are deemed necessary, they are considered and reviewed by a variety of healthcare professionals with the goal of ensuring that all modifications are safe and appropriate. Given the acknowledgement that the expertise and input of many different healthcare professionals is often required for decision-making about ODF modifications, this raises concerns about community dwelling older adults and their carers.

The vast majority of older adults in Ireland, 94.7% of those aged ≥65 years and 78.3% of those aged ≥85 years, are resident in private households (24). Therefore, the task of medication management falls to the patient and/or a carer. There are limited data on the prevalence of ODF modifications amongst community dwelling older adults. As discussed in Chapter 2, previous studies have suggested that approximately 14% of community-dwelling older adults experience difficulty swallowing solid ODFs (217, 218, 236). A study conducted in 17 community pharmacies found that; of customers suspected by pharmacists as potentially experiencing difficulty swallowing medication, 60% had difficulty taking a tablet or capsule and of these, 68% modified solid ODFs to facilitate administration (87). As regards modifications for fractional dosing, a study conducted amongst a community-dwelling adult population in Germany (mean age 67.3 years), found

that 24.1% of all tablets were split prior to administration (96). It has been reported that patients do not inform healthcare professionals about difficulties experienced with ODFs (86, 87, 252). Therefore, older adults or their carers may be modifying ODFs without appreciating the potential for adverse events and without the input of healthcare professionals. Qualitative research would help to reveal the knowledge, attitudes, beliefs and experiences of community-dwelling older adults and carers around ODF administration and modification. Ultimately, the most important stakeholders for any qualitative research on medication formulation suitability are the patients and carers who are administering medications on a daily basis. However, as identified in the qualitative systematic review in Chapter 3, research investigating the views of these key stakeholders is limited (289). Of the four qualitative studies involving patients that discussed medicine modification, only one addressed modifications in detail (252), while in the remaining three studies, modifications were briefly mentioned as part of broader discussions around medication related problems or factors that affected adherence (251, 253, 254). No studies have investigated the views of carers in relation to ODF modification. Therefore, research is needed to address this gap in the literature. This will be vital to ensure that healthcare professionals, policy makers, regulatory agencies and the pharmaceutical industry are aware of the priorities and needs of patients and carers who are tasked with managing medication in a community setting. This study will provide valuable and novel insights into the issue of ODF administration and modification in the community setting, which should help to identify areas for more focused and targeted investigation.

7.3 Aim of the study

The aim of this study was to investigate the knowledge, attitudes and beliefs of community-dwelling older adults and carers of community-dwelling older adults about the modification of ODFs.

7.4 Methods

7.4.1 Ethical approval

Ethical approval to conduct this study was granted by the Clinical Research Ethics Committee of the Cork Teaching Hospitals, Cork, Ireland (Appendix 7).

7.4.2 Study design

Semi-structured, face-to-face qualitative interviews were conducted with community-dwelling older adults (aged 65 years or older), and carers of community-dwelling older adults, who experience difficulty swallowing ODFs or who require ODFs to be modified to meet their needs. Various qualitative research methodologies have been used in healthcare research to gain an understanding of the views, perceptions and priorities of patients and carers (193, 194, 327). Little is known about the experiences of community-dwelling older adults and carers around ODF administration and modification (289). Therefore, given the deficits in this research area, semi-structured interviews were chosen as the data collection method to facilitate a broad investigation of this under-explored topic whilst

ensuring that a detailed insight into the personal experiences and perspectives of individuals could be elucidated (288, 328, 329).

7.4.3 Study setting and sampling

Eligible participants for this study were: (i) community-dwelling older adults (≥65 years) who experience difficulty swallowing ODFs or who require ODFs to be modified to meet their needs or; (ii) carers who provide, or have provided, care to community-dwelling older adults (≥65 years) who experience difficulty swallowing ODFs or who require ODFs to be modified. Carers included both family carers and employed carers. Employed carers, in an Irish setting, are commonly known as "home helps" and they perform essential personal care and domestic duties for older adults in the community (330). Home helps are primarily provided by the HSE, who either directly provide a home help service or contract a private provider to supply the necessary services (330). For the purposes of this study, modifications were considered to be required if they were undertaken to: facilitate fractional dosing; overcome swallowing difficulties; or due to patient preference to modify ODFs. Participants were recruited from community pharmacies throughout County Cork, in Ireland. A sampling matrix was developed in an attempt to ensure that the pharmacies and participants included would be representative of the range of experiences encountered by community-dwelling older patients and carers (Table 7.1). Community pharmacies were purposively sampled to include pharmacies located in socioeconomically "advantaged" and "less advantaged" areas, in both rural and urban settings. Pharmacies were classified as: "advantaged" if they were

located in: “marginally above average”, “affluent” or “very affluent” electoral divisions and “less advantaged” if they were located in: “marginally below average”, “disadvantaged” or “very disadvantaged” electoral divisions based on the 2011 Pobal HP Deprivation Index (331).

Table 7.1 Sampling matrix for study

Pharmacy Characteristics		Modifications for Fractional Dosing	Modifications for Swallowing Difficulties
Advantaged areas	Rural	1 Patient	1 Patient
		1 Carer	1 Carer
	Urban	1 Patient	1 Patient
		1 Carer	1 Carer
Less advantaged areas	Rural	1 Patient	1 Patient
		1 Carer	1 Carer
	Urban	1 Patient	1 Patient
		1 Carer	1 Carer

Note: represents the minimum number of patients or carers from each category sought for inclusion in the study

A member of the research team contacted the identified pharmacies, provided the pharmacist with an information sheet about the study and explained what the study would involve. Once the pharmacist agreed to participate, a suitable time for conduct of the study at the pharmacy was arranged. In participating pharmacies, a number of sampling strategies were used to recruit patients and carers including purposive sampling, convenience sampling and snowballing, whereby interview

participants were asked to suggest other potential participants. The primary researcher (AMG) approached patients and carers who presented at the pharmacy and explained the study to them. Individuals were screened for eligibility and eligible participants were invited to participate. Pharmacists were also asked to suggest potentially eligible patients and carers; a member of the research team or the pharmacist invited these individuals to participate in the study. This combination of convenience and more targeted purposive sampling was used in an attempt to include participants whose healthcare professionals were aware that they modified ODFs, as well as those who may not have previously discussed their requirements with a healthcare professional. During recruitment, participants were informed that participation was voluntary and that they were free to decline to participate. No incentive for participation was offered.

7.4.4 Data collection

Two topic guides were developed; one for interviews with patients and one for interviews with carers. The topic guides were devised based on the findings of Chapter 3, the systematic review of qualitative literature on medicine modification (289), taking into consideration the aims of this study. The general content of the topic guides was the same for patients and carers however the language was tailored to address the varied roles and perspectives of each cohort. The topic guides were piloted by interviewing two patients and one carer. The first patient interview was excluded from analysis. During the study, the topic guides underwent iterative refinement to ensure that any unexpected or emerging themes could be

investigated further. All authors reviewed and approved the initial topic guides and any revisions. Table 7.2 provides a summary of the content of the topic guides.

Table 7.2 Summary of the interview topic guides

Interview Topics
Experiences of medicine administration and modification
Decision-making around medicine modification
Knowledge about medicine modification
Views and knowledge about medicine formulations
Strategies used to overcome difficulties with formulations
Healthcare professional support and involvement
Supports

Prior to the initiation of the interviews, the purpose of the study was described to the participants and the interviewer explained the consent form in detail. All participants provided written, informed consent for participation. All interviews were conducted by AMG, a research pharmacist with previous training in, and experience conducting, qualitative research involving semi-structured interviews. No relationship was established between the interviewer and participants prior to initiation of the study. The participants were aware that the interviewer was a pharmacist and researcher working in the School of Pharmacy at the local University. The participants were informed that the research team were interested

in understanding the views and experiences of patients and carers about medicines administration and modification. The interviews were conducted between May 2017 and June 2018 in the private consultation room at participating pharmacies, in the interviewee's home or the interviewer's home, depending on the participant's preference. If participants requested the presence of an additional person during the interview this was facilitated. Demographic data collection forms were completed by participants prior to initiation of the interview. For carers the following details were collected: gender of carer, age and medical conditions of the person for whom they care and the carer's relationship to the person for whom they care. For patients the following details were collected: gender, age, medical conditions and who looks after his/her medications. Repeat interviews were not conducted. Interviews were audio-recorded, anonymised and transcribed verbatim by AMG. Transcripts were not returned to participants for review. Detailed field notes were written by AMG following each interview.

7.4.5 Analysis

Data were analysed thematically according to the method described by Braun and Clarke (295). Transcripts were input into QSR International's NVivo 11 Qualitative Data Analysis Software to facilitate analysis (332). Table 7.3 summarises the phases of analysis undertaken.

Table 7.3 Data analysis process (Adapted from Braun and Clarke (295))

Phase of analysis	Tasks completed	Research team member involved
Phase 1: Familiarisation with data	Transcription, reading and re-reading of interview transcripts. Reading of selection of interview transcripts	AMG LJS, AC, MK
Phase 2: Generating initial codes	Initial, non-hierarchical, open coding of entire data set	AMG
Phase 3: Searching for themes	Categorisation of codes into potential themes	AMG Discussed with MK, LJS, AMC
Phase 4: Reviewing themes	Confirming themes – ensuring the internal homogeneity and external heterogeneity of themes.	AMG Reviewed by, and discussed with, MK, LJS, AMC
Phase 5: Defining and naming themes	Further refinement of themes	AMG Confirmed with MK, LJS, AMC
Phase 6: Producing the report	Production of the manuscript, selection of illustrative quotes	AMG Reviewed by, and discussed with MK, LJS, AMC

In this study, data analysis began at an early stage with interview transcription and reading and re-reading of the interviews. The research team determined *a priori* that an inductive, flexible approach to analysis would be undertaken. It was initially thought that the interviews for patients and carers would be analysed together

given the similarity of the topic guides. However, following initial coding of three patient and three carer interviews, the research team made the decision to analyse the data for patients and carers separately, in order to capture nuanced differences in the codes that were emerging at this stage. A flexible, iterative approach to analysis is a key tenet and strength of qualitative research (295, 333). It was agreed that in the presentation of the findings of the study, any relevant differences between the patient and carer groups would be fully described. The Francis method was used to determine when data saturation had been reached, and therefore, determined the sample size (294). As the patient and carer cohorts were being analysed separately, an initial analysis sample of ten and a stopping criterion of three for each cohort was agreed by the authors, once the decision to analyse the cohorts separately was made. Once data saturation had been achieved for each cohort, the findings were integrated to identify convergence and divergence of the themes from each cohort.

To ensure aligned thinking amongst the research team, each co-author read a random sample of patient and carer interviews to confirm that the codes and themes generated were truly reflective of the interview content. Group meetings were held when necessary and any disagreements were resolved through discussion and a consensus was reached amongst all co-authors. Participants were not asked to provide feedback on the study findings.

7.4.6 Reflexivity

Reflexivity is considered to be essential in the conduct of rigorous qualitative research (296, 334, 335). Reflexivity has been defined as, "*An attitude of attending systematically to the context of knowledge construction, especially to the effect of the researcher, at every step of the research process*" (334) and involves the research team acknowledging, identifying and considering their own unique role, perspectives, backgrounds and beliefs and how these can influence the research (296, 334). All four members of the research team are female pharmacists and, at the time of study initiation, two authors (AMG and MK) were Clinical Pharmacy PhD students, while the remaining authors (LJS and AMC) were academic staff members, at the School of Pharmacy in the local University. The research team have all been involved in research investigating ODF modifications for older adults and have previously undertaken qualitative research. The research team approached this study with the belief that ODF modifications are likely to be required for community-dwelling older adults. The research team had previously identified a lack of data investigating the views, experiences and beliefs of community-dwelling older adults and/or their carers about ODFs and modification practices (289). As such, the research team sought to elucidate the knowledge, attitudes and beliefs of these key stakeholders around ODF modifications by using a comprehensive sampling strategy involving broad, purposive sampling as well as convenience and snowball sampling, and by using an inductive approach to analysis to allow the priorities and views of participants to predominate.

7.4.7 Reporting

This study is reported in accordance with the "Consolidated Criteria for Reporting Qualitative Research" (COREQ) guidelines (296) (Appendix 11).

7.5 Results

7.5.1 Study sites

Twenty one pharmacists were approached and asked if their pharmacies would be part of the study. Of these, seventeen agreed to participate, one did not respond and three declined to participate (two cited a lack of older patients and one was already involved in an ongoing research project). In four of the seventeen pharmacies that agreed to participate, pharmacists chose to only participate in purposive identification of participants and not convenience sampling by a member of the research group at the pharmacy. However, no participants were recruited from any of these four pharmacies. A member of the research team (AMG) attended the thirteen participating pharmacies and conveniently sampled patients and carers attending the pharmacy. Participants were also recruited following purposive identification by pharmacists.

7.5.2 Characteristics of interview participants

In total, twenty six interviews were conducted: 13 with patients and 13 with carers. Figure 7.1 presents a flow diagram of the participant recruitment process. The majority of interview participants were female (76.9%). Interviews ranged in length

from 6 minutes 5 seconds to 35 minutes 15 seconds. The median interview duration was 11 minutes 17 seconds (IQR 8 minutes 3 seconds to 16 minutes 23 seconds). The median interview lengths were similar for patients (11 minutes 13 seconds) and carers (11 minutes 20 seconds). Of the 13 patients interviewed, 61.5% were female. The median age of the interviewed patients was 77.0 years (IQR 72.5 to 84.0). The majority of patients (76.9%) looked after their medication themselves, while 23.1% reported that a family member took responsibility for medication management on their behalf. Seven of the patient interviews were conducted in the private consultation rooms at the participating pharmacies, while six patients were interviewed in their homes. Three of the patients requested the presence of a family member during the interviews, however only the patient contributed to the interview. Of the 13 carers interviewed, the majority (92.3%) were female. Nine of the carers were related to the person for whom they cared (7 daughters, 1 daughter-in-law, 1 husband), while four were employed as carers. Interviews were conducted in the consultation rooms at the participating pharmacies (n=7), at the carer's home (n=4) and at the interviewer's home (n=2).

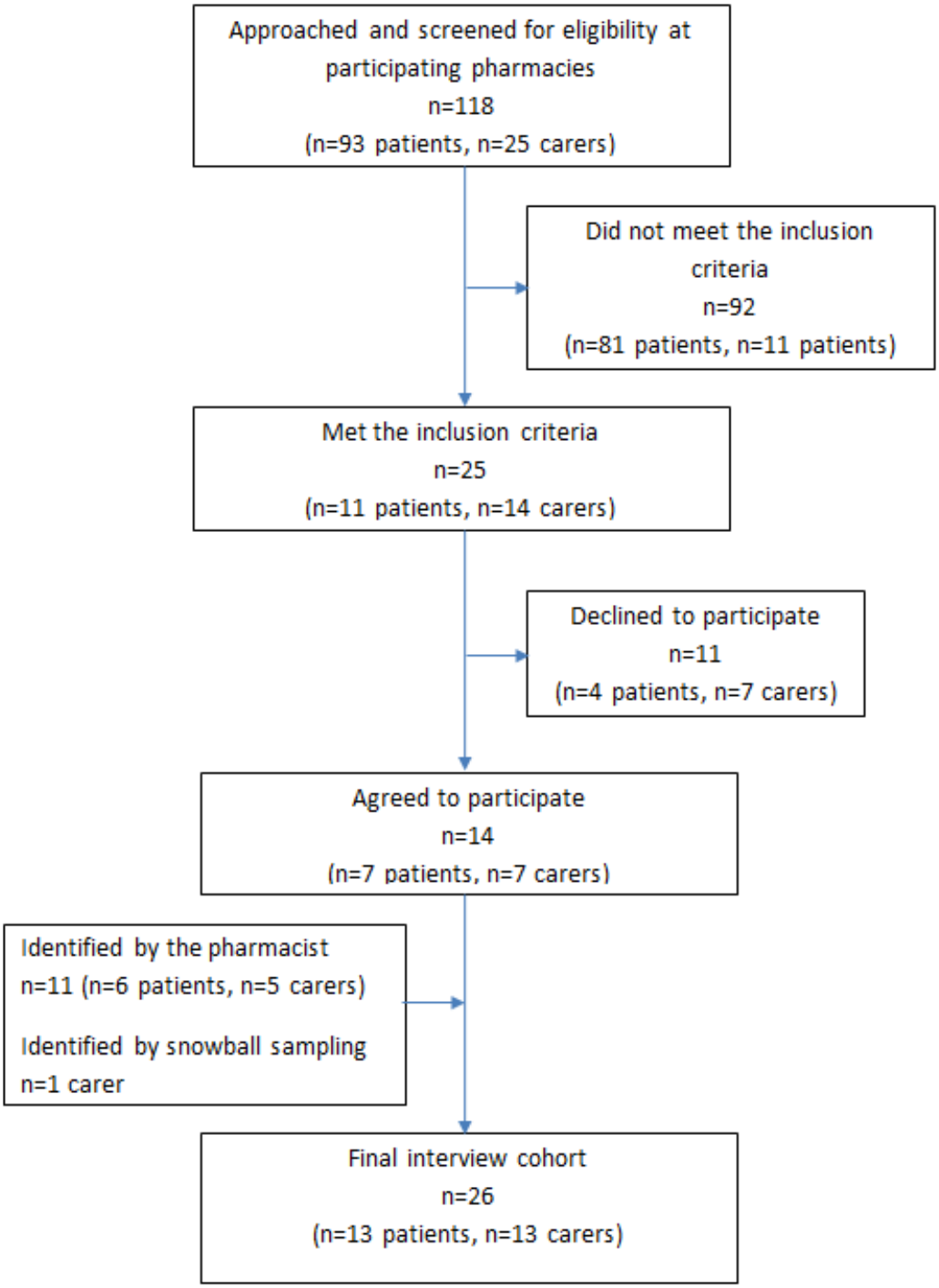

Figure 7.1 Flow diagram of participant recruitment

7.5.3 Themes

As discussed previously, the patient and carer interviews were analysed separately in order to identify any differences in themes or experiences between these groups. Once initial coding, categorisation and searching for themes were completed, the potential themes were examined and integrated to determine where similarities and differences lay. The themes that emerged were broadly similar, however some differences were seen and these are explicitly highlighted.

7.5.3.1 Variation in medical needs and preferences

It was clear from the interviews that there was substantial variation in the complexity of medical conditions experienced by community dwelling older adults. Interview participants ranged from very active, independent individuals who managed their medications themselves through to carers of older adults who required full assistance with medication as well as activities of daily living. This underlines the challenging context within which healthcare is provided in a community setting given the range of abilities, health statuses and medical complexities encountered by healthcare professionals in their daily practice.

Unsurprisingly, given this variability in medical conditions and needs, formulation suitability and modification requirements were seen to differ considerably from person to person. Patients who required modifications to overcome swallowing difficulties existed on a spectrum, ranging from those who halved large formulations due to slight discomfort swallowing large tablets, *"I find them huge…*

so I was cutting them in half" (Patient 9), to patients who required all solid ODFs to be modified due to significant dysphagia which not only affected medication administration but also impacted on food and fluid intake, *"Yeah, it* [solid oral medicines] *was all crushed"* (Carer 3). One carer modified medications for administration via a PEG tube to a patient who was nil by mouth. Similarly, amongst individuals who required fractionally dosed medication, a range of experiences was once again seen, from those who required only a low dose of a medication to achieve the desired therapeutic effect through to those who required multiple medications to be halved as they perceived that they experienced adverse events on higher doses, *"… a lot of my tablets were halved… they can't give me the full dose because I've such low blood pressure and all the medications I'm on bring my blood pressure down"* (Patient 11).

Modifications to overcome swallowing difficulties are a reality for patients in the community. Once again, the individual nature of this phenomenon was evident when the reasons for modifying medications were probed. For many patients, particular formulation characteristics contributed to difficulty swallowing the dosage form e.g. the type of formulation, the size of the tablet or capsule, tablet shape, and tablet coating. However, considerable variability was evident with some participants describing formulation characteristics as detrimental to swallowing while others found the same characteristics to be beneficial, *"A lot of the antibiotics that are big, I'd find you'd have to break those. Now capsules are fine, I don't have a*

problem" (Patient 1), *"Older people who'd say, 'oh, I can't take them big capsules'"* (Carer 2).

A number of factors unrelated to the formulation influenced the need to modify ODFs including: general swallowing difficulties, often attributed to the effects of ageing or inherited swallowing issues; fear of choking on medication due to a previous bad experience; or a perception that they do not "know" how to swallow medications properly. Carers were particularly likely to mention medical conditions that affected swallowing, including stroke, dementia and Parkinson's disease. Although in some instances, healthcare professionals provided advice to participants about modifications to facilitate intake, many participants made the decision to modify on their own. In contrast, modifications for fractional dosing were generally initiated by the prescriber with low doses being prescribed when the medication was started. However, in some instances the need for fractional dosing was only identified when the dose proved to be too high for the patient and resulted in the development of side effects. Whilst the doctor was generally responsible for making the decision regarding dosing, in some instances family members led the decision to decrease the dose and subsequently informed the prescriber who was happy to continue the lower dose, *"We decided ourselves, as a family... that we would half a tablet because she is a very small woman and she'd been complaining, not complaining, but that she was constantly tired. So eventually we put two and two together and decided to reduce that to half a tablet… we just informed the doctor and he said that's fine"* (Carer 7).

Although modifications are commonly performed, it was evident that a wide variety of methods are used. Medication administration is very personal, with each individual patient and carer developing their own techniques and coping strategies to best suit their needs. Various methods to crush tablets were described including commercially available crushing devices, mortar and pestle, crushing between two spoons, crushing using a plastic bag, between a plate and a glass etc. Again, in administering these modified medications, patient preference governed the choice of administration vehicle with modified medications being administered with water, yoghurt, petit filous, ice-cream, jam or with breakfast. Participants reported that medicines were fractionally dosed using a variety of methods including breaking tablets by hand, using a knife, a tablet splitter, or getting the pharmacy to split the tablets in advance.

Perhaps unsurprisingly, the “ideal” formulation differed from patient-to-patient, yet again highlighting the individual nature of formulation suitability and preference. In relation to fractional dosing, some participants expressed a desire for the prescribed dose to be available, which would avoid the need to modify. Others suggested that formulations should be made easier to halve e.g. by including score lines. Other participants stated that they had no issue with fractional dosing as long as it was performed by the pharmacist in advance. In relation to general preferences around ODFs, considerable variability was seen. Some participants expressed no preference, others preferred liquids, while others preferred tablets or described certain “model” tablet characteristics related to the coating, shape or size

of the formulation. However, there was no consensus here, as one participant said, *"But sure I mean everybody's different like. You know, I mean I couldn't sort of legislate for somebody taking medicines, one way or another"* (Patient 6).

7.5.3.2 Balancing acceptance and resignation

The views of older patients and their carers around medicines and modifications were elucidated throughout these interviews. In general, both patients and carers recognised the importance of medication in the maintenance of health and quality of life: "*You either have that* [minor side effect with medication] *or you have the problem of… the heart, it's one or the other, at least this way it's keeping you going"* (Carer 10); *"Like you think you're anti-medicines until you need a medicine and then you're not anti-medicine anymore. You know, you have a different thinking"* (Carer 5); *"If I have to take them, I have to take them"* (Patient 3). As a result, the interview participants tended to be very accepting of the medications prescribed and formulations dispensed to them, with many expressing satisfaction with their current medication regimen: *"I've no complaint with what I have really"* (Patient 5); *"Whatever the doctor prescribed she got, nothing else, good, bad or indifferent because we believe in, strongly, in doing what doctors tell us and that's it"* (Carer 11). However, despite individuals expressing satisfaction with their regimen many voiced a desire to be on fewer medications and questioned the number of medications prescribed to older adults, *"I'd like to reduce tablets. I was on more before… I'd love to have them reduced again but I mean if that's what they say, I take them"* (Patient 4). As the views of patients and carers were probed further, it

became clear that although individuals were accepting of the importance of medication, there was a sense of resignation and lack of autonomy, *"I mean if you are in hospital they just give you the medication and say take it, they give you the tablets in the little container and they bring you in water and they maintain that you are going to take them like and that's it"* (Patient 6).

This sense of acceptance tending towards resignation around medications was echoed in views about ODF modifications. Interviewees modified ODFs to facilitate administration of the prescribed dose, or to facilitate intake due to difficulty swallowing the dosage form. Participants felt that they had no option but to modify the medication, *"But like when somebody's elderly you just have to make the best of it"* (Carer 1), *"Well, the taste isn't very nice, but I'd be just worried in case it won't have the same, you know reaction when I take it, but there's nothing much I can do only take it that way* [break tablets to overcome swallowing difficulties] (Patient 1). Whilst some individuals had no concerns and were happy to perform modifications, for many individuals, modifying medications, despite being their accepted reality of medicine administration, was not without challenges. Concerns about fractional dosing mainly centred on the whether the correct dose was administered due to uneven splitting or fragmentation of tablet halves on storage. In addition to these concerns, difficulties associated with fractional dosing were described including: physical difficulty splitting the tablets, even if a pill splitter is used or a score line is present; and tablet halves fragmenting on storage. For modifications to facilitate intake, concerns were expressed about the accuracy of dosing due to loss of

medication when a modification is performed and subsequent difficulty administering the full dose due to drug remaining in the administration vehicle, *"…you don't know then are you getting a full dose even though you brought out as much as you could"* (Patient 12). Both patients and carers noted additional concerns, including the potential for alterations in the action of the drug or the possibility that modified medicines could damage the oesophagus or stomach. Both groups also reported challenges around performing the actual modification and the palatability of the newly modified medicine. However, despite this, participants continued to modify as they felt this was the only viable option.

This necessity to modify medications was also felt to be unlikely to change given that there was a lack of suitable formulations, *"You could never halve them equally and they didn't make the tablet in a smaller size which was an awful nuisance for them here in the pharmacy and for me because you know I'd be breaking and I'd think, well this is not a half and this is more than a half but what can you do"* (Patient 11). It is likely that attitudes to medication i.e. that they are necessary, informs attitudes towards modification, which may lead to harmful modifications being undertaken. Whilst some individuals were knowledgeable that certain medication formulations should not be modified, this was not universally known or understood, *"I saw on that medication now, 'do not crush or chew' and I was thinking like, if I have to, do I just go ahead and do it?"* (Carer 12). This resulted in a number of participants expressing incorrect beliefs e.g. all scored tablets can be

divided in two to give equal doses or all capsules can be opened to facilitate administration.

7.5.3.3 Healthcare professional engagement

Both patients and carers discussed healthcare professionals, particularly doctors and pharmacists, and the role they played in healthcare provision in the community setting. In general, interview participants had very positive views of both pharmacists and doctors, *"They are very good in my chemist"* (Patient 9). In particular, continuity of care provision was valued with a preference for attending the same general practitioner and pharmacist. An important role centred on information provision, with both doctors and pharmacists seen to be an important source of information and advice regarding medicines and medical conditions in general. Whilst each healthcare professional was seen to have a distinct area of expertise, pharmacists were seen to be more accessible for general queries than GPs, however, information and healthcare provision was seen to require the combined input and expertise of both categories of healthcare professionals. An interesting point raised by one carer was the importance of having a GP and pharmacist who had a good relationship, as this ensured that they liaised and communicated on issues related to the patient, and this was seen to be the ideal situation, *"We stayed with the same GP and pharmacist and then also the GP and pharmacist know each other so that all ties in, he can ring the doctor and he can, you know… it wouldn't be the same if you had a pharmacist over here that didn't know your GP"* (Carer 5).

Interestingly, differences were seen between patients and carers in their level of engagement with healthcare professionals about ODF modifications and formulation suitability. Many patients reported that healthcare professionals did not seem to consider formulation suitability and did not enquire about patient's preferred formulations or whether they experienced any issues when taking ODFs. However, this was unsurprising given the acknowledgement that many healthcare professionals were unaware of patients' difficulties with formulations given that patients tended to persevere on their own, developing techniques and coping strategies to overcome difficulties, "K*eep on till I got it down"* (Patient 1). Many patients seemed reluctant to inform doctors or pharmacists about the difficulties they experienced or even simply to ask questions related to their medicine or health, *"I don't ask and I think afterwards why didn't I ask him…"* (Patient 3). Amongst pharmacists, there was a tendency to dispense the formulation prescribed without seeking further information from the patient, *"They'd give me whatever is on my prescription"* (Patient 7), which also hindered engagement. This tends to result in a vicious cycle in which the patient is left without the correct information and the pharmacist is blissfully unaware of their predicament. Patients appeared to only engage with healthcare professionals when a problem with a formulation became very significant and the coping strategies they used previously proved ineffective or if they received modified medicines during a hospital admission. However, in the case of modifications for fractional dosing, pharmacists appeared to be more proactive, offering to split the medication for patients as well as carers. This is likely to be due to the fact that, from the dose prescribed and formulations

available, it is obvious that a modification is necessary, *"One of the girls there* [in the pharmacy] *told me that they'd half them"* (Patient 6).

In contrast to patients, carers were more likely to report that doctors and pharmacists were aware of the patient's swallowing difficulties or formulation preferences. This was particularly true when the patients they cared for suffered with significant swallowing difficulties. In these instances healthcare professionals were more likely to consider formulation suitability and enquire about preference, *"…their pharmacist... he was super. I mean he'd always come out and he'd say you know you can't crush this… he would have been very helpful*" (Carer 3). However, even in situations where healthcare professionals were aware of difficulties, carers were cognisant of the need to remind them of patient's requirements as they occasionally forgot. Carers reported a sense of responsibility and advocacy which empowered them to ask questions and raise any concerns that they had, *"I would question everything, I don't have a problem… I would ring the pharmacist if I was having a problem with a particular tablet, would there be an alternative?"* (Carer 4). However, this enhanced engagement was not universal, predominantly seen amongst carers who provided care to patients with significant needs. The views of those providing care for patients with fewer requirements were more in line with those of patients, and they were often unaware of the availability of alternative formulations. Therefore, lack of engagement by both patients and carers seems to stem from lack of knowledge about medications and formulations. This also led to an important observation regarding the role of carers in the community setting.

Both family carers and "home helps" were interviewed in this study. Although home helps described that their role centred on personal care and they did not administer medication, they were extremely knowledgeable about, not only the patient in general, but also the challenges they experienced when using medication. Carers, both family carers and home helps, were cognisant of the need to support and supervise older adults and stated that they would always intervene if they were concerned that the patient was not coping with medication management, *"Like you visually have to keep contact with them, visual contact all the time, you can't just turn away or you know, put a tablet there on the table and let them do it"* (Carer 4), *"There was a problem with her medication actually… I had to get on to the public health nurse"* (Carer 9). Many patients in the community setting relied on their carers to liaise with healthcare professionals, *"I would yeah* [contact a patient's doctor or pharmacist]*, and they are very good, you know. Once the patient is okay with you speaking to the doctor or whatever, there is no problem"* (Carer 8), and to advocate on their behalf. This highlights the importance of the patient-carer relationship in the community setting.

When healthcare professionals were aware of patient's needs they were reported as being extremely helpful: advising about the different formulation options available; providing information about the appropriateness of modification; advising on the best methods of modification and administration. However, lack of engagement, both by patients and carers, and by healthcare professionals appeared to be a substantial barrier to formulation optimisation for older adults.

7.5.3.4 Opportunities for optimising formulation suitability

The knowledge, attitudes and beliefs of participants about ODF modifications demonstrated a need for initiatives to support community-dwelling older adults and their carers in the area of formulation suitability and medicine modification. The majority of participants were of the opinion that more supports are required, with a strong preference for these supports to be delivered in the community setting by their regular healthcare providers. Both patients and carers felt that greater engagement by healthcare professionals in this area would be beneficial. There was a desire for healthcare professionals to enquire about patient's formulation preferences and swallowing difficulties more frequently, *"If the doctor or the pharmacist suggest, asked, like, you are prescribed a certain thing now and you can either have it in… whatever form, you know"* (Patient 2). This was linked with a perceived need for more regular review of patient's medication regimens, *"I find that in Ireland, if you are prescribed something, you are on it for life. There is no follow-up… once they are prescribed it's just a continuing process"* (Carer 7). Notwithstanding the finding that healthcare professionals already play an important role in information provision, the majority of participants were of the opinion that information provision should be improved. Again, it was felt by both groups, that this information should be delivered by their regular doctors and pharmacists and tailored to their requirements. Topics that were suggested included: general information on medications; the formulations that are available; advice regarding the appropriateness of modifications and; how to perform modifications. In particular, accessible information that is consistent across all healthcare professionals and settings was seen to be vital as one carer previously

encountered inconsistencies in advice regarding PEG administration which created uncertainty and worry. A variety of methods of information provision were suggested including: information delivery at the point of prescribing or dispensing; leaflets and booklets on modification and; workshops or educational sessions for both patients and carers on administration, *"Workshops that come into the community... and get the carers to come in for one hour and say, look this is what's out on the market, do you realise that this is available and there's an alternative and if you do have doubts this is who you should ask... if the workshops were open to everybody and not just focused on one sector"* (Carer 4). Carers often described how, over time, they developed their own techniques and strategies to overcome challenges with administration and that they gradually learnt about various formulations that were available and who to approach for help. As such, caring for older adults was a learning experience, however, proactive information provision and education sessions, would help to empower carers to feel more confident and knowledgeable in this area, *"Like it's a learning curve for all of us... but you know small kids and old parents are very similar in that you kind of have to do so much and I think…it's a life skill"* (Carer 2).

Most of the supports suggested centred on healthcare professionals. However, some participants raised the need for greater consideration of the medication requirements of older people by the pharmaceutical industry, "*It's a pharmaceutical company so they're doing for the majority… it* [a formulation] *might suit six out of the ten, but there's four that they're not suiting"* (Carer 4), *"…if the*

pharmaceutical industry reduced the size of their tablets, very definitely, because some people just can't swallow them" (Patient 13). Increased development and availability of alternative formulations, such as liquids and patches or easily modifiable medicines, were suggested as methods of improving formulation suitability for older adults, *"More liquids and patches and that kind of thing, that'd be great"* (Carer 1).

7.6 Discussion

This study has examined the views of patients and carers regarding ODF modification. Four themes emerged: variation in medical needs and preferences; balancing acceptance and resignation; healthcare professional engagement and; opportunities for optimising formulation suitability. The findings of this study highlight the variability associated with the formulation requirements and preferences of community-dwelling older adults. While both patients and carers tend to be very accepting of medications and formulations as prescribed and dispensed, this acceptance may stem from a sense of resignation to the need to take the medication and the perception that there are simply no alternatives other than their current medication and/or modification regimen. This may ultimately result in a lack of engagement with healthcare professionals, with patients and carers adopting various coping strategies to overcome the challenges they encounter. As a consequence, healthcare professionals are often unaware of the difficulties experienced by their patients. However, the role of the carer was seen to be vital, with carers appearing to be more likely to engage with healthcare

professionals regarding formulation suitability. As a result, there is scope and desire for further supports and initiatives to be implemented to optimise formulation suitability for community-dwelling older adults.

It is clear from this study that older adults in a community setting cannot be considered a homogenous cohort. Rather, healthcare professionals providing care to community-dwelling older adults encounter a wide-range of health statuses, medical conditions, support structures and abilities that substantially contribute to the complexity of healthcare provision in a community setting. Whilst ageing is frequently defined as a progressive deterioration of physiological function (336), many commentators argue that ageing itself should not be considered a pathological condition, commensurate with frailty and dependence (337-339). However, neither is active, independent living a reality for all older adults, particularly given that age-related physiological changes are, in themselves, risk factors for the development of many diseases (337-339). In reality, a wide spectrum is seen from independent, ambulatory individuals with excellent health through to individuals requiring considerable support and care from healthcare professionals as well as carers (338). This variation in medical complexity and care requirements has implications for formulation suitability and ODF modifications. This is evident from the wide range of experiences and views detailed by those interviewed, which concurs with the findings of the systematic review of qualitative literature (Chapter 3) which reported that patient-centred individuality and variability was a key factor influencing the need to modify ODFs (289). Therefore, the issue of formulation

suitability is one that must be considered routinely. However, it is important for healthcare professionals to recognise that, as highlighted in the qualitative systematic review (289) and further emphasised in this study, medical complexity alone is not the only factor influencing ODF modifications.

It has been established that, amongst the community-dwelling cohort, medicine formulation suitability varies substantially which adds to the complexity of optimising medical care for these patients. An important finding from this, and other studies, is that many patients, not just those with dysphagia, find medication intake challenging and resort to modifying medicines, often unbeknownst to their healthcare professionals (86, 87, 221, 289). It appears that healthcare professionals in a community-setting are more likely to consider formulation suitability for individuals with medical conditions with dysphagia as a co-morbidity e.g. stroke, dementia, Parkinson's disease etc. This may be due to a combination of healthcare professionals' awareness of the prevalence of dysphagia in these cohorts and the associated complications around medication intake, as well as the fact that these patients may have carers who take on the role of patient advocate. However, the literature consistently demonstrates that patients without documented diagnoses of dysphagia or difficulty swallowing, experience difficulty with medication intake and modification (86, 87, 221, 289). Therefore, relying on medical complexity alone to guide decisions regarding formulation suitability is likely to be insufficient to identify individuals who require greater support. As the population ages, and there is an increased preference amongst older adults to remain in the community (340),

which is backed by government policy (341), healthcare professionals are being tasked with providing care to patients with a wider variation in medical needs. There needs to be increased appreciation of the patient-related factors that contribute to complexity related to formulation suitability. Increased awareness of the challenges encountered by all patients and carers, in managing and administering medications on a daily basis, would help to ensure that all patients, particularly those who may not have the support or input of a carer, receive the optimum formulation to suit their needs. The value of this research is that the themes identified provide clear directions for further research and interventions, which take into account the substantial variability encountered in the community setting.

Participants in this study were very accepting of medications, with the general consensus being that medications are necessary to maintain health and quality of life. Central to this appeared to be the trust that was placed in healthcare professionals, with participants frequently describing the need to adhere to doctors' recommendations regarding treatment. However, there was a distinct sense of resignation to the need to take medication long-term, often despite a preference to be on fewer medications. Previous research has investigated whether patients' beliefs about medication impact on adherence (342). It has been shown that higher necessity scores (i.e. a view that medications are a necessity) are positively correlated with adherence, whereas higher concerns about medication were correlated with lower adherence (343, 344). Whilst previous studies have

reported that difficulty swallowing medication can lead to poor adherence (84, 86, 87), in contrast, in this study, participants' beliefs about the necessity of medicines resulted in them persisting in taking formulations, even when this proved challenging, by developing their own coping strategies to facilitate administration. The beliefs of participants towards medication appeared to influence their views on formulation suitability and medicine modification, with the sense of acceptance and resignation around medicines promoting a sense of resignation towards the formulations prescribed and dispensed. Although the findings regarding adherence appeared to diverge from previous reports (84, 86, 87), in keeping with previous studies, difficulty taking medication resulted in many participants' modifying medications (84, 86, 87). While some participants reported that they would ask about the availability of alternative formulations or check if the modification was appropriate, many undertook modifications without any appreciation that modifications may be inappropriate or that alternative formulations may be available. This may be partly explained by the observation that participants were resigned to the formulation prescribed and viewed the medication as being vital. Therefore, their primary consideration centred on administration. This finding reflects the view expressed by nurses in the study conducted by Barnes *et al.* (156) that the imperative is ensuring that all prescribed medication is administered. This raises concerns that given that the dominant imperative is to administer medications, inappropriate or potentially harmful modifications may be performed without input from healthcare professionals. Previous research has highlighted that many healthcare professionals are unsure of their responsibilities in relation to medicine modification given that numerous disciplines have distinct roles to play in

this area (156, 157). However, as experts in medication, with a unique understanding of formulation and dosage form design, pharmacists have a vital role to play and must engage in this area, to ensure that patients receive maximum benefit from their medication, while minimising potential harms.

Participants in this study had positive views about their healthcare professionals, including doctors and pharmacists, and described that they provided excellent care and support to them. However, despite this, patients acknowledged that many of their doctors and pharmacists were unaware that: they experienced difficulty taking solid ODFs; they modified ODFs or; they had difficulty performing modifications. This echoes findings from previous research which found that patients do not inform healthcare professionals about difficulty taking ODFs and healthcare professionals do not enquire about patient preference (85-87, 221). This lack of engagement by patients, and some carers, with healthcare professionals is a serious concern and the factors contributing to this reticence to inform healthcare professionals about their difficulties must be addressed. The reluctance to actively seek assistance around formulation issues may, ironically, be related to the fact that patients are accepting of the healthcare provided to them because they trust and rely on their healthcare professionals to make decisions on their behalf. This passive approach, in which patients do not take an active role in decision making around healthcare, is reflective of a more traditional, paternalistic approach to healthcare professional-patient interactions (345). Perhaps the fact that the patient cohort was over 65 years of age may partly explain their lack of engagement as

older adults often have a more traditional approach to healthcare, preferring to rely on their healthcare professionals' judgement (346, 347). In recent years, there has been a move away from this paternalistic approach to one in which shared decision-making is encouraged (348). It has been suggested that outcomes may be improved when patients participate in decision-making around medical treatment and care, although data are limited (349-351). Older patients in particular should be encouraged to become more active participants in the clinical decision making process and patient autonomy should be encouraged. This may help to encourage and empower individuals to become partners in their own care, sharing issues and communicating challenges with their healthcare professionals. However, research has also highlighted that some patients prefer not to be involved in healthcare decision making (346). Whilst patients and carers should be encouraged to inform healthcare professionals about the difficulties they experience, the onus should not solely be on the patient and/or carer. Healthcare professionals must be encouraged to consider formulation suitability at every instance of prescribing, dispensing and administration, particularly for patients who assume a more passive approach (352). In this study, patients with significant dysphagia or difficulty swallowing medication reported that healthcare professionals were aware of, and considered, their issues with formulations. However, given that individuals who do not suffer with dysphagia are modifying medicines routinely; healthcare professionals must be encouraged to ask all patients about formulation preferences and difficulties experienced. This may necessitate healthcare professional education, particularly to raise awareness of the variety of factors, not just medical conditions, which can impact on formulation suitability. Further research will be required to identify these

factors, both at the patient and formulation level. In Chapter 2, it was suggested that there is a need for the development of a screening tool to identify patients who experience difficulty taking medication (236). Routine incorporation of such a screening tool as part of the general consultation with a patient would encourage greater consideration of the formulation requirements of older adults. The "SWAllowing difficulties with MEdication intake and COping strategies" (SWAMECO) tool was developed by a research group in the University of Basel, to identify swallowing difficulties with medication intake thereby facilitating healthcare professionals to select the most appropriate formulation and to provide tailored counselling to reduce inappropriate modifications (353). This tool has recently been translated into English and undergone preliminary validation in an Irish community pharmacy setting (354). Further validation is required, however, routine use of a tool such as this may help to overcome issues associated with lack of engagement, thereby ensuring that healthcare professionals are aware of the difficulties that patients experience, which should ultimately facilitate them in optimising formulation suitability for their patients.

Another possible reason for the lack of engagement may be related to a knowledge deficit around medications and formulations amongst patients and carers. It has been shown in this, and previous studies (84, 86, 87, 221), that patients lack awareness about medications and formulation types, and therefore, they may not enquire about the availability of alternatives due to an assumption that the medication dispensed to them is the only formulation available. In addition,

knowledge that modifications can potentially be hazardous is not commonplace. Therefore, patients and carers often do not realise that these modifications should be reviewed by a healthcare professional to ensure that they are safe and appropriate. There is a need for greater education of patients and carers about salient features of medications. However, it must be acknowledged, that some participants, particularly carers, described seeking alternatives or verifying if modifications were appropriate. This suggests that some patients and carers, particularly those with significant experience performing medication management and modification, are knowledgeable in this area. However, as described by these participants, caring for older patients with significant needs is a learning experience. As previously highlighted by Cowan (355) , experience is what makes the carer the expert in patient care. This provides support to the fact that knowledge about formulation alternatives and the supports that are available is not intrinsic, but rather develops over time. One carer made the analogy that caring for an older parent is, in some ways, similar to caring for a young child, where the carer undergoes a significant learning curve but expresses a willingness to advocate and speak out on behalf of their loved one, who may not be able to vocalise their own needs. Greater information and support should be provided to carers to facilitate them in advocating for their loved ones. At present, it appears that carers learn by experience, when difficulties and challenges are encountered. However, a more proactive approach to the provision of information and support should be encouraged.

Carers play a vital role in healthcare provision in the community setting and greater engagement with carers may present an additional means of optimising formulation suitability for older patients. Carers, particularly those caring for older patients with significant morbidities, reported that they informed healthcare professionals about formulation suitability and/or healthcare professionals considered formulation suitability. It was an interesting finding that carers appeared more likely to inform healthcare professionals about difficulties with formulations than patients themselves. Various studies have investigated the role of carers, and in particular, carers' view of their role. As Cowan reported, carers have a unique knowledge of the patient's needs and want to be viewed as an "expert partner" in care provision (355). In Chapter 5, it was found that nurses, in acute and long term care settings, advocate on behalf of their patients', which helps to optimise formulation suitability. Carers in a community setting are taking on a similar role, and engage with healthcare professionals to act as patient advocates (356). Therefore, carers represent a vital resource who can help to overcome the lack of engagement and associated information deficits around formulation suitability for individual older adults.

This study has provided a detailed and useful insight into the knowledge, attitudes and beliefs of community-dwelling older adults and their carers about the modification of ODFs. A key strength of this study was the inclusion of both patients and carers. This facilitated an in-depth investigation of the range of challenges encountered in the community setting. Patients who were able to participate

generally represented more independent, ambulatory patients who were able to manage medication on their own behalf. However, by including both cohorts, a thorough appreciation of the community care setting was obtained. Particularly novel was the inclusion of carers, as no previous study specifically investigated the views of carers around ODF modifications, despite the fact that carers frequently assume responsibility for medication management for community-dwelling older adults. Therefore, this study has addressed this significant gap in the literature. In addition, the use of the defined sampling strategy ensured that the full range of experiences and perspectives were elucidated. The large number of participants included in this qualitative study is also a significant strength of the study, and the time frame of the study allowed for in-depth analysis to be undertaken. In addition, providing participants with the opportunity to decide upon the location of the interview ensured that participants felt comfortable and at ease during the interview. There are a number of potential limitations associated with this study. The majority of participants were female and therefore, the findings may not reflect the male perspective on ODF modifications. However, in this study, no variations in views or experiences were evident between the male and female participants. The carer cohort, in particular, was predominantly female. However, this is likely to reflect the reality encountered in Ireland, as females tend to be more likely to take on the role of carer, both for family members and as employed carers (357, 358). While the transferability of the findings may be questioned given that interviews were conducted in one county in Ireland, the use of a sampling matrix and inclusion of participants from different socioeconomic regions and both urban and rural areas helped to overcome this limitation. It is possible that given that the

interviewer was a pharmacist, this may have resulted in participants providing socially desirable responses. However, given that no relationship was established with participants prior to the interviews and the participants only had knowledge of the interviewer in the capacity of a researcher, this would have helped to overcome this potential limitation. Participants were assured of the confidentiality of their responses and it was evident during the interviews that participants expressed their opinions honestly and openly.

7.7 Conclusions

From this study, the knowledge, attitudes and beliefs of community-dwelling older adults and their carers have been elucidated. It is clear that the diverse, community-dwelling older population experiences substantial variability in their formulation and modification requirements and preferences. Whilst good relationships with doctors and pharmacists were reported by both patients and carers, there was a sense of acceptance veering towards resignation around medications and formulations. This sense of resignation often resulted in lack of engagement with healthcare professionals, who in turn were unaware of patients' formulation requirements. There is a clear need to enhance engagement with this cohort and various supports and initiatives are likely to be required to optimise formulation suitability for older adults. A key first step will involve raising awareness amongst healthcare professionals of the pervasiveness of challenges with formulations so as to encourage healthcare professionals to consider formulation suitability when prescribing and dispensing medications for older

adults. In addition, carers and patients should be provided with information about medications in order to enhance knowledge and encourage greater engagement with healthcare professionals.

7.8 Acknowledgements

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Chapter 8: Discussion

8.1 Discussion

This thesis investigated ODF suitability for older adults by examining ODF modifications in an Irish setting. In this chapter, the thesis, as a complete body of work, is discussed and the overall findings are interpreted. The chapter will begin with a summary of the key findings from each individual chapter, before integrating these findings to provide greater insights. This will involve a discussion of the implications of the research, taking into consideration previous literature, as well as healthcare policy. Following this, the overall strengths and limitations of the thesis will be described. Finally, recommendations for future work will be provided.

8.2 Summary of findings

The first objective of this doctoral research was to systematically review the quantitative and qualitative literature to provide an evidence-base to inform the development of research questions for the primary research studies. The quantitative systematic review (Chapter 2) identified that approximately 14% of community-dwelling older adults experience difficulty swallowing ODFs whilst between one-quarter and one-third of occasions of medicine administration to older patients in care facilities involved the modification of ODFs. However, a key finding was the paucity of data investigating ODF modifications amongst the older cohort, with only two studies assessing the prevalence of difficulty swallowing medicines and three investigating ODF modifications. In addition, there were issues associated with how direct observation studies reported the prevalence of ODF modifications, reporting at the level of occasions of drug administration rather than

at a patient level. Given the limited number of studies, the need for further research to investigate the prevalence and practice of ODF modification was identified. The qualitative systematic review (Chapter 3) identified that the variable and individual nature of patients' needs and requirements is a key factor influencing the modification of ODFs. Optimisation of formulation suitability is hindered by the observation that communication, both between patients and healthcare providers and between different members of the healthcare team, is often poor, resulting in a lack of awareness of patients' individual formulation needs. The review also identified that both healthcare professionals and patients are often uncertain about the appropriateness of modifications which stems from a lack of knowledge; due to an absence of easily accessible, evidence-based information resources. The findings of these reviews served to inform the generation of research questions for the primary research studies by identifying a number of key areas for further investigation.

The retrospective audit of drug charts described in Chapter 4 provided the first data on ODF modifications for older adults in an Irish setting. This study demonstrated that ODF modifications are commonly required to tailor ODFs to meet the needs of older adults in an ACF, with 35% of patients requiring at least one medicine to be modified to meet their needs. A particularly novel finding was that modifications were most commonly undertaken to facilitate fractional dosing. This was of interest given the lack of consideration of the issue of dose suitability in the literature. A total of 68 instances of modification were recorded, of which, almost half were neither licensed nor recommended in BPGs. The necessity to modify ODFs

appeared to arise predominantly due to a lack of appropriate, licensed dosage forms; however, reimbursement policies also appeared to play a role. It was clear that clinicians lack evidence-based information sources to support decision making around modifications when appropriate alternatives are unavailable.

The qualitative interview study described in Chapter 5 was designed to address gaps identified in previous chapters: a lack of studies investigating the views of nurses (Chapter 3); and to further probe the potential factors influencing ODF modifications in an Irish setting (Chapter 4). Three major themes: modifying – a necessary evil; nurses' role as patient advocate and; modifying – we are working very much as a team; emerged from the data. Nurses viewed modifications as being a common and necessary occurrence when providing care for older adults, due to limitations of available formulations and the presence of age-related challenges around medication administration. Whilst the systematic reviews (Chapters 2 and 3) identified that a lack of communication hinders formulation optimisation, nurses helped to overcome this issue by advocating on behalf of patients to raise awareness of their individualised needs. The nurses' knowledge of the individual patient greatly facilitated this advocacy role. However, nurses expressed concerns and uncertainty around modifications and sought information, advice and reassurance from members of the MDT, particularly pharmacists, in an effort to overcome knowledge deficits and concerns about modifications.

The direct observation of medicine administration (Chapter 6) undertaken in five ACFs sought to further develop the evidence-base on ODF modifications in an Irish setting and address some areas for further research identified in previous studies.

This study confirmed that ODF modifications are a reality for older adults in ACFs in Ireland with almost half of patients having at least one solid ODF modified to meet their needs. Modifications to overcome swallowing difficulties were more common than in the retrospective review. Particularly interesting were findings related to the methods of modification which showed that the techniques used helped to overcome concerns regarding cleanliness and cross-contamination. Both modified and non-modified ODFs were frequently administered using food vehicles and thickened fluids, highlighting the difficulties experienced in administering medications safely to older adults.

Chapter 7, the qualitative interview study with community-dwelling older adults and their carers, once again highlighted the wide variability in medical needs and formulation requirements amongst the older cohort, which concurred with the results from the systematic reviews (Chapters 2 and 3), as well as the quantitative and qualitative studies (Chapters 4 to 6). While overall, patients and carers tended to be extremely accepting of their medications and the formulations dispensed, there was a sense of resignation towards medication which resulted in patients and carers persisting with formulations even when challenges were encountered. This resignation resulted in lack of engagement with healthcare professionals who were frequently unaware of the difficulties experienced by patients in a community setting. In contrast, carers appeared to be more likely to engage with healthcare professionals, informing them of patient's formulation requirements and needs. Participants expressed a desire for supports to be implemented to assist them in managing medications in a community setting including: greater engagement and

information provision by healthcare professionals; delivery of workshops on medication and; the development of more formulations.

8.3 Interpretation, and implications, of findings

Reviews discussing potential challenges associated with oral drug administration for older adults continue to be published (164, 165, 182, 184, 311, 359). The principal contribution of this thesis has been the generation of evidence, from both long-term care and community settings, demonstrating that ODF modifications are not only common, but also necessary to meet the needs of older adults. The findings from this thesis concur with, and add to, previous studies that have described ODF modifications in community (87, 217, 254) and long-term care settings (100, 102, 156, 219, 220, 287, 297). In particular, this thesis has developed the evidence-base related to modifications for fractional dosing. It is now clear that modifications should not be considered unusual nor are they only undertaken in exceptional circumstances. Rather ODF modifications represent a normal, day-to-day reality for many older adults. The findings of this thesis should serve as the impetus for greater engagement with this issue through the provision of direction for future research. Two key areas for engagement by different stakeholder groups have been identified: formulation suitability and medicine acceptability by academics, the pharmaceutical industry and regulatory bodies and; medicines optimisation by healthcare professionals and academics. In particular, the findings of this thesis should also serve to inform the reflection paper on the pharmaceutical

development of medicines for use in the older population which is currently under preparation by the EMA (174).

8.3.1 Formulation suitability and medicine acceptability

One of the most predominant and recurring themes present throughout this thesis, in both the quantitative and qualitative research, was variability and individuality of older patients' needs and preferences in relation to ODFs. In the qualitative studies, there was substantial variability around the formulation characteristics that contributed to difficulty with intake and/or modification, as well as the types of dosage forms that were preferred by patients. In addition, there was no consensus regarding the ideal formulation for older adults amongst patients, carers or nurses. In the quantitative study, forms which proved to be acceptable and usable to many, were unacceptable for others. This diversity concurs with previous studies that investigated the prevalence of difficulty swallowing ODFs amongst community-dwelling adult patients, that reported substantial variability in the formulation factors that impacted on ease of intake (85, 86, 360). While none of these studies were conducted exclusively in an older population (85, 86, 360), they substantiate the finding that specific formulation characteristics contribute to difficulties with intake. A recent review sought to objectively investigate how the physical characteristics of ODFs affected oesophageal transit (182). Factors including size, shape, density, surface characteristics and type of formulation were found to impact on swallowability and oesophageal transit of tablets and capsules amongst adult patients (182). The authors acknowledged that literature reports pertaining to

older adults are limited, however, they emphasised that as difficulties are likely to be even more pronounced amongst the older cohort, the findings provide useful guidance on formulation factors that affect swallowability for the older cohort (182).

Increasingly, medicine acceptability, *"the ability and willingness of a patient to self-administer, and also of any of their lay or professional caregivers, to administer a medicinal product as intended"* (174), is being recognised as an important consideration for older adults and their carers (182). A significant contribution of this thesis is in highlighting that patient factors, not just medical conditions and formulation factors, influence the need to modify medications for older patients. Therefore, "medicine acceptability", is the best approach for assessing formulation suitability for older adults as it considers the variety of factors that can affect acceptability from a patient or carer perspective. It is vital that the acceptability of ODFs for older adults is considered early in the drug development process, when formulations and doses are being identified and selected for further development and commercialisation. However, this will necessitate the development of validated methods to assess medicine acceptability, as well as improving awareness that factors other than the formulation characteristics and patient's medical conditions affect acceptability. Whilst significant improvements have been made in the area of medicine acceptability for paediatric patients, primarily due to regulatory requirements (185, 361), medicines for the geriatric cohort have lagged behind. A recent systematic review of methods used to assess the acceptability of oral

medicines identified seventeen studies that reported on the formulation characteristics that affect the acceptability of ODFs for older patients (362). The review authors reported a lack of standardisation of methods used to assess acceptability and called for a consensus agreement between academia, the pharmaceutical industry and regulators to harmonise methodology for assessing acceptability of pharmaceutical products (362). Therefore, this thesis adds weight to calls for the development of methods to assess medicine acceptability for older adults, but in addition, highlights the need for these methods to incorporate all of the potential contributing factors, including formulation characteristics, patient preferences, social influences etc., given the finding that many individuals without objective evidence of swallowing dysfunction and without any co-morbid medical conditions report difficulties with formulations. A recent attempt has been made by Vallet *et al.* (363) to take account of both user and product characteristics that influence acceptability, by developing a decision support tool to assist in the design of acceptable medication for older adults. This study used data from an observational study conducted in hospitals and nursing home settings to develop an acceptability reference framework using a multivariate data analysis approach. Efforts such as this should help the pharmaceutical industry and regulators to evaluate the acceptability of medicines for older adults, taking into account the various and complex user and formulation factors that influence acceptability.

As stated previously, the issue of dose suitability for older adults has yet to be extensively addressed in the literature; however, evidence from this thesis

highlights that modifications for fractional dosing are commonplace, despite a lack of data on the accuracy of tablet splitting for individual formulations (Chapter 4 and 6). This thesis has underlined the need for dose selection to be made relevant to the target patient population and for greater consideration of the neglected issue of modifications for fractional dosing.

In Chapter 1, the regulatory perspective on medications for older adults was summarised. The increased focus by regulatory agencies on the issue of medication suitability for older adults has led to increased engagement, by both academics and the pharmaceutical industry, with older adults and carers in an attempt to identify their priorities related to medication (165, 359). The challenge now is to translate the learnings from this, and similar research, into improved medicines for older patients. This will undoubtedly be a challenging task for the pharmaceutical industry, given that, as highlighted by Page *et al.*, a "one-size-fits-all approach" to geriatric medicine formulation will not be sufficient (364). However, the current approach, where extrapolations are made from adult populations and a one-size-fits-all approach is applied throughout the entire adult population is obviously ignoring fundamental challenges encountered by the older populations. The findings of this thesis highlight the need for the pharmaceutical industry and regulators to engage with this area and consider the factors that affect medicine acceptability for older patients. This is likely to ultimately require the development of novel formulations or multiple formulation types, as well as the provision of information on the safety and efficacy of modified medications.

8.3.2 Medicines optimisation

Whilst it is vital that the issues of medicine acceptability and the development of patient-centric formulations are addressed by the pharmaceutical industry and regulatory agencies, the marketing of new, more suitable formulations will take time. In the interim, the onus is on healthcare professionals and academics to consider what supports they can offer to help optimise medicines for older adults. This thesis has helped signpost some of the key areas for prioritisation of engagement.

The research in this thesis has primarily focused on the aged care or long-term care setting. There have been numerous reports in the literature of interventions that sought to reduce inappropriate tablet crushing in nursing homes and geriatric units of hospitals (261, 304), as well as tablet splitting for fractional dosing in a community setting (259, 260). Various approaches were used including the dissemination of good practice recommendations and a list of medicines that cannot be crushed (261), use of warning symbols in combination with staff education (304) and computerised decision support systems (259, 260). These studies have demonstrated statistically significant reductions in inappropriate modifications (261, 304) and inappropriate tablet splitting (259, 260). However, none of these studies were performed in an Irish setting. Given that this research is the first to evaluate ODF modification practices in Ireland, the potential impact of similar interventions in an Irish setting should be assessed in light of the evidence gained in this thesis. These studies were designed based on the assumption that

inappropriate modifications are being undertaken, either at the prescribing, dispensing or administration level, despite appropriate alternatives existing (259-261, 304). However, based on the results of the thesis, it is our contention that the modifications that are being undertaken in ACFs in Ireland cannot be attributed to aberrant practices by healthcare professionals, but rather arise due to limitations of marketed formulations and re-imbursement policies combined with a substantial variation in the medication needs and requirements of older adults. Therefore, the utility of similar interventions in the Irish setting is questionable. A factor that may contribute to the optimisation of modification practices in the Irish nursing home sector, within the constraints of available licensed formulations, is regulation. The nursing home sector in Ireland is heavily regulated, with HIQA responsible for monitoring, inspecting and registering nursing homes (365). A strict policy on medicine administration, which incorporates guidance on medicine modification, exists and nursing homes must demonstrate adherence to this policy to the satisfaction of the regulators (151). One intervention that may be warranted in an Irish setting would centre on improving knowledge, given that in Chapter 5, nurses reported concerns and uncertainty about modifications. Previous literature has described an intervention to improve healthcare professional knowledge about ODF modifications (262) and a similar intervention in an Irish setting may help to improve nurses' confidence and knowledge around ODF modifications.

Another striking finding, evident throughout this thesis, was the lack of sufficient engagement on the issue of formulation suitability by healthcare professionals,

patients and carers. This issue is not unique to an Irish setting, having been documented extensively in other studies investigating ODF modifications, particularly in the community setting (84, 86, 87). The need for increased engagement and various strategies that could be utilised to facilitate this have been discussed at length throughout the thesis. In Chapter 5, it was found that advocacy by nurses, in acute and long-term care settings, facilitates the optimisation of formulation choice for individual older adults. When combined with the findings of Chapter 7, it appears that the priority area for engagement and intervention, in the Irish context, is the community setting. The National Positive Ageing Strategy (341), which is being implemented under the Healthy Ireland framework (366), seeks to improve the delivery of services and supports for older people so that the challenges associated with population ageing are addressed. The Department of Health has identified that a key goal of this strategy is to support people as they age to maintain, improve or manage their physical and mental health and well-being (341). A central component to the maintenance, improvement and management of health is ensuring that patients receive safe, effective medication. The findings generated in this thesis highlight that the issue of ODF suitability represents one area where further supports are required to help patients and carers maintain, improve and manage their medicine. A key first step will be to increase awareness amongst healthcare professionals of the challenges faced by community-dwelling older adults and their carers around formulation suitability which should help to improve information provision and dosage form selection for these individuals. Whilst the dissemination of this research represents one method of improving awareness, more targeted interventions are likely to be required including:

undergraduate education of healthcare students; provision of continuing professional development resources for qualified healthcare professionals and; public information campaigns. Educational campaigns such as this should encourage a more proactive, rather than reactive, approach to assessing formulation suitability for older adults. Similar campaigns have been run in the area of antibiotic awareness which involved healthcare professional education, as well as media campaigns to increase knowledge amongst the public about the appropriate use of antibiotics (367). Similar interventions may be useful in the area of ODF suitability.

8.4 Strengths and limitations

The individual primary research studies (Chapters 4-7) were designed based on the findings of two comprehensive systematic reviews of the literature. Systematic reviews are viewed as the gold-standard in evidence synthesis and both reviews adhered to best practice recommendations for the conduct and reporting of systematic reviews (213, 216, 248). The findings of these reviews defined the current evidence on ODF modifications and allowed the identification of key gaps in the literature. Subsequently, the research studies undertaken were designed to address the aims and objectives of the thesis overall, whilst ensuring that these key deficits in the literature were addressed.

A key strength of this thesis is the use of a mixed methods approach. In Chapter 1, a brief overview of the strengths and weaknesses of quantitative and qualitative research methods, and the advantages of using a mixed methods approach, was provided. The rationale for using a mixed methods approach to investigate this topic was justified. The findings of the individual quantitative and qualitative components of this thesis are complementary and in many instances, the findings from one study helped explain observations from previous studies and led to the generation of research questions for subsequent studies. It is clear that the use of mixed methods has facilitated the generation of deeper insights than could have been elucidated by either method alone.

This thesis is the first to formally investigate ODF modifications for older adults in an Irish setting. Particularly novel, from an international perspective, was the investigation of ODF modifications to facilitate fractional dosing as well as to facilitate intake. Both of these topics represent ways in which ODFs, as currently formulated, are not meeting the needs of older adults, however, these topics have not been examined in tandem previously. This thesis sought to investigate ODF suitability for older adults by investigating ODF modifications to meet older adults' needs, which represents a novel approach to assessing formulation suitability.

In addition, a major contribution of the thesis was the qualitative investigation of the views of community-dwelling older adults and carers. Research on ODF

modifications for older adults has primarily focused on the long-term care setting. The voice of the community-dwelling cohort has been neglected in the literature up until now and this thesis highlights the imperative for engagement with this cohort.

The quality of the research conducted as part of this doctoral thesis is evidenced in the number of peer-reviewed academic publications and conference presentations achieved. This highlights that this research is: of value; of scientific merit; of interest to academic and healthcare colleagues and; of sufficient quality and rigour. Therefore, dissemination of the important findings of this research is already underway. In addition, the publication strategy targeted a number of different journals with a diverse audience including healthcare professionals and academics (236, 240, 289, 326), industry and regulatory representatives (240), as well as open-access publication to encourage broader dissemination (326). Endeavours will be made to further broadcast the findings of this research to patients, healthcare professionals working in clinical practice, as well as regulatory and industry bodies in order to maximise the impact of this research.

The issue of medication acceptability for the older cohort is gaining increasing traction and recognition amongst healthcare professionals, academics and importantly, regulatory bodies. This research provides crucial and comprehensive data which can serve as the basis for further research. These findings should

provide a stimulus for further engagement in the area of medication suitability for the geriatric cohort.

Whilst there are numerous strengths associated with this research, a number of limitations must also be acknowledged. Firstly, this study was conducted in the Cork region of Ireland. Therefore, the study is limited to one geographical area, which could be seen to limit the generalisability and transferability of study findings. The healthcare structure in Cork is comparable to that throughout the Republic of Ireland and therefore, the study findings would be relevant throughout Ireland. In addition, many of the issues identified would also be of relevance in other jurisdictions given that problems experienced by the geriatric cohort in Ireland are likely to be reflective of issues encountered in many other jurisdictions. Literature reports from other countries have described similar issues with formulations and many of the same formulations are marketed throughout the EU, particularly given the increased utilisation of the centralised procedure for licensing of medicines.

The individual chapters provide greater detail on the potential sources of bias associated with each research study. In addition, methods to minimise the impact of these biases are described. For the quantitative studies, issues related to data collection were encountered. As detailed in Chapter 4, there were limits to the depth of information that could be obtained using retrospective data collection. In Chapter 6, the limitations associated with retrospective data collection were

addressed by undertaking a direct observation of medication administration. This provided more detailed information on the methods of modification and administration of modified medicines and also provided the researcher with a first-hand insight into the challenges associated with drug administration in a nursing home setting. Although it was anticipated that more nursing homes would be included in this study, issues around engagement, time-frame and the requirement for consent, limited the number of nursing homes that could be included in the study. However, the findings proved extremely useful and concurred with many of the findings from the retrospective audit, as well as the findings from the interviews with nurses, thereby adding to the confirmability of study findings.

8.5 Recommendations for future work

This thesis has provided novel insights into ODF modifications in an Irish setting and the factors that influence this practice. As such, it represents an ideal starting point for further research that aims to optimise formulation suitability for older patients. Future research should investigate the following areas:

i) Exploration of the views of doctors and pharmacists around ODF modifications for older adults. This should take the form of qualitative investigations supplemented by a larger, quantitative study to elucidate the views of healthcare professionals nationwide.

ii) Investigation of the availability and use of guidelines and information sources on ODF modifications, particularly amongst pharmacists.

iii) Engagement with representatives of the pharmaceutical industry and regulatory bodies to elucidate their perspectives on medication suitability for older adults. Again, both qualitative and quantitative approaches are likely to be necessary.

iv) There is a need for greater investigation of the factors that affect formulation suitability or medication acceptability from the perspective of older patients and/ or their carers. This should include assessment of ideal formulation characteristics, preferred formulation types, palatability, ease of modification and ease of use.

v) Healthcare professionals should be educated about the need to engage with patients and carers about formulation preferences. In addition, education of healthcare professionals, patients and carers about modifications, particularly inappropriate modifications, is also necessary.

vi) Further research in the community-setting is warranted. This should take the form of a large scale quantitative study to elucidate the prevalence of ODF modification and also patient characteristics and formulation types that are associated with increased likelihood of modification. This would facilitate the targeting of interventions to support those most affected.

vii) Further validation and testing of a screening tool to identify patients and/or carers who are modifying ODFs to facilitate administration is required. The utility of the screening tool from the perspective of healthcare professionals should also be investigated.

8.6 Conclusions

The overall aim of this thesis was to investigate ODF modifications for older adults and to gain an understanding of the factors influencing this practice in an Irish setting. The research presented provides detailed insights into ODF modification and administration practices for older adults in ACFs in Ireland. It was demonstrated that between one-third and one-half of patients in ACFs required medicines to be modified to meet their needs, highlighting the prevalent nature of ODF modifications. Particularly novel were the findings relating to the prevalence of modifications for fractional dosing given that previous research has focused on the suitability of ODFs from a swallowing perspective, with dosing suitability a neglected consideration. The lack of evidence-based information to support clinician decision-making was striking, given that two out of every five modifications were neither licensed nor recommended in BPGs.

Through qualitative investigation, the knowledge, attitudes and beliefs of nurses, community-dwelling older patients and carers about ODF modifications were elucidated and again highlighted that modifications are a routine practice. The research highlights that nurses advocate on behalf of their patients and work closely with members of the MDT to ensure that the needs of the individual are met and medicine administration practices are optimised. In contrast, research found that in the community-setting, patients and carers tend to be very accepting of the medications prescribed and dispensed to them, resulting in lack of engagement around the issue of formulation suitability. However, it was found that

carers helped to bridge this lack of engagement by advocating on behalf of patients, particularly those with advanced needs.

Taking into consideration all of the findings, this thesis demonstrates that ODFs are not meeting the needs of the older cohort and that the dosing requirements and swallowing capabilities of older adults are a neglected consideration in the design and authorisation of ODFs. This thesis substantially contributes to the literature, through the provision of comprehensive, novel data on the reality of ODF use for older adults. The value of this research is that it adds weight to calls for increased engagement with the issue of ODF suitability for older adults, by providing evidence from a “real-world setting” that ODFs are not fit for purpose and are routinely required to be modified.

Significantly, the insights gained from this thesis provide direction for further research, with two key research streams required: greater engagement with patients, particularly in the community, to support them on the issue of formulation suitability and; the development of patient-acceptable ODFs and increased availability of evidence about the suitability and appropriateness of modification and administration practices.

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Appendices

Appendix 1: Search strategy for quantitative systematic review

Database searched: PubMed

Date searched: 11/11/14

Search number	Search terms
#1	Search **((((((((((((pharmaceutical preparations) OR tablets) OR capsules) OR dosage forms) OR administration, oral) OR pharmaceutical solutions) OR tablet*) OR capsule*) OR dosage form*) OR medicine*) OR medication*) OR pill*) OR solution*) OR suspension*) OR syrup***
#2	Search **(((((dysphagia) OR deglutition disorders) OR swallow* difficult*) OR swallow* disorder*) OR swallowing) OR deglutition**
#3	Search **((((((((crush*) OR grind*) OR cut) OR split) OR manipul*) OR modif*) OR dissolv*) OR dispers*) OR thicken*) OR mix**
#4	Search **((#1) AND #2) AND #3**

Search strategy for other databases: As for PubMed using index terms and truncation where appropriate.

Appendix 2: PRISMA checklist for quantitative systematic review

Section/ topic	#	Checklist item	Reported on page number
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	50
Abstract			
Structured Summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	51, 52
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	53 – 55
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	55
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	57 – 59
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	56

Section/ topic	#	Checklist item	Reported on page number
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility).	56, 57
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	60
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions / simplifications made.	58 – 60
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	60
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	61
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	60
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	61, 62

Section/ topic	#	Checklist item	Reported on page number
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	63 – 66
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	67, 68
Results of individual studies	20	For all outcomes considered (benefits or harms), present for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	69 – 72
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies.	67, 68
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression).	69 – 72
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	73 – 78
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	79
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	79, 80
Funding			
Funding	27	Describe sources and role of funding for the systematic review and other support (e.g., supply of data).	80 and Thesis Acknowledgements

Appendix 3: Search strategy for qualitative systematic review

Database searched: PubMed

Date searched: 23/9/2015

Search number	Search terms
#1	Patients [MeSH] OR Physicians [MeSH] OR Nurses [MeSH] OR Pharmacists [MeSH] OR Caregivers [MeSH] OR patient OR doctor OR nurse OR pharmacist OR speech and language therapist OR speech therapist OR carer OR caregiver
#2	"Pharmaceutical Preparations" [MeSH] OR "Tablets" [MeSH] OR "Capsules" [MeSH] OR "Dosage Forms" [MeSH] OR "Administration, Oral" [MeSH] OR tablet* OR capsule*OR medicine OR medication OR "medicine management" OR "medication management" OR "medicine administration" OR "medication administration"
#3	"Deglutition" [MeSH] OR "Deglutition Disorders" [MeSH] OR dysphagia OR swallow OR "swallowing difficulty" OR "fractional dosing" OR manipulation OR modification OR modify OR manipulate OR crush OR grind OR cut OR split OR mix
#4	#2 AND #3
#5	Knowledge OR attitude OR belief OR view OR perception OR experience
#6	"Qualitative Research" [MeSH]OR "Focus Groups" [MeSH] OR "Grounded Theory" [MeSH] OR qualitative OR interview OR "focus group" OR narrative OR "grounded theory" OR theme
#7	#1 AND #4 AND #5 AND #6

Search strategy for other databases: As for PubMed using index terms, free text terms and truncation as appropriate.

Appendix 4: ENTREQ statement for qualitative systematic review

Item	Description	Reported on page number
1. Aim	To synthesise the available qualitative literature on the knowledge, attitudes and beliefs of patients, healthcare professionals and carers about oral dosage form (ODF) modification.	86
2. Synthesis methodology	Thematic synthesis (Thomas and Harden (2008)).	90
3. Approach to searching	Comprehensive, systematic, pre-planned strategy to identify all available studies.	86, 87
4. Inclusion criteria	Inclusion Criteria: Studies using qualitative data collection and analysis methods. Population: Adult patients (≥18 years) who require ODFs to be modified to meet their needs or healthcare professionals or carers providing care to such patients. Topic: Oral dosage form modification. Language: Full-text available in English (no language restriction on initial search). No date restrictions on search. Exclusion Criteria: Quantitative studies, systematic reviews, meta-analyses, meta-syntheses, editorials, commentaries, letters and conference abstracts.	88, 89
5. Data sources	Electronic databases: PubMed, Medline (EBSCO), EMBASE, CINAHL, PsycINFO, Web of Science, ProQuest Databases, Scopus, Turning Research Into Practice (TRIP), Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR). Grey literature: OpenGrey database, internet searching, personal knowledge. Citation tracking of included studies. Reference lists of included studies were searched. Initial search: September 2015. Updated search: June 2016.	86, 87

Item	Description	Reported on page number
6. Electronic search strategy	A combination of index and free text terms related to the following were used: (i) Patients or carers or healthcare professionals AND (ii) Medicine modification AND (iii) Knowledge AND (iv) Qualitative research The search strategy is provided in Appendix 3. The search strategy used was approved by a qualified medical librarian.	86, 87, Appendix 3
7. Study screening methods	Titles were screened by the primary author (AMG) to remove any clearly irrelevant results. Abstracts were screened by 2 reviewers independently (AMG screened all abstracts, AMC and LJS screened half each). Full texts were assessed for inclusion by two independent reviewers (AMG reviewed all full texts, AMC and LJS reviewed half of the full-texts each). In the case of discrepancies between the two authors at any stage, the third reviewer independently examined the study and following discussion, consensus was reached by all three reviewers.	87
8. Study characteristics	Details of the study characteristics are provided in Table 3.1.	93 - 97
9. Study selection results	The study selection process is outlined in Figure 3.1.	91, 92
10. Rationale for appraisal	The appraisal process was undertaken to assess the quality of the included studies. The rigour, credibility and relevance of the studies were assessed. Quality appraisal was not used to guide inclusion or exclusion of studies but rather to moderate the findings of the review based on the quality of the studies contributing to the final analytical themes.	89
11. Appraisal items	The Critical Appraisal Skills Programme (CASP) tool for Qualitative Research was used to appraise the studies.	89
12. Appraisal process	Quality appraisal was undertaken independently by two reviewers (AMG and LJS). In the case of any discrepancies, a third reviewer independently appraised the study quality and following discussion, consensus was reached by all three reviewers. Referral to the third reviewer was not necessary.	89

Item	Description	Reported on page number
13. Appraisal results	Results of quality appraisal are presented in Table 3.2.	98, 99
14. Data extraction	Data from the studies was extracted by one reviewer (AMG) into a modified version of the data extraction form developed by the National Institute for Health and Care Excellence. A second reviewer (AMC) independently verified the extracted data. For the thematic synthesis: any section of the primary study labelled "Results" or "Findings" was considered to be eligible for analysis.	89
15. Software	QSR International's NVivo 10 Qualitative Data Analysis Software	90
16. Number of reviewers	Four authors for the study.	90
17. Coding	Followed the stages of thematic analysis outlined by Thomas and Harden (2008): Stage 1: Free line-by-line coding of the findings of primary studies - independently performed by two reviewers (LJS and AMG); Stage 2: Organisation of the free codes into descriptive themes - undertaken by two reviewers during a group discussion (LJS and AMG), verified by third reviewer (AMC); Stage 3: Development of analytical themes – independently generated by two reviewers (AMG and LJS) and consolidated through group discussion.	90
18. Study comparison	Thematic synthesis was used to synthesise the findings of the primary studies. This approach allowed the advantage of *"staying 'close' to the results of the primary studies, synthesising them in a transparent way, and facilitating the explicit production of new concepts and hypotheses"* (Thomas and Harden 2008). Table 3.1 shows the contribution of each study to the analytical themes.	90, 94 - 97
19. Derivation of themes	Data labelled "Results" or "Findings" in eligible studies were analysed to generate initial free line-by-line codes. The free codes were organised into descriptive themes. Finally, analytical themes were generated based on the descriptive themes.	90
20. Quotations	Quotations are provided throughout the results section of the review to substantiate the findings.	100 - 111
21. Synthesis output	The analytical themes generated provide new interpretations that "go beyond" the results of the primary studies.	100 – 111

Appendix 5: Ethical approval for retrospective audit study

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University College Cork, Ireland

COISTE EITICE UM THAIGHDE CLINICIÚIL
Clinical Research Ethics Committee
Lancaster Hall,
6 Little Hanover Street,
Cork,
Ireland.

Our ref: ECM 4 (b) 04/11/14

16th October 2014

Dr Laura Sahm
Lecturer in Clinical Pharmacy Practice
School of Pharmacy
University College Cork
Cavanagh Pharmacy Building
College Road
Cork

Re: Tailored medicines to optimise medicines administraion to the older patient.

Dear Dr Sahm

Expedited approval is granted to carry out the above study at:

- Marymount University Hospital and Hospice
- Mercy University Hospital.

The following document has been approved:

- Signed Application Form.

We note that the co-investigators involved in this study will be:

- Dr Abina Crean, Dr Catherine Sweeney, Ms Ann Carmicael, Ms Aoife McGillicuddy and Dr Kieran of O'Conner.

Yours sincerely

Professor Michael G Molloy
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospitals

The Clinical Research Ethics Committee of the Cork Teaching Hospitals, UCC, is a recognised Ethics Committee under Regulation 7 of the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004, and is authorised by the Department of Health and Children to carry out the ethical review of clinical trials of investigational medicinal products. The Committee is fully compliant

Ollscoil na hÉireann, Corcaigh - National University of Ireland, Cork

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University College Cork, Ireland

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Clinical Research Ethics Committee

Lancaster Hall,
6 Little Hanover Street,
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Our ref: ECM 3 (ww) 04/11/14

20th October 2014

Dr Laura Sahm
Lecturer in Clinical Pharmacy Practice
School of Pharmacy
University College Cork
Cavanagh Pharmacy Building
College Road
Cork

Re: Tailored medicines to optimise medicines administraion to the older patient.

Dear Dr Sahm

The Chairman approved the following:

- Amendment Application Form
- Addition of Cork University Hospital as a study site
- Addition of Jean Hosford as a co-investigator in the above study.

Yours sincerely

Professor Michael G Molloy
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospitals

The Clinical Research Ethics Committee of the Cork Teaching Hospitals, UCC, is a recognised Ethics Committee under Regulation 7 of the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004, and is authorised by the Department of Health and Children to carry out the ethical review of clinical trials of investigational medicinal products. The Committee is fully compliant with the Regulations as they relate to Ethics Committees and the conditions and principles of Good Clinical Practice.

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Lancaster Hall,
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Our ref: ECM 3 (ggggg) 06/01/15 and ECM 4 (b) 04/11/14

15th December 2014

Dr Laura Sahm
Lecturer in Clinical Pharmacy Practice
School of Pharmacy
University College Cork
Cavanagh Pharmacy Building
College Road
Cork

Re: Tailored medicines to optimise medicines administraion to the older patient.

Dear Dr Sahm

The Chairman approved the following:

- Amendment Application Form dated 17th November 2014
- Data Collection Sheets – Please note the amendment form states that these documents are Version 2 dated November 2014 but there is no version or date on the data collection sheets. Amend and submit copies for our files.

Yours sincerely

Professor Michael G Molloy
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospitals

The Clinical Research Ethics Committee of the Cork Teaching Hospitals, UCC, is a recognised Ethics Committee under Regulation 7 of the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004, and is authorised by the Department of Health and Children to carry out the ethical review of clinical trials of investigational medicinal products. The Committee is fully compliant with the Regulations as they relate to Ethics Committees and the conditions and principles of Good Clinical Practice.

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Clinical Research Ethics Committee
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6 Little Hanover Street,
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Our ref: ECM 3 (tttttt) 14/04/15 and ECM 4 (b) 04/11/14

14th April 2015

Dr Laura Sahm
Lecturer in Clinical Pharmacy Practice
School of Pharmacy
University College Cork
Cavanagh Pharmacy Building
College Road
Cork

Re: Tailored medicines to optimise medicines administraion to the older patient.

Dear Dr Sahm

The Chairman approved the following:

- Amendment Application Form dated 1st April 2015
- Data Collection Sheets Version 3 dated April 2015.

Yours sincerely

Professor Michael G Molloy
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospitals

Appendix 6: STROBE checklist for retrospective audit study

	Item No.	Recommendation	Reported on page number
Title and abstract	1	a)Indicate the study's design in the title or abstract	118
		b) Provide in the abstract an informative balanced account of what was done and what was found	119, 120
Introduction			
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	121 – 123
Objectives	3	State specific objectives	124
Methods			
Study design	4	Present key elements of study design early in the paper	124
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up and data collection	124 – 127
Participants	6	Give the eligibility criteria and sources and methods of selection of participants	125
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders and effect modifiers	125 – 127
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment.	125 – 128
Bias	9	Describe any efforts to address potential sources of bias	128

	Item No.	Recommendation	Reported on page number
Study size	10	Explain how the study size was arrived at	This was an initial investigation. Data from this study will be used to inform a larger study.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	127, 128
Statistical methods	12	a) Describe all statistical methods	127, 128
		b) Describe any methods used to examine subgroups and interactions	127, 128
		c) Explain how missing data were addressed	128
		d) If applicable, describe analytical methods taking account of sampling strategy	N/A
		e) Describe any sensitivity analyses	N/A
Results			
Participants	13	a) Report numbers of individuals at each stage of study e.g. numbers potentially eligible etc.	128
		b) Give reasons for non-participation	N/A
		c) Consider use of a flow diagram	N/A- reported in results section.

	Item No.	Recommendation	Reported on page number
Descriptive data	14	a) Give characteristics of study participants	128, 129
		b) Indicate number of participants with missing data for each variable of interest	128 – 138
Outcome data	15	Report numbers of outcome events or summary measures	128 – 138
Main results	16	a) Give unadjusted estimates and if applicable, confounder adjusted elements	128 – 138
		b) Report category boundaries when continuous variables were categorized	
		c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done	128 – 138
Discussion			
Key results	18	Summarise key results with reference to study objectives	139 – 145
Limitations	19	Discuss limitations of the study	145
Interpretation	20	Give cautious overall interpretation of results	139 – 145
Generalisability	21	Discuss the generalisability of the study results	145
Other information			N/A
Funding	22	Give the source of funding and role of the funders	Thesis acknowledgements

Appendix 7: Ethical approval for qualitative interview studies

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Lancaster Hall,
6 Little Hanover Street,
Cork,
Ireland.

Our ref: ECM 4 (o) 19/01/16

18th January 2016

Dr Laura Sahm
Senior Lecturer in Clinical Pharmacy
School of Pharmacy
Room UG01
Cavanagh Pharmacy Building
School of Pharmacy
University College Cork

Re: The knowledge, attitudes and beliefs of nurses, patients and their carers on the modification of oral medicines for older patients.

Dear Dr Sahm

Expedited approval is granted to carry out the above study at:

- University College Cork, Marymount University Hospital and Hospice, Mercy University Hospital, Cork University Hospital and Designated Centres for Older People in Cork.

The following documents have been approved:

- Signed Application Form
- Data Collection Form for Patients Version 1 dated December 2015
- Data Collection Form for Nurses Version 1 dated December 2015
- Data Collection Form for Carers Version 1 dated December 2015
- Topic Guide for Interviews with Carers Version 1 dated December 2015
- Topic Guide for Interviews with Patients Version 1 dated December 2015
- Topic Guide for Interviews with Nurses Version 1 dated December 2015
- Invitation to Participate Version 1 dated December 2015
- Nurses Information Sheet and Consent Form Version 1 dated December 2015
- Patients/Carers Information Sheet and Consent Form Version 1 dated December 2015
- List of Study Sites.

We note that the co-investigators involved in this study will be:

- Aoife McGillicuddy, PhD Candidate, UCC and Dr Abina Crean, Lecturer in Pharmaceuticals, UCC.

Yours sincerely

Professor Michael G Molloy
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospitals

The Clinical Research Ethics Committee of the Cork Teaching Hospitals, UCC, is a recognised Ethics Committee under Regulation 7 of the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004, and is authorised by the Department of Health and Children to carry out the ethical review of clinical trials of investigational medicinal products. The Committee is fully compliant with the Regulations as they relate to Ethics Committees and the conditions and principles of Good Clinical Practice.

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Clinical Research Ethics Committee

Lancaster Hall,
6 Little Hanover Street,
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Our ref: ECM 4 (o) 19/01/16 & ECM 3 (ggg) 05/07/16

7th July 2016

Dr Laura Sahm
Senior Lecturer in Clinical Pharmacy
School of Pharmacy
Room UG01
Cavanagh Pharmacy Building
School of Pharmacy
University College Cork

Re: The knowledge, attitudes and beliefs of nurses, patients and their carers on the modification of oral medicines for older patients.

Dear Dr Sahm

The Chairman approved the following:

- Cover Letter dated 29th June 2016
- Study Amendment signed 29th June 2016.

Yours sincerely

Professor Michael G Molloy
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospitals

The Clinical Research Ethics Committee of the Cork Teaching Hospitals, UCC, is a recognised Ethics Committee under Regulation 7 of the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004, and is authorised by the Department of Health and Children to carry out the ethical review of clinical trials of investigational medicinal products. The Committee is fully compliant with the Regulations as they relate to Ethics Committees and the conditions and principles of Good Clinical Practice.

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Our ref: ECM 4 (o) 19/01/16 & ECM 3 (yyyyy) 06/06/17

6th June 2017

Dr Laura Sahm
Senior Lecturer in Clinical Pharmacy
School of Pharmacy
Room UG01
Cavanagh Pharmacy Building
School of Pharmacy
University College Cork

Re: The knowledge, attitudes and beliefs of nurses, patients and their carers on the modification of oral medicines for older patients.

Dear Dr Sahm

The Chairman approved the following:

- Cover Letter dated 29th May 2017
- Amendment Application Form signed 29th May 2017
- Addition of Maria Kelly, PhD Student and Carol McCarthy, BPharm as co-investigators in the above study.

Yours sincerely

Professor Michael G Molloy
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospitals

The Clinical Research Ethics Committee of the Cork Teaching Hospitals, UCC, is a recognised Ethics Committee under Regulation 7 of the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004, and is authorised by the Department of Health and Children to carry out the ethical review of clinical trials of investigational medicinal products. The Committee is fully compliant with the Regulations as they relate to Ethics Committees and the conditions and principles of Good Clinical Practice.

Ollscoil na hÉireann, Corcaigh - National University of Ireland, Cork.

Appendix 8: COREQ checklist for qualitative nurse interview study

Topic	Item no.	Description	Reported on page
Domain 1: Research team and reflexivity			
Personal characteristics			
Interviewer	1	AMG (the primary author).	147
Credentials	2	BPharm, MPharm, MPSI, PhD student.	Cover page
Occupation	3	Pharmacist, PhD student.	158
Gender	4	Female.	158
Experience and training	5	Training in qualitative research methods and qualitative interviewing techniques completed in 2015.	155, 158
Relationship with participants			
Relationship established	6	No	155
Participant knowledge of interviewer	7	Participants were aware that the interviews were being completed as part of the interviewer's PhD studies. Participants were informed that the study was being undertaken to investigate the knowledge, attitudes and beliefs of nurses regarding the modification of oral medicines for older patients. The overall goal of the study was presented to participants as being to investigate the suitability of oral medicines for older adults.	156 – 158, 180
Interviewer characteristics	8	This study forms part of AMG's PhD studies which aims to investigate if oral medicines are meeting the needs of older adults. The interviewer is a pharmacist which could potentially introduce bias into the study. In addition, all co-authors are pharmacists. Discussed potential bias introduced by this and chose to use a very inductive approach to try to overcome this possible bias and ensure that primacy is given to the interview participants experiences and not allow researchers assumptions and biases to predominate.	156 – 158

Topic	Item no.	Description	Reported on page
Domain 2: Study design			
Theoretical framework			
Methodological orientation and theory	9	Thematic analysis as per Braun and Clarke.	157
Participant selection			
Sampling	10	Care settings were purposively selected. Participants were conveniently sampled at the purposively selected sites.	153, 154
Method of approach	11	E-mail or telephone contact with medical director or nurse in charge at each site. Nurses were then conveniently sampled from these locations.	154
Sample size	12	Guided by Francis method. Initial analysis sample of 15 and stopping criterion of 3 specified (18 nurses from 16 study sites)	156
Non-participation	13	All sites approached agreed to participate.	N/A
Setting			
Setting of data collection	14	In a private area at the participant's workplace.	155, 156
Presence of non-participants	15	Only the interview participant and interviewer were present.	156
Description of sample	16	Detail provided in Section 5.5.1 and Table 5.2.	159, 160
Data collection			
Interview guide	17	Topic guide developed by authors based on a review of the literature, observations from a prevalence study and authors' practical knowledge of the research area. The topic guide was piloted with an experienced geriatric nurse who provided feedback on the content and language of the guide. In addition, the topic guide underwent iterative revision throughout the study to ensure that any emergent themes were captured in subsequent interviews.	155

Topic	Item no.	Description	Reported on page
Repeat interviews	18	No, repeat interviews were not conducted.	156
Audio/ visual recording	19	Interviews were audio-recorded.	156
Field notes	20	Relevant notes made by interviewer.	156
Duration	21	Mean interview duration (SD): 16 minutes 29 seconds (6 minutes 21 seconds) Range: 7 minutes 19 seconds to 31 minutes 41 seconds.	159
Data saturation	22	Guided by Francis method: initial analysis sample of 15 and stopping criteria of 3. Sampling continued until data saturation.	156
Transcripts returned	23	No, transcripts were not returned to participants.	156
Domain 3: analysis and findings			
Data analysis			
Number of data coders	24	Outlined in the text. AMG coded all transcripts, MK independently coded 3 transcripts, all co-authors read 6 transcripts and confirmed that themes were reflective of interview content.	157, 158
Description of the coding tree	25	N/A	N/A
Derivation of themes	26	Themes were derived using thematic analysis, as described by Braun and Clarke. An inductive approach to coding was used.	157, 158
Software	27	QSR International's NVivo 10 Qualitative Data Analysis Software.	157
Participant checking	28	This was not conducted.	157
Reporting			
Quotations presented	29	Supporting quotations are present throughout the results sections.	161 – 174
Data and findings consistent	30	Yes. All co-authors confirmed that the findings were consistent with the interview transcripts and illustrative quotes are presented to substantiate findings.	161 – 174

Topic	Item no.	Description	Reported on page
Clarity of major themes	31	Major themes are clearly discussed, with relevant supporting quotes, in the results section. Any variations in knowledge, attitudes and beliefs are also presented.	161 – 171
Clarity of minor themes	32	Two minor themes emerged and are clearly discussed in the results section.	171 – 174

Appendix 9: Ethical approval for direct observation of medication administration study

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Clinical Research Ethics Committee

Lancaster Hall,
6 Little Hanover Street,
Cork,
Ireland.

Our ref: ECM 4 (z) 10/05/16

11th May 2016

Dr Laura Sahm
Senior Lecturer in Clinical Pharmacy
Room UG01
Cavanagh Pharmacy Building
University College Cork
College Road
Cork

Re: Medicine administration to older adults: a direct observation study.

Dear Dr Sahm

Expedited approval is granted to carry out the above study at:

- University College Cork, Mercy University Hospital, Cork University Hospital, St Finbarr's Hospital and 70 designated centres for older people in Cork registered with HIQA.

The following documents have been approved:

- Cover Letter dated 14th April 2016
- Application Form signed 19th April 2016
- Insurance Details
- Study Protocol Version 1 dated April 2016
- Information Sheet and Consent Form for Nurses Version 1 dated 14th April 2016
- Information Sheet and Consent Form for Patient's Representative Version 1 dated 14th April 2016
- Information Sheet and Consent Form for Patients Version 1 dated 14th April 2016
- Invitation to Participate Version 1 dated 14th April 2016
- Invitation to Participate for Nurses Version 1 dated 14th April 2016
- Invitation to Participate for Patient's Representative Version 1 dated 14th April 2016
- Invitation to Participate for Patients Version 1 dated 14th April 2016
- Patient Details Data Collection Form Version 1 dated 14th April 2016
- Ward Round Observation Data Collection Sheet Version 1 dated 14th April 2016
- Anonymisation Sheet for Study Sites Version 1 dated 14th April 2016
- Anonymisation Sheet for Patients Version 1 dated 14th April 2016
- Study Site List.

We note that the co-investigators involved in this project will be:

- Aoife McGillicuddy, PhD Candidate and Dr Abina M. Crean, Lecturer.

Yours sincerely

Professor Michael G Molloy
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospitals

UCC

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Coláiste na hOllscoile Corcaigh, Éire
University College Cork, Ireland

COISTE EITICE UM THAIGHDE CLINICIÚIL
Clinical Research Ethics Committee

Lancaster Hall,
6 Little Hanover Street,
Cork,
Ireland.

Our ref: ECM 4 (z) 10/05/16 & ECM 3 (vvvvv) 10/01/17

9th January 2017

Dr Laura Sahm
Senior Lecturer in Clinical Pharmacy
Room UG01
Cavanagh Pharmacy Building
University College Cork
College Road
Cork

Re: Medicine administration to older adults: a direct observation study.

Dear Dr Sahm

The Chairman approved the following:

- Cover letter dated 20 December 2016
- Amendment application form signed (no date)
- Ward Round Observation Data Collection Sheet version 2 dated 20 December 2016
- Invitation to participate version 2 dated 20 December 2016.

Full approval is granted to implement this amendment.

Yours sincerely

Professor Michael G Molloy
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospitals

The Clinical Research Ethics Committee of the Cork Teaching Hospitals, UCC, is a recognised Ethics Committee under Regulation 7 of the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004, and is authorised by the Department of Health and Children to carry out the ethical review of clinical trials of investigational medicinal products. The Committee is fully compliant with the Regulations as they relate to Ethics Committees and the conditions and principles of Good Clinical Practice.

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Clinical Research Ethics Committee
Lancaster Hall,
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Our ref: ECM 4 (z) 10/05/16 & ECM 3 (ccc) 07/03/17

21st February 2017

Dr Laura Sahm
Senior Lecturer in Clinical Pharmacy
Room UG01
Cavanagh Pharmacy Building
University College Cork
College Road
Cork

Re: Medicine administration to older adults: a direct observation study.

Dear Dr Sahm

The Chairman approved the following:

- Cover letter dated 6th February 2017
- Amendment Application Form signed 6th February 2017
- Study Protocol Version 2 dated 6th February 2017
- Information Letter for Doctors Version 1 dated 6th February 2017
- Information Sheet and Consent Form for Patient's Representative Version 2 dated 6th February 2017.

Yours sincerely

Professor Michael G Molloy
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospitals

The Clinical Research Ethics Committee of the Cork Teaching Hospitals, UCC, is a recognised Ethics Committee under Regulation 7 of the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004, and is authorised by the Department of Health and Children to carry out the ethical review of clinical trials of investigational medicinal products. The Committee is fully compliant with the Regulations as they relate to Ethics Committees and the conditions and principles of Good Clinical Practice.

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Clinical Research Ethics Committee
Lancaster Hall,
6 Little Hanover Street,
Cork,
Ireland.

Our ref: ECM 4 (z) 10/05/16 & ECM 3 (xxxx) 06/06/17

6th June 2017

Dr Laura Sahm
Senior Lecturer in Clinical Pharmacy
Room UG01
Cavanagh Pharmacy Building
University College Cork
College Road
Cork

Re: Medicine administration to older adults: a direct observation study.

Dear Dr Sahm

The Chairman approved the following:

- Cover letter dated 29th May 2017
- Amendment Application Form signed 29th May 2017
- Addition of Maria Kelly, PhD Student and Carol McCarthy, Bpharm as co-investigators in the above study.

Yours sincerely

Professor Michael G Molloy
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospitals

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Our ref: ECM 4 (z) 10/05/16 & ECM 3 (mmmm) 07/03/18

14th February 2018

Dr Laura Sahm
Senior Lecturer in Clinical Pharmacy
Room UG01
Cavanagh Pharmacy Building
University College Cork
College Road
Cork

Re: Medicine administration to older adults: a direct observation study.

Dear Dr Sahm

The Chairman approved the following:

- Cover letter dated 23rd January 2018 (received 1st February 2018)
- Amendment Application Form signed 23rd January 2018
- Data collection extension.

Yours sincerely

Professor Michael G Molloy
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospitals

The Clinical Research Ethics Committee of the Cork Teaching Hospitals, UCC, is a recognised Ethics Committee under Regulation 7 of the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004, and is authorised by the Department of Health and Children to carry out the ethical review of clinical trials of investigational medicinal products. The Committee is fully compliant with the Regulations as they relate to Ethics Committees and the conditions and principles of Good Clinical Practice.

Appendix 10: STROBE checklist for direct observation of medication administration study

	Item No.	Recommendation	Reported on page number
Title and abstract	1	a)Indicate the study's design in the title or abstract	183
		b) Provide in the abstract an informative balanced account of what was done and what was found	184 – 186
Introduction			
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	187, 188
Objectives	3	State specific objectives	188, 189
Methods			
Study design	4	Present key elements of study design early in the paper	190
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up and data collection	190 – 193
Participants	6	Give the eligibility criteria and sources and methods of selection of participants	190 – 192
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders and effect modifiers	192, 193
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment.	192, 193

	Item No.	Recommendation	Reported on page number
Bias	9	Describe any efforts to address potential sources of bias	192 – 194
Study size	10	Explain how the study size was arrived at	194, 195
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	194
Statistical methods	12	a) Describe all statistical methods	194
		b) Describe any methods used to examine subgroups and interactions	194
		c) Explain how missing data were addressed	193, 194
		d) If applicable, describe analytical methods taking account of sampling strategy	N/A
		e) Describe any sensitivity analyses	N/A
Results			
Participants	13	a) Report numbers of individuals at each stage of study e.g. numbers potentially eligible etc.	195, 196
		b) Give reasons for non-participation	195, 196
		c) Consider use of a flow diagram	196
Descriptive data	14	a) Give characteristics of study participants	196 – 199
		b) Indicate number of participants with missing data for each variable of interest	197, 198

	Item No.	Recommendation	Reported on page number
Outcome data	15	Report numbers of outcome events or summary measures	199 – 208
Main results	16	a) Give unadjusted estimates and if applicable, confounder adjusted elements	199 – 208
		b) Report category boundaries when continuous variables were categorized	
		c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done	199 – 208
Discussion			
Key results	18	Summarise key results with reference to study objectives	208 – 217
Limitations	19	Discuss limitations of the study	218 – 221
Interpretation	20	Give cautious overall interpretation of results	221
Generalisability	21	Discuss the generalisability of the study results	218
Other information			N/A
Funding	22	Give the source of funding and role of the funders	Thesis acknowledgements

Appendix 11: COREQ checklist for qualitative patient and carer interview study

Topic	Item no.	Description	Reported on page
Domain 1: Research team and reflexivity			
Personal characteristics			
Interviewer	1	AMG (the primary author).	223
Credentials	2	BPharm, MPharm, MPSI, PhD student.	Cover page
Occupation	3	Pharmacist, PhD student.	238
Gender	4	Female.	238
Experience and training	5	Training in qualitative research methods and qualitative interviewing techniques completed in 2015.	234, 238
Relationship with participants			
Relationship established	6	No	234
Participant knowledge of interviewer	7	Participants were aware that the interviewer was a pharmacist and researcher working in the School of Pharmacy at the local University. Participants were informed that the research team were interested in understanding the views and experiences of patients and carers about medicines administration and modification.	234, 235
Interviewer characteristics	8	This study forms part of AMG's PhD studies which aims to investigate if oral medicines are meeting the needs of older adults. The interviewer is a pharmacist which could potentially introduce bias into the study. In addition, all co-authors are pharmacists. Discussed potential bias introduced by this and chose to use a very inductive approach to try to overcome this possible bias and ensure that primacy is given to the interview participants experiences and not allow researchers assumptions and biases to predominate.	238

Topic	Item no.	Description	Reported on page
Domain 2: Study design			
Theoretical framework			
Methodological orientation and theory	9	Thematic analysis as per Braun and Clarke.	235 – 237
Participant selection			
Sampling	10	Participants were recruited through community pharmacies. The community pharmacies were purposively sampled to include pharmacies located in socioeconomically "advantaged" and "less advantaged" areas, in both rural and urban settings. Individual participants were recruited using a combination of: convenience sampling at the participating pharmacies; purposive identification by pharmacists and; snowball sampling.	231 – 233
Method of approach	11	A member of the research team contacted pharmacists at the identified pharmacies and provided them with an information sheet about the study. Following agreement to participate, a member of the research team approached potential participants in the participating pharmacies (convenience sampling). A member of the research team or the pharmacist approached purposively identified participants. Participants were also asked to suggest any other potential participants.	231 – 233
Sample size	12	Guided by Francis method. Initial analysis sample of 10 and stopping criterion of 3 for both the patient and carer cohorts.13 patients and 13 carers participated.	237
Non-participation	13	All sites approached agreed to participate.	239 – 241

Topic	Item no.	Description	Reported on page
Setting			
Setting of data collection	14	In the private consultation room at participating pharmacies, in the interviewee's home or the interviewer's home, depending on the participant's preference.	235
Presence of non-participants	15	Three of the patients requested the presence of a family member during the interviews, however only the patient contributed to the interview.	240
Description of sample	16	Detail provided in Section 7.5.2.	239, 240
Data collection			
Interview guide	17	Two topic guides were developed; one for interviews with patients and one for interviews with carers. Topic guides were devised based on the findings of the qualitative systematic review, taking the aims of the study into consideration. General content was the same, but language was tailored to address the varied roles and perspectives of each cohort. Topic guides underwent iterative refinement during the study.	233, 234
Repeat interviews	18	No, repeat interviews were not conducted.	235
Audio/ visual recording	19	Interviews were audio-recorded.	235
Field notes	20	Field notes were written by the interviewer after the interview.	235
Duration	21	Total cohort: median interview duration 11 minutes 17 seconds (IQR 8 minutes 3 seconds to 16 minutes 23 seconds).	240
Data saturation	22	Guided by Francis method. Initial analysis sample of 10 and stopping criterion of 3 for both the patient and carer cohorts.13 patients and 13 carers participated. Recruitment continued until data saturation was achieved.	237

Topic	Item no.	Description	Reported on page
Transcripts returned	23	No, transcripts were not returned to participants.	235
Domain 3: analysis and findings			
Data analysis			
Number of data coders	24	Outlined in the Section 7.4.5 and in Table 7.3.	235 – 236
Description of the coding tree	25	N/A	N/A
Derivation of themes	26	Themes were derived using thematic analysis, as described by Braun and Clarke. An inductive approach to coding was used.	235, 236
Software	27	QSR International's NVivo 11 Qualitative Data Analysis Software.	235
Participant checking	28	This was not conducted.	N/A
Reporting			
Quotations presented	29	Supporting quotations are present throughout the results sections.	242 – 255
Data and findings consistent	30	Yes. All co-authors confirmed that the findings were consistent with the interview transcripts and illustrative quotes are presented to substantiate findings.	237, 242 – 255
Clarity of major themes	31	Themes are clearly discussed, with relevant supporting quotes, in the results section. Any variations in knowledge, attitudes and beliefs are also presented.	242 – 255
Clarity of minor themes	32	No minor themes presented.	N/A