Patient Centric Medicine Design- An Investigation into Understanding and Enhancing Older People's Adherence to and Acceptance of Oral Solid Dosage Forms

Doctor of Philosophy

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Thesis Summary

Background: Older people are increasingly taking a greater number of medications. Optimising the use of these medicines is important to ensure that patients are taking their medication as intended. Patient centric medicine design can help ensure that the needs of the target population are identified and addressed during the manufacture of pharmaceuticals.

Aim: To investigate the characteristics of oral solid dosage forms that contribute to age appropriate, patient centric medicines that help to improve medication adherence and acceptance in older people.

Methods, results and key findings: Firstly, a systematic review investigating if and how the formulation of oral solid dosage forms affects adherence and acceptance in older people was conducted. Characteristics were categorised into three inter-related topic areas: dimensions, palatability and appearance. A major finding of this review was the limited number of studies published; in particular, a lack of qualitative studies. This was addressed in the second stage of this project. Fifty-two semi-structured interviews were conducted with older people, informal (family) carers, and health and social care professionals. Formulation characteristics were found to impact three key stages of the medication taking process: medication identification and memorability, medication handling, and swallowability. Health and social care professionals were found to have a key role in ensuring patient centric medicines are provided; however, this role is dependent on several key barriers and facilitators. The final stage used results from the semi structured interviews to create oval, shield and biconcave disc shaped models using 3D printing.

Conclusions: The development of patient centric medicines for the older population requires a holistic, patient-centric approach. Manufacturers should consider the dimensions, palatability and appearance alongside the medication taking process. In all cases, patient centric medicines must then be prescribed, dispensed and administered appropriately so that patients receive the most suitable formulation.

Key words: Acceptance, Adherence, Older People, Oral Solid, Patient Centric

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Z. Shariff, D. Kirby, C. Miller, S. Missaghi, A. Rajabi-Siahboomi and I. Maidment. *Characteristics of oral solid dosage forms that contribute towards the safe and effective use of medication in older people.* Poster Presentation. APS International PharmSci Conference, September 2019 (Greenwich)

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Z. Shariff, D. Kirby, C. Miller, S. Missaghi, A. Rajabi-Siahboomi and I. Maidment. *Patient Centric Medicine Design to Improve Adherence in Older People.* Poster Presentation. HSRPP, April 2019 (Birmingham)

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Z. Shariff, D. Dahmash, D. Kirby, C. Miller, S. Missaghi, A. Rajabi-Siahboomi and I. Maidment. How does the formulation of oral solid dosage forms affect adherence and acceptance in older people? A Systematic Review. Poster Presentation. APS@FIP Conference, September 2018 (Glasgow)

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Table of Contents

List of Tables

List of Figures

List of Abbreviations

ABS	Acrylonitrile Butadiene Styrene
BASE	Bielefeld Academic Search Engine
CAD	Computer Aided Design
CAT	Critical Appraisal Tool
CCG's	Clinical Commissioning Groups
CHMP	Committee for Medicinal Products for Human use
CNS	Central Nervous System
DLP	Digital Light Processing
EMA	European Medicines Agency
ENRICH	Enabling Research in Care Homes
ETHOS	Ethesis Online Service
FDA	Food and Drugs Administration
FDM	Fused Deposition Modelling
GDPR	General Data Protection Regulation
HRA	Health Research Authority
ICH	International Conference on Harmonisation
MAR	Medication Administration Record
MMAT	Mixed Methods Appraisal Tool
NICE	National Institute for Health and Care Excellence
PICOC framework	Population, Intervention, Comparison, Outcome(s), Context
PIPS	Paediatric Investigation Plans
PPI	Patient and Public Involvement
PRAC	Pharmacovigilance Risk Assessment Committee
PROSPERO	International Prospective Register of Systematic Reviews
QbD	Quality by Design
QTPP	Quality Target Product Profile
QWP	Quality Working Party
REC	Research Ethics Committee
RMBI	Royal Masonic Benevolent Institution
SLA	Stereolithography

Chapter 1- Introduction

1.1. Introduction

The overall aim of this PhD was to investigate the characteristics of oral solid dosage forms that contribute to age appropriate, patient centric medicines that help to improve medication adherence and acceptance in older people. This introductory Chapter will start by exploring the needs of the older population and defining patient centric medicine design. The Chapter will go on to explore current regulations in this area and will discuss the importance of adherence and acceptance as outcome measures. The Chapter finishes by providing a brief description of the overall aims and objectives and the layout of this Thesis.

1.2. The older population

Older people are set to account for a third of the global population by 2050 [1]. While an older person can be chronologically defined as someone over the age of 65, the complexities associated with ageing suggest that this is an inadequate definition of an older patient [2]. Rather, older people or patients should be classified according to their specific needs due to differences in impairments that affect them [3]. Older people represent a very heterogeneous patient population and are a major user group of prescribed medicines [4]. This patient group are also increasingly taking a greater number of medications; the number of people taking five or more medications has increased from 12 to 49% over the last two decades [5]. These medicinal products play an important role in helping older people remain independent and improving their quality of life [6].

Medication optimisation ensures that patients are taking medication as directed to manage long term conditions effectively. Medication optimisation has been defined as “a person-centred approach to safe and effective medicines use to ensure people obtain the best possible outcomes from their medicines” [7]. Optimising the formulation of the drug product (for example, the tablet size, shape, colour and embossing [3]) can be seen as a key part of medication optimisation. However, medication optimisation is much more complex in older people [6]. The following section highlights some of the key areas that need to be reflected during the development, approval and use of medications for this population.

1.2.1. Polypharmacy

Polypharmacy amongst older people is an important concern and has been associated with increased adverse drug reactions, hospitalisation and mortality [8]. Studies have found that patients with polypharmacy have reported poorer health, psychological troubles, more memory problems and have a higher risk of multiple falls [8]. The consequences of polypharmacy may further be enhanced due to the reduced drug clearance associated with ageing [9]. There can, however, be clinical indications for

polypharmacy such as in hypertension or diabetes [10]. There is therefore a growing interest in "appropriate polypharmacy" [11], where healthcare professionals are tasked with ensuring that medication use is optimised according to the individual patient's clinical needs [12]. Ensuring that an appropriate formulation is selected is an important part of this; studies have found, for example, differences in preferences for colour amongst patients taking more than 10 tablets per day [13]. Optimising formulation may therefore help to improve the patient's experience of taking a large number of tablets, improving overall adherence and acceptance.

1.2.2. The role of family carers

Managing medication is one of the many domains of care provided by informal carers [14]. This is an important role; good medication management by informal carers can contribute to improved health outcomes [15]. Their role often includes ordering and collecting medication, setting them up, administering medication and attending appointments with healthcare professionals [16]. This caring role can, however, have an adverse impact on the carer's employment, finances, relationships and their own health [17]. Decisions on medication management are often made in isolation and a lack of knowledge, training and support all increase the stress associated with this role [16].

Interventions to enhance medication optimisation must therefore consider the needs of carers so that they can be supported to manage medications in a safe and effective manner [18]. This includes interventions to optimise the formulation; the ability and willingness of a carer to administer medication could determine the outcome of the treatment [19] therefore formulations should be as easy as possible to administer.

1.2.3. Changes in cognition

A gradual decline in cognitive function over time is a physiological change that is associated with the normal ageing process [20]. Other modifiable risk factors for cognitive decline include the increased use of anticholinergic medications [21], the central effects of which include delirium and cognitive impairment [22]. Benzodiazepines and Z-drug hypnotics (usually prescribed for insomnia and anxiety) have also been associated with cognitive impairment [23]. Reduced or gradually impaired cognition can result in difficulties remembering when and how to take a medicine, swallowing oral preparations and understanding instructions [3].

It is also increasingly important to consider age related conditions such as dementia, the prevalence of which are increasing with the ageing population [24]. The voices of people with dementia are often missing from the literature, making it more difficult to gain an in-depth understanding of coping strategies for medication management within this population [24]. Declining cognitive function makes

understanding and retaining knowledge in regards to medication regimes difficult and responsibility is often passed to informal carers who can find this role challenging. The formulation of the medication in particular can pose a challenge for carers managing medication for people with dementia; studies have reported informal carers having to mask the taste of some preparations with liquorice or crushing tablets which was sometimes a concern for enteric coated preparations [25].

1.2.4. Changes in motor function

Changes in motor function can lead to dysphagia [3]; the prevalence of dysphagia in patients over 65 ranges from 7-13% and this number increases with age [1]. The natural process of ageing is associated with structural, motoric and sensory changes [26] which lead to a decline in swallowing function in all three phases of the swallowing process [27]. Certain diseases may also predispose older people towards developing dysphagia; neurological disorders such as Parkinson's, Alzheimer's and stroke are all associated with an increased prevalence of dysphagia [26]. Changes in motor function can also lead to reduced hand eye co-ordination, trembling hands and impaired manual dexterity [3].

All of these changes can lead to difficulties administering and taking medication. Swallowing difficulties, for example, can result in a need to modify oral dosage forms and this is most commonly due to a lack of appropriate, licensed dosage forms [28]. Modifications may include splitting/crushing tablets, opening capsules or mixing medications with food. Altering medication dosage forms can change the bioavailability, toxicity and stability of medicines [19]; faster absorption and a higher bioavailability that arise as a result of modifications can be especially dangerous for narrow therapeutic index drugs, where small changes in systemic concentrations can lead to toxic effects [1]. These changes in motor function can often be addressed by the use of more appropriate formulations; for example, the shape, density and surface characteristics can all affect swallowability of tablets and capsules [19].

1.2.5. Changes in sensory function

Impairments in sensory functions, including impaired overall vision, can also affect medication administration in this population. The causes of impaired vision in older people vary and can be due to glaucoma, diabetes, macular degeneration, hypertensive retinopathy, or retinal detachment [29]. Impaired vision can lead to difficulty reading medication information and patients taking the wrong/incorrect dose of medication [30]. Patients with visual impairment therefore report increased anxiety in relation to medication management and must often rely on others to provide necessary medication information [30]. As well as changes in vision, impairments in sensory function can also include a change in the sense of taste and smell both of which deteriorate as part of the ageing process

[31]. Taste and smell appear to play an important role in swallowing; sensory input is essential to initiate and regulate swallowing [32].

Formulating tablets so that they are easily differentiated can aid identification of different drug products and this can be achieved through the use of colour or imprints [33]. Previous studies have found that patients with Alzheimer's Disease gain substantial help from colour cues and that colour should be taken into account within the healthcare environment [34]. Colour can also be associated with certain tastes and flavours; for example, pink tends to be associated with sweet flavours while yellow is often associated with a salty taste [35]. This may help address some of the issues associated with impairments in sensory functions but requires further exploration within the older population.

Due to the range of challenges associated with drug therapy for older people, formulation scientists must work closely with both patients and carers in order to develop patient centric medicines that improve patient adherence and acceptance [36].

1.3. Patient Centric Medicine Design

1.3.1. Defining Patient Centric Medicine Design

When considering patient centric medicine design, it is helpful to first define the concept of patient centric care. The term "patient centric care" is increasingly being used within clinical settings and involves considering patients' individual preferences, beliefs and values when selecting therapeutic options [37]. In contrast to simply "involving" or "engaging" the patient, the use of the word "centricity" highlights the importance of placing the patient at the centre, taking into account factors such as the patient's preferences to help them navigate the decision making process [38]. Choosing the most appropriate treatment option is an important part of this process, allowing patients to choose therapies that are most likely to meet their individual needs and therefore increasing the efficacy of prescribed treatments [39].

Patient centric medicine design has been defined as: "the process of identifying the comprehensive needs of the target patient population and utilising the identified needs to design pharmaceutical drug products that provide the best overall benefit to risk profile for that target patient population over the intended duration of treatment" [40]. Through predicting the behavioural and psychological characteristics of a target population, potential sources of medication error can be identified and reduced [40]. For example, patients with dexterity issues such as arthritis may have trouble with child resistant packaging, or those with low health literacy may experience difficulties understanding the product label [41,42].

Developing these patient centric medicines requires a deep understanding of the real-world experiences, priorities and needs of the target population [43]. Conducting clinical trials is a key part of drug development, and there is the potential to ensure these are more patient centric in their overall approach so that patients are empowered from the outset [44]. Involving patients, for example, when designing the study protocol, can help ensure that studies are more sensitive to the patient's needs and comfort [44].

However, older people have been routinely under-represented in clinical trials [45] and this disadvantages patients while also leading to difficulties for physicians when making clinical decisions [46]. Exclusion of older people with frailty and multimorbidity results in them being denied potentially beneficial treatments and increases their exposure to harm due to evidence being extrapolated from younger, more physiologically resilient populations [47]. While clinical trials in older people can present complex challenges, particularly in relation to recruitment and retention [45], more pragmatic inclusion and exclusion criteria can help to improve the inclusion of under-served groups, leading to more inclusive research [47]. All those involved therefore have an obligation and an opportunity to address age discrimination including sponsors, researchers, clinicians, government agencies and ethics committees [46].

In particular, to develop patient centric medicines, it is important for all stakeholders to collect and submit patient experience data when developing medical products, establishing what is important to patients in regards to the burden of disease and the burden of treatment [48]. Gaining a deeper understanding of the patient's experiences, priorities and needs is key for disease management and for improving the lives of patients [49]. Once these needs are understood, all stakeholders including regulators, industry, patients and family carers, and health and social care professionals can work together to ensure patients receive the best therapeutic outcome from their medication [43]. However, while guidance has been introduced that intends to bring patient perspectives into an earlier stage of drug development [48], these recommendations were only recently made in 2020 and the extent to which they are followed remains to be seen.

Considering patient experiences, priorities and needs results in patient centric medicines that are a key tool towards ensuring healthy ageing and improving the patients' quality of life [40]. Approximately 50% of patients do not take their medicines as prescribed [50] and the reasons for this, particularly within the older population, are complex. Non-adherence can be intentional, where a patient consciously chooses not to follow a recommended measure, or unintentional, where patients fail to follow recommendations without making a conscious decision to do so [51]. As discussed in Section 1.2., there are a number of factors to consider when optimising medications for this

population. New and innovative products may help address some of these factors. Examples of these alongside some of the further considerations in relation to the use of these innovations have been provided in Table 1.1.

Table 1.1 Examples of innovations and further considerations for their use in older people

Area for consideration	Examples of innovations leading to a more patient centric product	Further considerations
Polypharmacy	3D printing has been used to create a multi-compartment poly-pill containing five active ingredients- an immediate release compartment with aspirin and hydrochlorothiazide and three sustained release compartments containing pravastatin, atenolol, and Ramipril [52].	How acceptable is this innovation amongst older people? Would the larger size of the polypill cause swallowing difficulties?
Role of family carers	Rather than traditional tablets for the treatment of Alzheimer's disease, carers reported a higher level of satisfaction with an orally disintegrating formulation of donepezil which is easier for the patient to swallow [53].	Orally disintegrating tablets require further consideration of palatability to ensure optimum acceptance. A balance is needed between preferences of the carer and those of the patient.
Changes in cognition	MyCite® combines an existing drug with an ingestible sensor that can track ingestion allowing healthcare professionals to track adherence [54], which is especially helpful for patients suffering from impaired cognition	How accepting would older people or their carers be of ingesting a tracking device? Would this be deemed as an invasion of privacy?
Changes in motor function	MyFID (My Flexible Individual Dosing), is an electronic dose dispenser for patients with Parkinson's disease. The dispenser is loaded with micro tablets and the patient is reminded of a dose with an alarm [55]. Tablets are fast dissolving and can be automatically dispensed into water.	Acceptability testing found some patients pushed the button to start the device for too long, or more than once due to tremor. Entering the dose on the device was also difficult for some patients [56]. Responsibility may sometimes be passed to informal carers- their acceptability of the device requires consideration
Changes in sensory function	A novel, easy to swallow jelly formulation of donepezil has been formulated that patients are able to swallow as a "dessert." There was an emphasis placed on ensuring an acceptable taste of this formulation [57]	The process of developing this formulation was difficult and required many trade-off decisions to be made for a product that was

	truly patient centric; for example, the use of a more expensive, single dose container.

As can be seen from Table 1.1, there are an increasing number of new and innovative products available; however, each is associated with their own unique set of challenges. Involving the patient from the outset during the design of these innovations will help ensure the final product is truly patient centric. MyFid, for example, was developed in co-operation with an advisory board of people with Parkinson's disease, and prototypes were evaluated by patients in different stages of the condition [56]. Feedback, such as the prototype being too large and heavy, was taken forward to design a new prototype that was better accepted [56]. A shift in the pharmaceutical industry to ensure that more dosage forms are designed in this way is key to ensure optimum patient adherence and acceptance of medication.

3D printing is an example of a promising new technology that provides the flexibility to adjust the dosage, release profile and physical appearance (e.g. size, shape, colour) of a drug delivery system to an individual patient's needs [58]. Manufacturing small batches of medications each with tailored characteristics may finally lead to the concept of patient centric medicines becoming a reality [59]; however, these must be made in partnership with patients and their carers. This is therefore an important, revolutionary technology and its potential application in the development of patient centric medicines requires further exploration.

While there has been a growth in pharmaceutical formulation technologies, the majority of drug products available remain as oral solid dosage forms; 65-70% of drug therapies available on the market are oral solid dosage forms [26]. The development of oral solid dosage forms is well established within the pharmaceutical industry and their cheaper price as well as the potential for technological applications (e.g. taste masking) means that they are often the formulation of choice [60]. Oral solid dosage forms can be formulated to optimise their shape, size, colour and overall finishing to improve adherence and acceptance. These factors must all be considered early on in the Quality Target Product Profile (QTPP) in order to ensure the final product meets the desired characteristics.

1.3.2. Patient centricity and the Quality Target Product Profile (QTPP)

The QTPP is an essential element of the Quality by Design (QbD) approach that was introduced by the Food and Drugs Administration (FDA) to ensure that quality is built into the pharmaceutical product

[61]. This approach starts by defining the QTPP, a prospective summary of characteristics that will ideally be achieved to ensure the desired quality, taking into account factors such as drug safety and efficacy [62]. The process of defining this profile provides an ideal opportunity to consider the needs of the target population and may include a discussion with clinicians, regulatory specialists and patient advocacy groups [63]. Factors considered during this stage include the likelihood of caregiver involvement to aid administration, the consequences of non-adherence and the potential for dosage form modification, e.g. crushing [63]. Table 1.2 below states some of the areas that are focused on when defining the QTPP, and provides examples on how these areas can be adapted to incorporate patient centricity.

Table 1.2 Areas for consideration when defining the QTPP and how to incorporate patient centricity [63, 90]

Area	Incorporation of patient centricity
Intended use in clinical setting	Consideration of whether the patient will self-dose at home, whether a carer will administer the medication, or whether it will be used within other settings such as a care home or hospital
Route of administration, e.g. oral, parenteral	Patient specific requirements such as dysphagia may impact the route of administration
Dosing regimen	Complex dosing regimens can be difficult for certain populations, e.g. people with dementia
Dosage form	The size, shape, and colour of the dosage form can be evaluated by considering the end user, e.g. ease of swallowing and handling
Dosage strength	The dosage strength is often defined by the clinical need; however, this should also be considered alongside the dosage form, for example two smaller dosage forms may be preferred to a single, larger formulation
Container closure system	This must meet the legal requirements for child proofing; however, consideration should also be given to patients who find child resistant packaging difficult to open
Attributes affecting pharmacokinetic characteristics and drug release or delivery	Renal and hepatic decline and changes within the GI tract can lead to altered drug pharmacokinetics, e.g. reduced absorption. This may lead to the need for dose adjustment

As can be seen from Table 1.2, there are multiple opportunities for the pharmaceutical industry to create patient centric drug products when developing the QTPP. One of the key aspects that can be optimised is the dosage form; oral solid dosage forms can be formulated to optimise their shape, size, colour and overall finishing. The importance of optimising formulation when considering medication optimisation has been discussed in Section 1.2, however this area requires further exploration

especially within the older population. The need to optimise the dosage form has been the focus of guidelines and reflection papers that discuss the development, approval and use of medications for older people [64].

1.4. Current regulations

The International Conference on Harmonisation (ICH) aims to bring together the pharmaceutical industry and regulatory bodies in developing guidelines to ensure the development of safe, effective and high-quality medicines. Regulatory bodies, including the European Medicines Agency (EMA) and the Food and Drugs Administration (FDA) adopt these guidelines, helping to ensure worldwide harmonisation in the registration, development and maintenance of drug products. There are a number of guidelines and papers that concern the development of medicines for older people published by both the EMA and ICH.

1.4.1 ICH

The ICH E7 guideline was published in 1994, entitled "Studies in Support of Special Populations: Geriatrics E7," and was adopted by both the EMA and FDA to address the expected increase in the older population at that time [65,66]. The guideline states: "the use of drugs in this population requires special consideration due to the frequent occurrence of underlying diseases, concomitant drug therapy and the consequent risk of drug interaction" [65]. However, while this guideline acknowledged the impact of the drug formulation on efficacy and safety, it did not address the suitability of the formulation for older people and there was a lack of focus on the patient. The subsequent ICH guideline (ICH Q8) was published in 2005 and stipulates that "the product should be designed to meet patients' needs and the intended product performance" and that "the Pharmaceutical Development section (of the Marketing Authorisation dossier) should describe the knowledge that establishes that the type of dosage form selected and the formulation proposed are suitable for the intended use" [67].

Recently, the ICH published a reflection paper on patient focused drug development. This paper identifies key areas where inclusion of a patient's perspective can improve the safety, efficiency and quality of drug development [68]. While not targeted and focused specifically at the older population, this paper highlights the need for regulators and drug sponsors to include patients and caregivers as 'partners' and to account for heterogeneity or subgroups [68].

1.4.2. EMA

The European Medicines Agency (EMA) published a Geriatric Medicines Strategy in 2011, marking its commitment to better addressing the needs of older people in the development and evaluation of medicines. The aim of the strategy is firstly to "ensure that the medicines used by older people are of high quality and are studied appropriately in the older population, throughout the medicinal product lifecycle" and secondly to "improve the availability of information for older people on the use of medicines" [69]. In order to achieve these aims, the EMA has set up a Geriatric Expert Group to provide scientific advice to the EMA Committee for Medicinal Products for Human use (CHMP). This group includes experts in the field, including physicians, clinical pharmacologists and independent experts from other fields as needed [69].

As part of the EMA Geriatric Medicines Strategy, a concept paper on the need for a reflection paper on quality aspects of medicines for older people was developed in 2013. It was proposed that this reflection paper would provide an overview of aspects that require special consideration in older people and would identify how current marketing authorisations may not be fully meeting the needs of this population [70].

A draft reflection paper on the pharmaceutical development of medicines for use in the older population was published in 2017 by the EMA Quality Working Party (QWP). The paper looks at the current status of discussions on this topic and examines factors which affect acceptability in this population through considering the route of administration and dosage form [3]. The draft paper was open for public consultation between August 2017 and January 2018, and the final reflection paper was published in October 2020 [71]. This reflection paper is primarily targeted at the pharmaceutical industry, however is also useful for pharmacists, physicians and patients due to the wide range of topics covered. The paper discusses the wide range of practical problems that older people experience and the need to consider factors such as multiple medication use, medication recognition and switching between medicines [71]. The paper does not provide any regulatory or scientific guidance however may contribute to the development of CHMP guidelines in the future.

In addition to the publication of a reflection paper, the Geriatric Medicines Strategy has resulted in the publication of a Good Practice Guide on "Risk minimisation and prevention of medication errors" issued by the Pharmacovigilance Risk Assessment Committee (PRAC). This guide includes specific considerations for preventing medication errors in high risk groups including older people and suggests the use of a wider range of colours, sizes and tablet shapes to help patients recognise their medicines [72].

1.4.3. Summary of regulations

Currently there are no regulations governing the development of medication for older people, rather there has been a focus on producing guidelines to guide the pharmaceutical industry [73]. This is in contrast to the paediatric regulation, which came into force in 2007. The aim of the Paediatric Regulation is to ensure that medicines for use in children are of high quality, ethically researched and authorised appropriately [74]. As part of this regulation, Paediatric Investigation Plans (PIPS) must be submitted when applying for a marketing authorisation for new medicines to show that necessary data has been obtained through studies in children [75]. In contrast, a large European project which explored the inclusion/exclusion of older patients in trials across nine European countries found that older people continue to be excluded unjustifiably from clinical trials [76], in spite of the ICH E7 guideline [65].

There have therefore been calls for a "Geriatric Regulation" and associated "Geriatric Investigation Plan" [73]. However, the EMA states that older people are the major user group of medicines and therefore their needs are better addressed by integrating the assessment of medicines used by older people in the general framework, adding targeted advice and guidance where appropriate [64]. Rather than creating a Geriatric Regulation, the focus is currently on improving the current guidelines and making use of experts such as the geriatric expert group to check for compliance to these guidelines [73].

1.5. Adherence and acceptance as outcome measures

The regulatory guidelines and reflection papers all refer to the importance of acceptability when considering the formulation of a pharmaceutical drug product. Acceptability has been defined as "an overall ability of the patient and caregiver to use a medicinal product as intended" [77]. The importance of acceptability as an outcome measure was defined early on when the Regulatory Authorities put forward the *Reflection Paper: Formulations of choice for the paediatric population* in 2005 [78]. This paper makes reference to acceptability throughout, and highlights how factors such as the taste, smell, texture and appearance all impact the acceptability of a formulation for the paediatric population [78]. The importance of acceptability was developed further in the guidelines on pharmaceutical development of medicines for paediatric use, published by the EMA in 2013 [79]. This paper states that acceptability is determined by both the characteristics of the user (e.g. age, ability) and by the characteristics of the medicinal product, such as the swallowability, required dose and route of administration [79].

The importance of acceptability was consequently bought forward when developing guidelines and reflection papers for the older population. The reflection paper published in 2020 states that acceptability is determined by the interplay between the medicinal product design and the characteristics of the patient and, where relevant, his/her caregiver (the patient product interface) [71]. In order to demonstrate adequate patient acceptability, pharmaceutical companies should:

a) identify patient needs across the subsets of a target patient population

b) consider if the drug product's portfolio covers all of these needs

c) evaluate if each drug product is sufficiently accepted by the subset(s) for which it has been designed

d) justify that the level of patient acceptability is commensurable with the level of risk involved [71]

Patient acceptability is likely to have a significant impact on patient adherence, which can subsequently have a significant impact on the perceived patient/caregiver quality of life [71]. Patient adherence is therefore a key outcome measure which is very much inter-related with patient acceptance. The term adherence is more commonly used and is preferred over the term compliance as it involves collaboration with a physician to include the patient's values and preferences [80]. Adherence can be defined as "the extent to which the patient's action matches the agreed recommendations" [81]. Improving adherence involves exploring the patient's perspectives about their treatments and the reasons why they may be unable to use them, or may not want to [81]. There is a need to therefore consider both acceptability and adherence when exploring the formulation of oral solid dosage forms. Although the EMA have published regulatory incentives to encourage the development of drug products that improve acceptance and therefore adherence, there is a need to ensure that these drug products are then prescribed and dispensed appropriately to obtain optimum patient benefit.

1.6. The need for a holistic approach

GPs, pharmacists, nurses and other health and social care professionals all play an important role in selecting the most appropriate formulation [40]. The individual needs of the patient must be taken into account to provide the best overall benefit to risk profile and therefore reduce medication errors and non-adherence [40]. Professionals need to be informed on any specific difficulties the patient may experience, such as swallowing difficulties [82-84], so that the most appropriate, patient centric dosage form is selected. The final decision should rely on the patient; however, an understanding of the healthcare needs of the patient can increase the efficacy of the prescribed treatment and potentially reduce hospitalisations [39,85]. There is a need to ensure that the views of health and social

care professionals are considered when developing patient centric medicines, and that their role in providing these medicines is explored.

When considering the interaction between the patient and the medicine in the older population, there is also a need to involve the views of the carer. Family carers often encounter difficulties when managing medications and lack appropriate forms of support [86]. It is therefore important to directly involve carers in topics that would be of importance to them so that effective interventions can then be developed [86]. This is especially important for CNS disease pathologies known to have the highest prevalence of dysphagia. The responsibility of medication administration often shifts to the caregiver in these circumstances, and this is further complicated by the presence of comorbidities and multiple medications [87]. Caregiver stress can be linked to negative outcomes for both the recipient of care as well as lead to further costs as a result of increased hospital admissions [88]. Their involvement in helping to design medicines that are easy for them to administer is therefore vital in future research.

1.7. Aims and objectives

The concept of patient centric medicine design is remarkably new, and is likely to transform the way medications are developed [89]. Characteristics such as the size, shape and colour have a significant impact on patient acceptance [90] and therefore adherence, and should be considered when defining the QTPP for a drug product [63]. The development of patient centric medicines for older people is especially important due to age related changes such as changes in sensory functions, motor functions and cognition [3]. The overarching aim of the work presented in this thesis is to investigate the characteristics of oral solid dosage forms that contribute to age appropriate, patient centric medicines that help to improve medication adherence and acceptance in older people. The specific research objectives are:

1) To systematically review the available literature on how the characteristics of oral solid dosage forms impact adherence and acceptance in older people (Chapter Two)

2) To collect data on the key issues faced by older people and carers when using/administering oral solid dosage forms and the characteristics that would help contribute towards a patient centric dosage form (Chapter Four)

3) To explore the role of health and social care professionals in the provision of patient centric medicines (Chapter Five)

4) To explore 3D printing as a potential tool to further understand preferences for characteristics (Chapter Six).

1.8. Thesis structure

This chapter (**Chapter One**) has provided a background to the study, including an introduction to patient centric medicines and the need to focus specifically on the older population. It also provides an overview of the current regulations in this area, the importance of adherence and acceptance as outcome measures and the need for a holistic approach when developing patient centric medicines.

Chapter Two details the mixed methods systematic review undertaken to study the available literature on whether the formulation of oral solid dosage forms affects adherence and acceptance in older people. This chapter identifies gaps in this field and provides the rationale for the subsequent work carried out as part of this project.

Chapter Three discusses the methodology and methods chosen for the next stages of this project. The chapter provides a detailed rationale behind the use of a qualitative approach, specifically the choice of semi-structured interviews. The use of thematic analysis to analyse these interviews is explained, and a proposed program of work is put forward.

Chapter Four presents the findings from the semi-structured interviews in relation to the key characteristics of oral solid dosage forms that improve adherence and acceptance in older people. The findings are presented by exploring each stage of the medication taking process, and evaluating how the characteristics impact each stage. Example images are provided from the semi-structured interviews and the findings are discussed in comparison to previous work in this area.

Chapter Five presents the findings from the semi-structured interviews in relation to the barriers and facilitators towards the increased involvement of health and social care professionals in the provision of patient centric medicines.

Chapter Six discusses how 3D printing can be used to create model tablets of varying characteristics to further understand preferences. The concept of 3D printing is introduced and 3D models that we developed using the results from Chapter Four are presented.

The final chapter, **Chapter Seven**, summarises the key findings and discusses the strengths and limitations of the project. Implications for practice and for future research are presented.

Chapter 2- Mixed Methods Systematic Review

The work in this chapter has been published in the following publication: “Shariff, Z.B.; Dahmash, D.T.; Kirby, D.J.; Missaghi, S.; Rajabi-Siahboomi, A.; Maidment, I.D. Does the Formulation of Oral Solid Dosage Forms Affect Acceptance and Adherence in Older Patients? A Mixed Methods Systematic Review. Journal of the American Medical Directors Association 2020, 21, 1015-1023.e1018.”

2.1. Introduction

A systematic review was chosen for the first stage of this project as it was necessary to identify the gaps in the literature and communicate the strength of the available evidence. The following chapter discusses in detail the steps undertaken during the review and how results informed future research in this area.

2.2. Background search of the literature

Systematic reviews use rigorous and explicit methods to bring together the results of previous research in order to answer a particular question [91]. They are the reference standard when making healthcare decisions for individual patients as well as for the development of public health policies, both of which should be informed by the best available research evidence [92]. The value of including a diverse range of studies in systematic reviews is increasingly being recognised [93]. There is less emphasis on the requirement to include controlled trials as the sole source of evidence and a greater significance is placed on the contribution that qualitative research can make in providing a critical perspective when answering complex questions [94]. Systematic reviews can therefore include a review of quantitative and/or qualitative studies, and defining the type of systematic review to conduct is an important step that will determine the rest of the review process [95].

In addition to defining the types of studies to be included, the initial steps of a systematic review also include formulating the review question. A systematic review should be based on an important, well focussed question from which all subsequent aspects of the review can be determined [96]. In order to formulate the research question, the scope of the review must be defined and this involves considering who the research question is about, what must be found out to answer the question, and how the study impacts the target population (the outcome) [97].

In order to develop a well-formulated, answerable question that would be used to guide the systematic review, a background literature search was conducted. The factors explored in this background search can be found in Table 2.1 below. These criteria were used to also define the inclusion and exclusion criteria for the review.

Table 2.1 Factors explored during a background search of the literature [98]

Criteria	Guiding question
Type of studies	Are studies quantitative or qualitative?
Number and source of studies	What is the source of studies and is there a need to use grey literature?

Common themes/gaps	Are there common themes/gaps that emerge from the studies that can be explored further in the systematic review?
Country	What countries are the studies from? Is there a need to include non-English language studies as well?
Sample	What sample and sample sizes do the studies use?
Timeframe	What length of time are the studies conducted over, and what time period?

The scoping search was carried out by searching the terms "oral solid dosage forms, adherence, older people" in Google Scholar. Relevant studies were tabulated; see Appendix 1.

2.3. Defining the inclusion and exclusion criteria

Evaluation of the studies retrieved from the background search led to the development of the following inclusion and exclusion criteria. These criteria are based on the PICOC (Population, Intervention, Comparison, Outcome(s), Context) framework which is a recognised approach to identifying the fundamental elements of the research question [99].

2.3.1. Population

The need to focus on the older population for this review has been explained in Chapter one. An older person is chronologically defined as aged 65 or older [100]; however, while this is the traditional marker for the start of old age, the definition of an older person in the literature varies. Some studies were retrieved from the database search that focused on older people aged 60 or over, for example a study investigating the acceptability of calcium and vitamin D supplements specifically targeted patients aged 60 years or more [101]. Therefore, while the initial target population was defined as patients over the age of 65, this was updated following the retrieval of results from the database search to over 60s to ensure all relevant studies were included in the final synthesis.

Scoping the literature also found a number of studies which included participants from a wider age group that had relevant information for older people [84,102]. Furthermore, the importance of considering the role of healthcare professionals and caregivers in medication management was also identified [83,103]. The inclusion criteria for the population being studied in the systematic review was therefore broadened. Studies including patients aged less than 60 were included and relevant data extracted, and studies that involved healthcare professionals, social care professionals (e.g. social workers, formal carers) and carers (informal) examining the phenomenon of interest in over 60s were also included.

As this review aimed to focus on the patient and patient related outcomes, studies that took a purely industrial perspective on developing oral solid dosage forms were excluded, as were those focusing exclusively on patients under 60.

2.3.2. Intervention

As discussed in Chapter one, the formulation of oral solid dosage forms was the main focus of this research project. The definition of formulation was taken from the European Medicines Agency as: "A dosage form with a particular composition and with specific product characteristics, e.g. tablet size, shape, colour, embossing, break mark" [3]. From scoping the literature, it was clear that studies investigating other dosage forms could still be relevant to the research question by extracting data relevant to oral solid dosage forms [4,104,105]. Therefore, studies comparing oral solid dosage forms to other formulations/routes of administration were included and relevant data extracted.

Studies investigating non-allopathic drugs, i.e. homeopathic remedies, herbal remedies, food supplements were excluded as these were not relevant to the research question. Studies focusing exclusively on packaging were also excluded as this would have been outside the scope of the project.

2.3.3. Comparison

This is optional and is not relevant for this review.

2.3.4. Outcome

Adherence has been defined by NICE (National Institute for Health and Care Excellence) as the extent to which the patient's action matches the agreed recommendations [81]. Adherence to a drug therapy is a primary determinant of treatment success and is preferred over the term compliance as it involves collaboration with a physician to include the patient's values and preferences [80]. Adherence was the main outcome measure that was studied for this review, and any other outcomes which indirectly gave an indication of patient adherence, such as quality of life, hospital readmission rates and medicine wastage, were also included.

Scoping the literature also led to the emergence of the term acceptance. Acceptability has been defined as "an overall ability of the patient and caregiver to use a medicinal product as intended" [77]. The outcomes being measured in the review were therefore expanded to include the term acceptance as this was highlighted as being critical to ensure adherence, especially in older people [106].

2.3.5. Context

A vast majority of the studies identified did not take place in the UK (see Appendix 1). The preliminary search therefore confirmed the need to adopt a broad search strategy that was not limited by country of origin or by time period in order to ensure that all relevant studies were identified. However, due to a limited timeframe and limited resources available, studies were limited to the English Language only.

2.3.6. Study design

Whilst the study design is not included in PICOC, it is an important aspect to consider and has therefore recently been introduced in other frameworks used to define the scope of the review [107]. The scoping search identified studies with a range of study designs including questionnaire surveys, in depth interviews, observations and reviews. Qualitative research can make a significant contribution towards a systematic review by providing a critical perspective when answering complex questions [94]. A mixed methods approach was therefore adopted for this review, where quantitative, qualitative and mixed methods were all study designs that were eligible for inclusion.

2.4. Defining the review question

The above inclusion criteria and results from the background search led to the development of the primary review question: *"Does the formulation of oral solid dosage forms affect patient adherence and acceptance in older people?"* The primary review question was answered through considering the main issues currently encountered when using/ administering oral solid dosage forms, the current methods which have been employed to optimise oral solid dosage forms for older people and how these methods have impacted patient adherence and acceptance.

2.5. Developing the search strategy

2.5.1. Identification of search terms

The background literature search identified common terms in relation to formulation, oral solid dosage forms, adherence and older people. These terms can be found in Table 2.2 below.

Table 2.2. Search terms identified from a background literature search

Title key word	Common terms identified	Examples
Formulation	Pharmaceutical design Dosage form design Medication/Medicine/Medicinal Product design Drug product design Pharmaceutical formulation Drug formulation Medication/Medicine formulation Formulation factors Patient-centric design Physical characteristics Physical attributes Appearance Tablet Dress	Colour Size Shape Score-Line Break-mark Coating Marking Embossing Taste Palatability Grittiness Texture Smell Surface Texture
Oral solid dosage forms	Oral solid Oral dosage Solid oral Solid dosage	Tablet Capsule Soft Capsule Hard Capsule Chewable Orodispersible tablet Effervescent tablet Small tablet Mini-tablet Fixed Dose combinations

Adherence	Appropriateness
	Acceptability
	Usability
	Swallowability
	Dysphagia
	Preference
	Persistence
	Adherence
	Compliance
	Nonadherence
	Noncompliance
	Concordance
Older people	Aged
	Elderly
	Older
	Geriatric

2.5.2. Example search strategy

Combinations of these synonyms were explored in order to develop an effective search strategy. Features of databases, such as truncation symbols, were used in order to retrieve a wider range of relevant results. Truncation enabled the search to be broadened to include various word endings and spellings, for example prefer* returned results that included prefer, preferred, preference and preferences. Database specific search strategies were developed which were subsequently approved by a qualified information specialist at Aston University's Library. Search terms included a combination of Medical Subject Heading terms (for use in Medline) and a comprehensive list of synonyms relating to (as in Table 2.2) formulation factors, oral solid dosage forms, adherence and older people. An example search strategy can be seen below:

1) "Pharmaceutical design" OR "dosage form design" OR "medic* design" OR "drug product design" OR "pharmaceutical formulation" OR "drug formulation" OR "medic* formulation" OR "formulation factors" OR "patient centric" OR "patient-centric" OR "physical characteristics" OR "physical attributes" OR appearance OR "tablet dress"

2) “Oral solid” OR “oral dosage” OR “solid oral” OR “solid dosage” OR *tablet* OR *capsule* OR chewable OR orodispersible OR effervescent OR “small tablet$” OR “mini tablet$” OR “hard capsule$” OR “soft capsule$” OR “fixed dose combination$”

3) Appropriate* OR acceptab* OR usab* OR swallow* OR dysphagia OR prefer* OR persist* OR adhere* OR complian* OR nonadhere* OR non-adhere* OR noncomplian* OR non-complian* OR concordan*

4) Elderly OR aged OR older OR geriatric OR “over 60”

5) 1, 2, 3 AND 4

The complete search strategy is available for reference in Appendix 2.

2.6. Database and grey literature search

A systematic search of the following databases from inception to May 2019 was undertaken: Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), MEDLINE, Scopus, and Web of Science. No language or time restrictions were placed on the initial search. The database search was supplemented by a grey literature search; reference lists of included studies and reviews were manually checked; reviews were then excluded from the final list of included studies. Grey literature sources included BASE (Bielefield Academic Search Engine), ETHOS (British Library Electronic Thesis Online), OpenGrey and Web of Science Conference proceedings. The grey literature search was further supplemented by checking a minimum of the first 100 hits on Google Scholar, and continuing until 10 or more consecutive irrelevant hits were retrieved.

2.7. The review protocol

Once the review question and search strategy had been defined, the review protocol was developed. A review protocol has three main functions including protecting against bias, providing a practical tool to conduct the methods of the review and staking a claim to the topic [108]. The protocol must outline the method for identifying, selecting and synthesising studies and any changes should be recorded and explained. Once developed, review protocols can be registered on PROSPERO, an international database of prospectively registered systematic reviews. This database provides a comprehensive list of systematic reviews registered at inception and therefore helps to avoid duplication. Registering the review also helps to reduce the potential for bias as the completed review can be compared to the protocol to ensure that all steps were followed. The protocol for this mixed methods systematic review was registered on PROSPERO registration number, CRD42018088969, available at:

http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018088969

The review was also conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. This guideline helps to improve the reporting of systematic reviews. The completed PRISMA checklist can be found in Appendix 3.

2.8. Study selection

The initial preliminary screening of the titles to exclude records that were clearly not relevant was performed by the primary researcher (ZS). Following this, the titles and abstracts of any relevant studies retrieved using the search strategy were screened independently by two review authors (ZS, DD) to identify studies that potentially met the inclusion criteria outlined above. A further team member (IM) was available to consult and if there was any doubt the full text article was retrieved for full review. The full text for all potentially eligible studies was retrieved and independently assessed for eligibility by two review team members (ZS, DD). A further team member (IM) was again available to consult regarding any disagreements.

2.9. Data extraction

Data were extracted and entered onto a standardised spreadsheet. Characteristics of included studies that were extracted included the country in which the study took place, the aim, study design, sample size and age, data collection methods and data analysis methods. Two review authors (ZS, DD) extracted data independently and any discrepancies were identified and resolved through discussion with a third author (IM). Using the EMA definition of formulation [3] data relating to the formulation characteristic(s) explored in each study were also extracted and tabulated.

2.10. Quality appraisal

There are a number of Critical Appraisal Tools (CAT) available and there is a need to take care when deciding which tool to use and how it is used [109]. When considering the most appropriate tool to use for this review, the types of studies that were being included was a key consideration. Both quantitative and qualitative studies were identified in the background search of the literature. While no mixed methods studies were identified in the background search, mixed methods studies are increasingly being used in health outcomes research [110]. There was a need to therefore use a tool that would allow for the critical appraisal of mixed methods studies. It was also important to ensure the tool chosen was tested and validated; a review of critical appraisal tools recently found they lack rigour and often do not consider comprehensive validation and reliability testing [109].

The Mixed Methods Appraisal Tool (MMAT- version 2018) [111] was considered the most appropriate tool for this review and was used to critically appraise the final list of studies. This tool is based on a constructionist theory and literature review, and has been pilot tested for reliability [111]. Studies are categorised into the study design and are then assessed based on the methodology used. Rather than provide an overall score, this recent version of the tool encourages the user to appraise studies by describing which areas are problematic. Following a review, this method of appraising studies was found to be more useful than providing a single global score with no description or explanation [111]. The two reviewers (ZS, DD) met in advance before reviewing the papers in order to discuss how to rate them, e.g. whether quality would be assessed based on the primary outcomes of the study or on the outcome(s) of interest in the systematic mixed studies review. Disagreements in MMAT-scores were resolved by discussion between the two reviewers.

2.11. Synthesis of findings

When conducting a mixed methods review, the synthesis process can be analysed according to three concepts: a) the synthesis method(s) b) the sequence and c) integration [112]. The synthesis method is dependent on the type of data collected: quantitative or qualitative. Qualitative synthesis methods are used when summarising data to generate themes, concepts, frameworks or theories [112]. Examples of qualitative synthesis methods include thematic synthesis, textual narrative synthesis and framework synthesis [113]. Quantitative synthesis methods, in contrast, are used for numerical values which are often summarised to generate measures of treatment effect, such as the risk ratio and incidence rate [114]. Examples of quantitative synthesis methods include meta-analysis, meta-regression and a configurative approach [115].

The sequence of data synthesis is determined by whether the results of one phase informs the synthesis of another. Within a sequential synthesis design, a two phased approach is used in which the analysis and synthesis of one type of study design informs the other; for example, a qualitative synthesis of qualitative studies is done first (phase 1), and the results from this used to inform the analysis of quantitative studies (phase 2) [112]. In contrast, a convergent synthesis design involves analysing both quantitative and qualitative studies at the same time in parallel or in a complementary manner [112].

When considering a convergent synthesis design, integration can occur at three key points. The first, a data-based convergent synthesis design, involves analysing all studies using the same method and presenting the results together [112]. As only one synthesis method is used, this design involves data transformation i.e. quantitative data is transformed to categories/themes or qualitative data is transformed into numerical values [112]. The second, a results-based convergent synthesis design,

involves analysing and presenting qualitative and quantitative evidence separately and then using another synthesis method to integrate the findings. Finally, a parallel-results convergent design involves analysing and presenting qualitative and quantitative evidence separately, with integration occurring during the interpretation of results in the discussion section.

Sandelowski et al also advocated a similar approach towards categorising review designs [116]. They define a "contingent design" as one in which a cyclical approach towards synthesis is taken, where findings from one synthesis inform the focus of the next; a similar concept to the sequential synthesis design. Sandelowski et al further define a "segregated design" as one in which quantitative and qualitative studies are treated independently (similar to results-based and parallel-results convergent synthesis designs) and an "integrated design" as one in which the differences between quantitative and qualitative studies are minimised (comparable to a data-based convergent synthesis design [116].

The present review aimed to identify both quantitative and qualitative studies that investigate if and how the formulation of oral solid dosage forms affects acceptance and adherence in older people. The aim was to define the main concepts in relation to this specific topic so that this could then inform future research. Studies that aim to identify the main concepts or themes in relation to a specific review question more commonly use a data based convergent synthesis design [112] and this was the approach taken for this review. By using data transformation and transforming quantitative data into categories, all studies could be analysed using the same synthesis method. Furthermore, there were a range of quantitative studies identified including quantitative descriptive studies, randomised crossover trials and cross-sectional observational studies. The use of a data based convergent synthesis design allowed for all of these studies to be analysed and compared simultaneously.

The thematic synthesis approach, as discussed by Thomas and Harden, was used to synthesise all findings [91]. Data were initially coded to develop categories and sub-categories of information, after which descriptive themes were identified by making explicit connections between these categories and sub-categories. Analytical themes were then generated by exploring the themes in relation to how formulation aspects of oral solid dosage forms affect adherence and acceptance in older people.

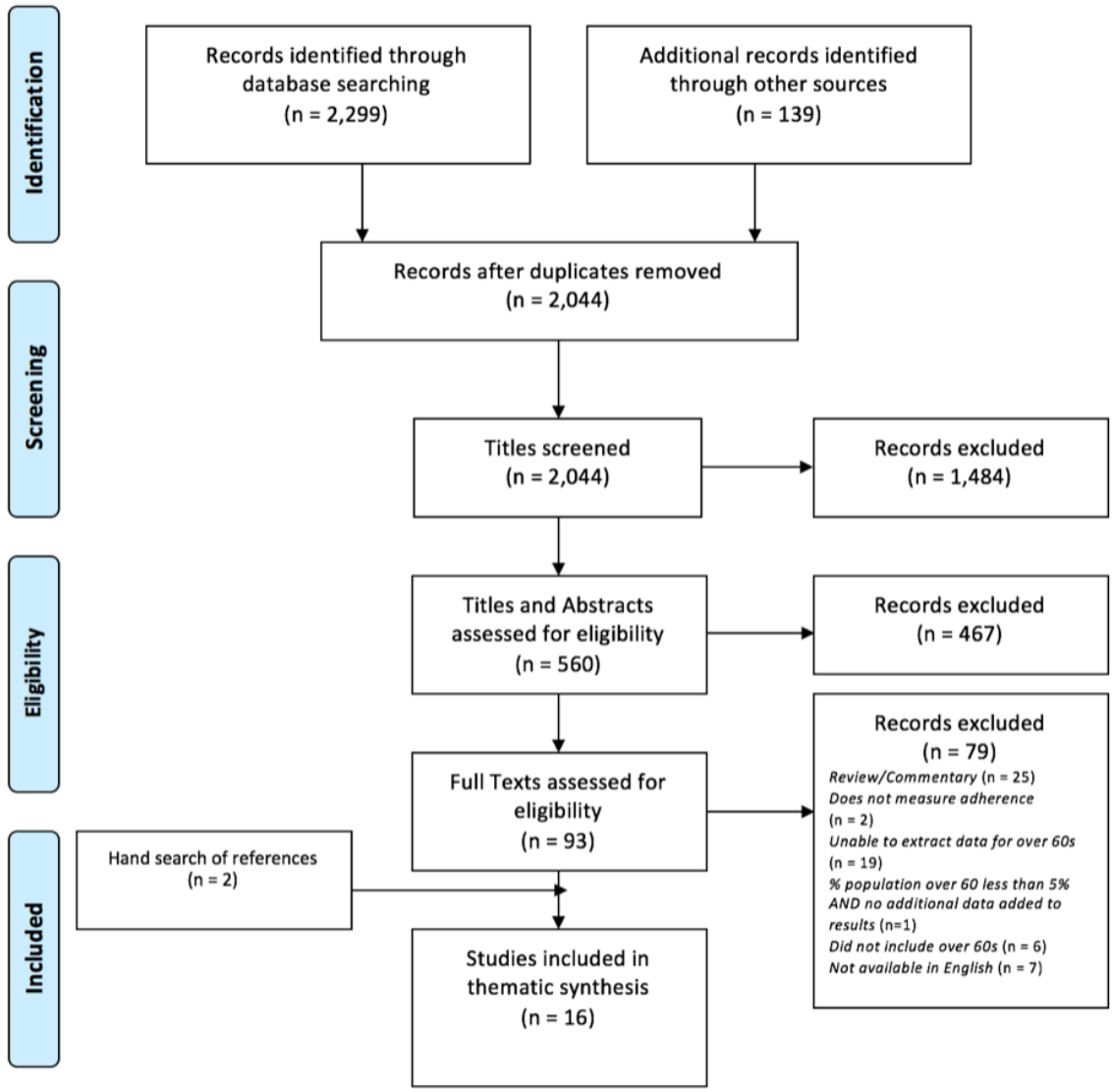
2.12. Results

2.12.1. Review Process

Figure 2.1 below summarises the review process. A total of 2299 articles were identified from the initial search of databases with a further 139 records identified from other sources. After removal of duplicates and screening, of the 77 articles included in the full text, 14 met the inclusion criteria (see

Appendix 4 for reasons for exclusion at full text). Two additional articles were included from the reference lists of selected articles.

Fig. 2.1. PRISMA flow chart depicting the main stages of the review process



2.12.2. Characteristics of Included Studies

The characteristics of the included studies are summarised in Table 2.3. Eight of these studies were conducted in over 60s exclusively [82,101,106,117-121], none of which were conducted in the USA and

only three of which were conducted in the UK [82,106,119]. Relevant data was extracted from the remainder. One study involved physicians as well as patients [84]. The formulation of oral solid dosage forms, as defined for the review, was explored directly by ten of the sixteen studies [101,106,119-126]. The majority of these (seven studies out of ten) investigated specific formulation characteristics by comparing preferences for separate formulations [101,119,120,122-125]. The remaining six studies (out of sixteen) investigated formulation indirectly, with a primary focus on generic substitution, general medicine taking practices and swallowing difficulties [82-84,117,118,127]. Relevant data was again extracted. The formulation characteristic(s) explored can be found in Table 2.4.

2.12.3. Quality Appraisal

The results from the quality appraisal of the included studies are shown in Appendix 5. All included studies had clear research questions and collected data that addressed the research question. The three qualitative studies [82,117,118] scored highly, using semi structured interviews to collect data from which quotes were extracted and used to illustrate the interpretation of the results. The quality of the six quantitative descriptive studies [83,84,106,124,126,127] varied with two studies scoring very low due to unclear sampling strategies, a non-representative sample, uncertainty over the validity of the survey used and few details reported in relation to the analysis of data [124,126]. All five randomised crossover studies [101,119,123,125,128] investigated the formulation of oral solid dosage forms directly; however, the quality of these studies again varied, with one study scoring very low due to insufficient details in the reporting of the study [119]. Five studies received financial support from or were sponsored by the pharmaceutical industry [123-125,128,129]. Despite the suboptimal quality of some of the studies, all studies were included in the final synthesis as it was important to include all findings in relation to the topic of interest. However, studies which were higher in quality were discussed more in the final synthesis.

2.12.4. Analytical Themes

Three themes were generated from the thematic analysis of data: i) Dimensions; ii) Palatability; iii) Appearance.

1. Dimensions

The dimensions of a dosage form include the shape and size and often also requires consideration of the presence/absence of a break mark, used to modify size. Qualitative studies that investigated formulation indirectly in the general older adult population (by exploring general medicine taking practices) illustrated the importance of this characteristic, with 29.6% of use difficulties (situations where the participant can complete a task but only with difficulty) attributed to the dosage form being

too large/small [118]. In general, there was a preference for smaller dosage forms; “tablet size was too big” was the most common cause of ongoing and past swallowing difficulties in patients with dysphagia [83]. However, tablets that were too small led to difficulties handling the tablet and locating the product in the mouth [118].

Shape was also important, partly because of the relationship between shape and size. The smooth oesophageal transit of oral solid dosage forms is dependent on a minimum cross-sectional area [84] and therefore preferences for size were often dependent on shape. Studies investigating swallowing difficulties within a general practice population found difficulties with oval tablets, for example, were only slightly more frequent than for round tablets, despite being almost twice the diameter [84]. Oval tablets have a smaller cross-sectional area and are therefore less likely to adhere to the oesophagus. This was supported by a further study, which found that just over 40% of older people with dysphagia selected the 11mm arched round tablet as having the potential to cause difficulties, compared to approximately 35% selecting the 13mm oblong tablet [106].

Table 2.3 Characteristics of included studies (listed alphabetically according to first author)

Reference (Year)	Country	Aim	Study Design	Sample Size and Age	Data Collection Methods	Data Analysis Methods
den Uyl et al[122] (2009)	Netherlands	To compare the preference and acceptability of two calcium plus vitamin D-3 formulations	Quantitative randomised, open, cross-over clinical trial	102 patients visiting an outpatient clinic aged between 34-83. Mean age 66	Acceptability questionnaire and overall preference assessment	A logistic regression model was used to analyse the difference between the two formulations and provide an estimate of the sequence effect. A linear mixed model was used to analyse the secondary efficacy end points
Heikkilä et al[127] (2011)	Finland	To explore the factors that influence the choice of medication following the introduction of generic substitution (GS)	Population based survey	1844 people divided among 18-59 year olds (61%) and 60-94 years olds (39%)	Questionnaire consisting of structured and open-ended questions	SPSS 17.0.1 statistical software using frequencies and cross-tabulations for descriptive analysis
Hofmanová et al[123] (2019)	UK	To investigate the oral sensory properties and swallowability of coated placebo tablets	Quantitative randomised double-blind study	Non-smoking healthy adults aged 18-75. Over 55s targeted and made up 50.6% of the overall population	Background questionnaire and tablet sample assessment using Visual Analogue Scales	A number of statistical analyses conducted using SPSS version 24 to explore the differences between each of the tablet samples and to explore the impact of patient demographics on responses
Jones et al[124] (2000)	USA	To compare the preference of softgel capsules versus	Quantitative Descriptive Study	300 consumers evenly divided among the age	Consumer Preference Survey	Exact analysis methods not stated

		conventional solid dosage forms.		groups of 25 to 39 years (31%), 40 to 59 years (33%), and 60+ years (36%).		
Kelly et al[82] (2010)	England	To explore the experiences of taking medication for older people with dysphagia	Qualitative study with semi structured face-to-face interviews	11 patients who had different degrees of dysphagia over the age of 60	Semi structured interviews	Content analysis to generate themes which were then integrated so that they could be related back to the research question
Liu et al[106] (2016)	England	To assess the acceptability of a range of oral solid dosage forms (OSDFs) in older ambulatory patients	Quantitative descriptive study	156 patients taking at least one oral solid medicine over 65	Sydney Swallow Questionnaire (assessing swallowing function). Pilot of the Medicines Acceptability Questionnaire. Patients shown samples of OSDFs	Data analysis was performed using the Statistical Package of the Social Sciences (SPSS) version 22.0
Marquis et al[83] (2013)	Two Swiss Regions: Basel and Lausanne	To determine the prevalence of swallowing difficulties, the strategies to overcome these and health professional's awareness of these problems	Quantitative descriptive study	410 enrolled patients taking at least 3 different oral solid dosage forms over 18 (mean age 66.5)	Interview combining closed ended, open ended and Likert-scale items	Data analysis was performed using the Statistical Package of the Social Sciences (SPSS) version 15.0

Notenboom et al[117] (2014)	Netherlands	To identify the practical problems that older people experience with the daily use of their medicines	Qualitative study with semi structured face-to-face interviews	59 community dwelling people aged 70 and older (mean age 78.4)	Semi structured interviews	Transcribed data were coded independently. Each practical problem/management strategy was classified on a 3-point scale according to the level of discomfort and clinical deterioration likely to result
Notenboom et al[118] (2017)	Netherlands	To identify design features of oral medicines that cause use problems among older patients	Qualitative study with semi structured interviews	59 community dwelling people aged 70 and older (mean age 78.4)	Semi structured interviews	Transcribed data were coded independently. Each practical problem/management strategy was categorised as a "use difficulty" or a "use error"
Phillips et al[119] (1992)	UK	To compare the ease of swallowing a single oral dose of a standard tablet of aciclovir versus a film-coated tablet	Quantitative randomised cross over study	104 volunteers from the department of medicine for older people at Orpington Hospital aged 71 to 94 (mean age 82)	Patients asked to swallow one formulation and then 24 hours later received a second formulation. Preference assessed	Tabulation detailing the number and percentage of patients who preferred the standard formulation, the coated formulation and who expressed no preference
Rees, T. P. & Howe, I.[101] (2001)	UK	To compare the acceptability and preference of two chewable preparations of calcium and vitamin D: Calcichew D3 Forte (CDF) and Ad Cal D3 (ACD)	Quantitative randomised, investigator-blind, cross over, multicentre study	94 patients aged 60 or over (mean age 72.6)	Visual Analogue Scales (VAS) used to assess acceptability. Overall preference assessment	The distribution of the VAS scores were tested using the Shapiro- Wilk test and univariate summary statistics. Data were log transformed before applying an ANOVA for a two-period crossover design

Reginster et al[125] (2005)	Belgium	To compare the preference for and acceptability of two formulations containing calcium and vitamin D	Quantitative randomised, open-label crossover trial	199 patients were included in the intent-to-treat analysis. Preference data were available for 178 patients. All aged 18 or over (mean age 66)	Acceptability questionnaire and overall preference assessment	A logistic regression model was used to analyse the difference between the two formulations and provide an estimate of the sequence effect. A linear mixed model was used to analyse the secondary efficacy end points. SAS version 8.2 was used in all statistical analyses
Rodenhuis et al[126] (2003)	Netherlands	To measure patient satisfaction with score lines on tablets	Quantitative descriptive study	140 patients with prescriptions for scored tablets that had to be broken (50% of prescriptions broken by over 60 year olds)	Survey conducted by pharmacies to explore patient experiences with the functioning of the score line	Tabulation analysing the prescriptions for scored tablets by age of breaker, negative evaluation and type of negative evaluation. Data also analysed to explore negative evaluations of specific drugs and actions taken by patient on negative evaluation
Schiele et al[84] (2013)	Germany	To assess the prevalence of difficulties in swallowing oral solid dosage forms in a general practice population and to explore the reasons, nature, and characteristics of tablets and capsules	Quantitative descriptive study	1,051 patients taking at least one oral solid dosage form aged 18 and over (mean age of those completing the medication list 62.7). 16 GPs	Two structured questionnaires. GPs completed a separate questionnaire to predict swallowing difficulties	For the main questionnaire, a statistical analysis was conducted using SAS statistical software package. Data from the medication lists were matched to a drug database. Medication characteristics such as the width, height and diameter were analysed in relation to any associations with swallowing difficulties

		causing these difficulties				
Scott et al[120] (2018)	UK	To explore the relationship between alendronic acid formulations and patient acceptance and adherence	Quantitative Descriptive Study	33 inpatients from an Older People's Medicine ward completed the tablet questionnaire (median age 84.0), of whom 25 completed the liquid questionnaire	Following questionnaire testing, the Medication Acceptability Questionnaire and Medication Adherence Report Scale were used to assess acceptance and adherence of tablet and liquid formulations	Mean and 95% Confidence Intervals or Median and interquartile range were calculated and used to describe global acceptability of the two formulations. The correlation between acceptability and each domain was calculated and a multiple linear regression model was estimated. This was used to identify which of the MAQ domains predict global formulation acceptability.
Vallet et al[121] (2018)	France	To confirm the validity of a multivariate approach towards assessing medicine acceptability and to develop a decision support tool for this multi-dimensional concept	Multicentre, cross-sectional observational study	1079 older patients in hospitals and nursing homes (mean age 86.4)	The Healthcare Professional observed medicine use and filled out a standardised questionnaire consisting of measures describing acceptability	The observational procedures were explored using mapping and clustering to summarise the information into a reference framework. This involved using a multivariate data analysis procedure, using the R packages "FactorMineR" and "MissMDA." Resampling statistics were also used to validate the model's reliability.

Table 2.4 Findings in relation to formulation characteristics

Author/Year of Publication	Oral Solid Dosage Form	Formulation Characteristic	Key Findings	% Patients Over 65	%Patients Over 60	Mean Age
den Uyl et al [122] (2009)	Chewable Tablets and Sachets	Taste	The mean acceptability score for taste was higher for the tablet than for the powder. There was an overall significant preference for the chewable tablet.	59.4		66
Heikkilä et al[127] (2011)	Tablets and Capsules	Shape Colour "Splittability"	External characteristics including the shape and colour were less significant than the familiarity of a medication, especially for older people.		39	54
Hofmanová et al[123] (2019)	Tablets	Coating Roughness Stickiness Slipperiness Palatability	Older people were able to distinguish between a coated and uncoated tablet. Coated tablets were more acceptable and stickiness and roughness were most strongly linked to tablet acceptance. Palatability was not found to be associated with acceptability.	38.6		N/A
Jones et al[124] (2000)	Softgels, compressed tablets, gelatin coated tablets, hard shell capsules	Shape	The clear oval softgel was preferred most often, followed by the clear oblong softgel. The round compressed tablet was the least preferred.		36	N/A
Kelly et al[82] (2010)	Tablets and Capsules	Shape Size	Torpedo-shaped tablets or capsules were preferred.		100	N/A

		Coating Texture Taste	Small tablets were generally easier to swallow; however, small round tablets were also troublesome. A smooth coating was preferred. A "chalky" texture was described as troublesome. Taste was not a major issue unless tablets were crushed.		
Liu et al[106] (2016)	Tablets, Hard Gelatin Capsules, Mini-tablets, Granules, Dispersible Tablets, ODTs, Chewable tablets	Size Shape Taste Appearance	Sizes of 11mm and 13mm started to cause difficulties swallowing. Mini tablets (4mm) were considered easier to swallow; however, concerns were raised in relation to seeing and handling. Oval and oblong shapes were considered slightly easier to swallow than flat round and arched. There were concerns on taste for all dosage forms (apart from tablets and capsules). There were concerns on the appearance of granules.	100	74.0
Marquis et al[83] (2013)	Tablets, Effervescent tablets, Chewable tablets, Powders, Granules	Size Coating Taste Shape	Size was the most commonly reported cause of swallowing difficulties- 63% of people with past/ ongoing swallowing difficulties said size was the main cause. Coating was the second most commonly reported cause of swallowing difficulties, with		66.5

			29.3% reporting difficulties with a "sticky tablet". 10.9% of those with past or ongoing difficulties said the "bad taste or smell" of the tablet was the cause of this. The main drawback of powders and granules was their taste. Shape was not mentioned as a trigger of swallowing difficulties.		
Notenboom et al[117] (2014)	Tablets Dispersible tablets	Appearance Break Marks Size Taste	Difficulties distinguishing between different strengths due to similarities in appearance led to discomfort and clinical deterioration. Breaking of tablets were reported as difficult or painful. 60.7% of problems relating to the taking of medicines were caused by the medicines lodging in the mouth or throat. 35% of problems relating to the taking of medicines were caused by the flavour of medicines, including ferrous fumarate.	100	78.4
Notenboom et al[118] (2017)	Tablets Dispersible tablets	Dimensions Surface Texture Appearance Break Mark Taste	29.6% of use difficulties were due to the dimensions of the dosage form, including problems holding the medicine and problems swallowing. 18.5% of use difficulties were due to the surface texture, which led to problems swallowing and medicines becoming stuck in the throat. Of the 16 medicines that became stuck in the throat, 11 were uncoated tablets.	100	78.4

			3 use difficulties and 7 use errors were the result of the appearance of OSDFs which led to difficulties distinguishing between tablets. 3 use difficulties and 5 use errors were due to break marks not functioning well. 6 use difficulties and 4 use errors were due to the unpleasant taste.			
Phillips et al[119] (1992)	Tablets	Coating	50% of patients reported no preference for a coated or uncoated formulation. Of those who expressed a preference, 79% preferred the film coated tablet, the main reasons being that it was "smoother" and "easier to swallow".		100	82
Rees, T. P. & Howe, I.[101] (2001)	Chewable Tablets	Taste Chewiness Grittiness Chalkiness Ease of Swallowing Stickiness	Two high dose preparations of calcium and vitamin D were compared: Calcichew D3 Forte (CDF) and Ad Cal D_3 (ACD). While these were similar in terms of dose and active constituents, there was a statistically significant difference in all scores except taste, indicating one formulation (CDF) was more acceptable than the other (ACD); overall 79.8% of patients stated a preference for CDF, 10.6% preferred ACD and 9.6% had no preference.		100	72.6
Reginster et al[125] (2005)	Chewable Tablets and Sachets	Taste	Mean acceptability score higher for the tablet than for the powder, however taste scored the lowest overall acceptability score out of all 5 acceptability variables. Overall significant preference for the chewable tablet; 73.3% of patients aged over 65 preferred the tablet.	56.3		66

Rodenhuis et al[126] (2003)	Scored Tablets	Score Line	A total of 24 out of 51 negative evaluations of the score line was reported in patients aged 60 and above, mainly due to a combination of “unequal halves,” “crumbs” and the tablet being “difficult to break.” The authors report that it was not possible to detect any significant differences between the groups 20-40 years and 60-75 years however this was not proven statistically.	50	N/A
Schiele et al[84] (2013)	Tablets and Capsules	Size Surface Shape Flavour	74.6% of difficulties related to the dosage form were due to size, however acceptable size was related to the shape e.g. swallowing difficulties were only slightly more frequent with oval tablets that had a length of almost twice the diameter of circular tablets 70.5% of difficulties related to the dosage form were due to surface. 43.5% of difficulties related to the dosage form were due to shape- hard gelatin capsules, soft gelatin capsules and oblong tablets caused a greater number of problems in comparison to round and oval tablets. 22.1% of difficulties related to the dosage form were due to "flavour". **NB**: The older people included in this study reported fewer swallowing difficulties. Therefore, they reported fewer preferences for dosage form characteristics- e.g. approximately 70% of patients without		61.8

			swallowing difficulties reported no preferences for the shape of OSDFs.		
Scott et al[120] (2018)	Tablet	Taste Appearance	When exploring the convenience, taste, appearance, efficacy and tolerability of the tablet versus the liquid, the median scores for both formulations were similar- there were no significant differences between the two formulations. The median global acceptability score was marginally higher for the tablet formulation, and the two factors that made a significant contribution towards predicting global acceptability of the tablet were taste and appearance.	100	N/A
Vallet et al[121] (2018)	Divisible tablet, Coated tablet, Divisible coated tablet, Capsule Tablet, Orally disintegrating tablet	Taste Size	13% of patients (140 patients) required the dose to be divided as it could not be taken whole. 19% of patients (205 patients) required the use of food or drink to mask the taste or ease swallowing. When exploring medicine "Y," differences in subpopulations of patients were found, with a higher acceptability in older patients without swallowing disorders.	100	86.4

The dimensions of the dosage form were studied in more detail in older people with dysphagia. A study with a total mean population age of over 65 found that "Tablet size was too big" was the most common cause of ongoing and past swallowing difficulties, reported by 46% of participants [83]. Studies comparing older adults with and without dysphagia found differences in results; 40% of older people without dysphagia deemed themselves to have no difficulties swallowing any of the capsule sizes presented, compared to only 6% with dysphagia [106]. Specifically, sizes of 11 mm and 13 mm were found to start causing difficulties in older people with dysphagia [106]. This led to patients with swallowing difficulties modifying dosage forms more often [121]; 19% of patients without swallowing difficulties modified the dosage form (crushed, halved or chewed) , compared to 80% of patients with swallowing difficulties (all of whom crushed the dosage forms) [121].

The presence of dysphagia was also found to influence whether older people had any preference for shape. Two studies reported that the older population reported fewer swallowing difficulties than younger people [84,123], and one of these went on to state that of patients who were not affected by swallowing difficulties, 69.7% did not care about tablet shape [84]. This is supported by a further study conducted exclusively in older people, which found that older people without dysphagia had fewer preferences for a particular shape [106]. In contrast, older people with dysphagia had a preference for "torpedo" shaped tablets or capsules: "the small torpedo-shaped capsules, which I think are by far the easiest to digest" [82].

The modification of oral solid dosage forms to reduce barriers due to the dimensions is often dependent on the presence of a break mark; however, difficulties can arise when the break mark does not function well, leading to use errors [118]. These include the tablet breaking into unequal portions/crumbling and unintended breaking of the tablet when removing it from the blister: "This one often breaks. When I push it out. Look because it has a line. A score line. And that one snaps almost every time" [118]. Management techniques, including taking unequal halves, were found to have the potential to result in severe discomfort or clinical deterioration [117]. These findings were supported by a further study investigating patient experiences with the performance of tablet score lines [126]: a total of 24 out of 51 negative evaluations of the score line were reported in patients aged 60 and above and the majority of these were due to a combination of "unequal halves," "crumbs" and the tablet being "difficult to break" [126].

2. Palatability

a. Texture, Mouthfeel and Coating

The surface texture was the second most commonly reported cause (relating to the dosage form) of swallowing difficulties in people with dysphagia, with 70.5% of participants identifying a problem with

this feature [84]. Surface characteristics further contributed to 18.5% of "use difficulties" (situations where the participant can complete a task but only with difficulty) in the general older adult population [118]. Participants used the term "chalky" to describe the texture of tablets that were difficult to take and further associated these tablets as being "cheaper to make" [82]. "Chalkiness" was also a variable that was directly measured to assess the acceptability of chewable formulations using the Visual Analogue Scale, alongside grittiness, ease of chewing and stickiness [101]. Higher acceptability scores for these variables were linked to overall preference, highlighting an overall preference towards "Not chalky at all" chewable formulations [101].

The coating of the formulation is also important in determining the texture and mouthfeel, and further impacts swallowability. In one study, 11 of the 16 occasions when the medicine became stuck in the mouth or throat occurred with uncoated tablets [118]. Comparing the preference for film coated tablets versus uncoated tablets found that of those that expressed a preference, 79% preferred the coated tablet [119]. Furthermore, patients taking uncoated tablets were found to require more water to swallow the tablet, took longer to swallow, and reported a higher incidence of the tablet being lodged within the oesophagus [123].

In addition to whether or not a tablet is coated, the nature of the coating is important in determining the acceptability, and is evaluated on smoothness, stickiness, slipperiness and palatability [123]. Paracetamol formulations that often have a "rugged coating" were most commonly reported as being the most difficult to swallow [83]. Furthermore, tablets with a "sticky coating" were reported to be the second most common cause of ongoing/past swallowing difficulties [83]. A smooth coating was therefore preferred; of the 41 older people preferring film coated tablets, 36 reported that preference was based on the formulation having a "smoother surface" and/or being "easier to swallow" [119].

b. Taste

Some active pharmaceutical ingredients have an inherently bitter taste, and the impact of this on acceptability was explored by several studies. Ferrous fumarate was one example of a drug that required taste masking with food: "Nowadays I take those that don't go down well with a little yogurt. I do this with the large one but also with the small ones, because one of them is bitter. And this is usually quite unpleasant"[117]. Further studies found that in 19% (205) of 1079 evaluations, older people used food or drink just before or after administration to mask the taste or ease swallowing of a range of formulations, including divisible and coated tablets [121].

Medications are often modified for people with swallowing difficulties, in whom the "bad taste/smell" of tablets was the 4th most commonly reported cause of swallowing difficulties, after size, surface, and "tablet stuck in throat" [84]. The need for taste masking was increased when medications were

crushed and older people with dysphagia used various substances such as milk, apple juice, bread, tea, and fruit smoothies to mask the “horrible” taste [82].

Alternative solid dosage forms, such as chewable tablets and granules are commonly used for people with swallowing difficulties; however, the taste is significantly more important for these formulations as they spend longer in the oral cavity. Taste was, therefore, consistently measured as a variable that would impact overall acceptability of these formulations using scales such as the 5-variable acceptability questionnaire and Visual Analogue Scale [101,125,128]. Whilst the taste of the chewable tablet was preferred to that of granules, comparing scores for all five acceptability variables (including taking the dose, time spent taking, removing the dose from the container and general convenience of taking) found that taste was given the lowest overall acceptability score [125,128]. 68.8% of patients rated the taste of the chewable formulation as 9 or 10 on the acceptability questionnaire, whilst the other four variables were rated as 9 or 10 by over 80% of patients [125]. The unpleasant taste of chewable formulations led to some older people swallowing the tablet whole instead of chewing [117] and the issue of taste was also highlighted as a drawback of dispersible formulations [83,106,118]. These results highlight taste as a significant challenge when developing these oral dosage forms.

The relationship between the taste and acceptability of traditional tablets was explored using the Medicine Acceptability Questionnaire and taste was found to be significant in predicting the acceptability of an alendronic acid tablet formulation [120]. Further studies also explored the “palatability” of coated and uncoated tablets, and found that palatability relates to the texture and mouthfeel (theme 2a) but is also often related to the appreciation of taste [123]. This study found acceptability scores for palatability were clustered in the middle of the scale, with patients having no strong opinion [123]. This may have been the result of using a tasteless formulation, leading to no association between palatability and acceptance [123]. The authors note that the presence of a bitter drug would lead to a significant association between palatability and acceptance, with patients finding it less acceptable [123].

3. Appearance

The number of medicines and complexity of the regimen both affect medication adherence [82] and can be further complicated when considering the appearance. Difficulties distinguishing between different strengths due to similarities in appearance led to discomfort and clinical deterioration [117], although sometimes additional markings such as embossments could help patients differentiate tablets [118]. Smaller tablets, including mini tablets, were also highlighted by older people as being difficult to see, especially for those with visual impairments [106].

The appearance of the oral solid dosage form is also significant in determining an older person's willingness to take medication. The dimensions determine swallowability (theme 1) but also have an important impact on acceptance prior to tablet ingestion. Whilst smaller tablets can lead to difficulties identifying the tablet [106], the large size of some formulations can lead to a psychological block and anxiety prior to taking tablets: "I cannot go through this again, I just cannot take it. End of story!"[118].

The type of dosage had an impact on appearance. Concerns were raised in relation to the appearance of granules, which were considered the least acceptable "alternative dosage form" alongside chewable tablets in older people [106]. Furthermore, when comparing tablet and liquid alendronic acid formulations, there was a general trend for the liquid to perform better in terms of appearance, although this difference was not statistically significant [120].

Colour is sometimes also used as a differentiation tool, although a preference survey conducted across ages found colour to have little importance [124]. This was, however, a consumer preference survey primarily looking at preference for soft gels rather than the impact of colour. A further study found external characteristics, including the colour of prescription medication, were less significant than familiarity although this was within the context of generic substitution [127]. No study was identified that directly investigated the impact of colour on acceptability of oral solid dosage forms within the older population.

2.13. Discussion

2.13.1. Summary of key findings

The major finding of this systematic review was the small number of studies directly investigating the impact of formulation characteristics on acceptance and adherence within the older population. The inclusion criteria for the study were broad, including studies that investigated formulation indirectly as well as those including the wider general adult population. Extracting relevant data from all studies identified resulted in the categorisation of characteristics into three inter-related topic areas: dimensions, palatability and appearance. No study was identified which explored formulation characteristics across all three categories directly in the older population. Formulations that do not take into account these considerations can lead to the use of techniques to overcome difficulties, such as taking unequal halves and taste masking with food; however, these have the potential to cause serious clinical deterioration.

2.13.2. Comparison to other studies

As far as we are aware, this is the first systematic review that has focussed on how the characteristics of oral solid dosage forms affect adherence and acceptance in the older population. A preliminary review to identify scientific evidence and studies investigating the appropriateness of medicinal products for older patients was conducted in 2015 [4]. Rather than focus on the physical characteristics of oral solid dosage forms, this preliminary review looked at the "appropriateness" of all medicinal products, including the route of administration, drug delivery technology and frequency of dosing [4]. The authors defined appropriateness as: "a means to evaluate the suitability of the pharmaceutical design of a medicinal product for use in and by the targeted age group or patient population" [4]. Both the present review and this preliminary review support the urgent need for further research within the older population, with the present review highlighting a specific gap in the literature in relation to formulation characteristics.

Previous work has tested the acceptability of tablets in adults aged 18-45 years by investigating preferences for the shape, size and colour of different placebo 3D printed tablet models [130]. Three-dimensional printing provides the opportunity to obtain personalised doses, on-site and on-demand [131] and allows for different geometries to be tested, including torus, sphere and tilted diamond shapes [130]. Results in this population found that perception of size was driven by the type of shape, supporting the findings of this review [130]. Results further found that colour affected the perception of the end-user, with black and dark green deemed to be the least favourable colours [130]. Only one study in this review studied the preference for different colours, stating that "colour had little importance" however this was not conducted exclusively within the older population [124]. Further work is required to explore which, if any, colours are preferred within this population.

In addition to the effect on acceptability, colour has an important role in medication recognition; other studies found bi-chromatic dosage forms (those with two colours) could be identified almost immediately [102]. Older people, in particular, often use external characteristics rather than the product label to recognise their medication [3] and the use of multiple medications increase the likelihood of a preference towards brightly coloured tablets [13]. The risk of clinical deterioration due to similarities in appearance was supported by only one study in this review [117], highlighting the urgent need for further research in this area.

The oesophageal transit of oral solid dosage forms is dependent on size and shape [132,133] and this review provides further support on the impact of both of these characteristics on swallowability [84,106]. Previous studies have found that the lack of appropriate, licensed dosage forms results in clinicians routinely modifying oral dosage forms to meet older patients' needs [28] and this review

provides evidence that older people also modify dosage forms themselves. Instead of obtaining support from care support, older people use characteristics such as the break mark to modify dosage forms and aid swallowability; however, this can affect the stability, safety and efficacy of the drug [134].

Older people also modify dosage forms to improve the taste and the present review has found that "palatability" has been the most extensively researched characteristic; 13 of the 16 included studies explored some aspect of palatability. This is partly due to the investigation of alternative oral solid dosage forms such as chewable tablets, powders and granules. This review supports the correlation between palatability and acceptance for these dosage forms. However, the review also found a clear link between palatability and the swallowability of traditional tablets and capsules. The importance of palatability has been frequently linked to paediatric formulations, with taste being cited as the most important factor determining acceptability in this population [19]. Optimising palatability for the older population can also contribute towards more age appropriate medication. Improving palatability through, for example, the use of a film coating can aid in taste masking, improve texture and further provide moisture protection [135].

This review is of particular relevance for clinicians working with older people; 1 in 9 older community dwelling adults have symptoms that amount to dysphagia that are likely to be under-reported and under-recognised [136]. Older people with degenerative neurological conditions such as dementia are at highest risk of dysphagia as the cognitive impairment impairs their feeding and swallowing abilities, however dysphagia is again often not recognised in these patients [137]. As patients rarely report any difficulties, healthcare professionals should proactively enquire about practical problems [82,83,117]. Pharmacists in particular can then use this information to select a dosage form that causes fewer swallowing difficulties [84,117]. Where no suitable oral solid formulation is available, this may involve collaboration between professionals to provide an alternative such as a liquid formulation. However, there is a greater need to ensure acceptable palatability for these preparations and studies have found that liquids are a suboptimal alternative to oral solid dosage forms in patients with swallowing difficulties [138]. Healthcare professionals must therefore work closely with patients to understand their attitudes towards their treatment and share decision making on formulation choice with older patients.

2.13.3. Strengths and Weaknesses of the study

This systematic review was conducted by an inter-disciplinary team with expertise in both formulation and clinical pharmacy. It used standard systematic methods to conduct an extensive literature search and screen relevant studies. The protocol was registered on PROSPERO prior to screening the results

to reduce the potential for bias. However, a key limitation is the inherent lack of research in this area. The inclusion criteria for the study were broad, although only five studies were identified that directly investigated this phenomenon in the population of interest [101,106,119-121]. The limitations of the included studies were: variable quality; two randomised crossover studies [119,125] and two quantitative descriptive studies [124,126] were rate poorer quality. Some studies did not report sufficient details for a more detailed analysis of the results [84]. The studies that scored highest in methodological quality were qualitative studies; however, these studies did not explore formulation directly [82,117,118] highlighting the paucity of qualitative studies directly investigating this topic in older people. Furthermore, there was a lack of data on ethnicity and on whether improvements in formulation led to any changes in clinical outcomes. Five studies were found to be sponsored by or receive funding from the pharmaceutical industry, which may further influence the results [120,122-125]. Research was mainly conducted in affluent countries and the inclusion of English language studies only may limit generalisability. Despite these limitations, this systematic review has brought together the current evidence relating to the formulation of oral solid dosage forms in older people, and has highlighted the need for further research in this area.

2.13.4. Future research

The three qualitative studies identified gave a deeper insight into the challenges older people face when managing medication, however all focussed on general medicine taking practices rather than a direct investigation of formulation. Nevertheless, the answers provided within these three studies highlight the importance of tablet characteristics when considering the medication management process. In-depth, focussed qualitative work should aim to specifically focus on formulation characteristics that will help to improve acceptance and adherence within this population, looking in particular at the three categories identified from this review.

Medication optimisation within the older population is complex, and requires a multidisciplinary approach [6]. The systematic review found a single study that involved GPs in which their awareness of swallowing difficulties was assessed [84] however no studies were identified that involved formal or informal caregivers; a major gap in the literature. Whilst the majority of studies in the review did not directly involve healthcare professionals or caregivers, a large number highlighted the importance of a multidisciplinary approach, including the need for healthcare professionals to actively enquire about difficulties [82-84]. Future research must therefore involve both informal carers and health and social care professionals to ensure gaps in perceived responsibilities in relation to medication optimisation can be addressed.

Eight of the sixteen studies included in the review included younger adults and the findings highlight preferences for dosage forms that are easy to swallow [83,84,123,124]. It would therefore be valuable for future research to consider a patient centric drug product for older people in comparison to that for the general adult population. This can highlight any significant differences and may further result in a QTPP that can improve adherence in other population groups.

2.14. Conclusions and Implications

Adherence to medication is complicated by a number of drug-therapy associated factors in older people, namely the number of medications, duration of treatment, tablet characteristics and the dosage regimen. While the majority of these are difficult to modify, ensuring that patients receive an acceptable formulation is a key intervention that can help reduce non-adherence. Manufacturers must take into account the practical problems older people may encounter when considering the dimensions, palatability and appearance of the final drug product. These characteristics should be optimised to aid visual identification and swallowability. Medical providers and pharmacists have an important role in ensuring that these patient centric drug products are prescribed and dispensed appropriately so that patients receive the most suitable formulation. Future work must therefore take a multidisciplinary approach so that gaps in perceived responsibilities in this area can be identified and addressed.

The findings from this systematic review informed the follow-on work conducted as part of this PhD. The paucity of qualitative research identified in this review led to semi-structured interviews being conducted to aid the development of an acceptable formulation for older people (Chapter four). The importance of a multidisciplinary approach further led to a focus on ensuring a range of health and social care professionals were interviewed (Chapter five). The next Chapter discusses in more detail the methodological approach taken towards conducting these interviews and further explains the rationale for undertaking semi-structured interviews supported by the use of placebo tablets.

Chapter 3- Research Design and Methodology

3.1. Introduction

The systematic review in Chapter 2 identified previous studies in this topic area and highlighted the paucity of qualitative research as well as the need to include all those involved in an older person's therapy. This chapter will detail the methods chosen for the next phases of the project and describe the rationale behind choosing a qualitative approach, specifically semi-structured interviews alongside the use of placebo tablets. The chapter will start by exploring qualitative research in comparison to quantitative research and will then go on to describe the specific approach taken for the research presented in this thesis.

3.2. Quantitative versus qualitative research

When considering the research process, there are two main "world views" that determine how investigators frame their research in their attempt to discover knowledge [139]. The first is underpinned by an objective reality. Truth and meaning exist independently to the mind of the investigator; contextual factors are removed and phenomena are studied independently [140]. The generation of knowledge is independent of the researcher's values, interests or interpretation [141]. Instead, there is an emphasis on precision, reliability and predictability [142]. The second view is underpinned by a subjective reality, in which there is no right or wrong truth, rather an attempt is made to understand the knowledge, purpose and values of individuals. The researcher attempts to lessen the distance between himself or herself and the research topic, becoming an "insider" as they spend time in field [143].

These two world views roughly characterise the "quantitative versus qualitative" divide [142]. Qualitative research is a form of inquiry that is used to capture data about beliefs, values, motivations and feelings that underlie behaviours [144]. It is used to learn directly from patients what is important to them, and to identify variables that are important to consider in future studies [144]. Quantitative research, in contrast, is focused on explaining phenomena by collecting numerical data that are analysed using mathematical methods, particularly statistics [145]. Examples include correlational research, surveys and experimental research [145]. While qualitative research aims to understand a phenomenon, quantitative research in general aims to generalise the truth to the wider population [145].

While the two approaches differ, both qualitative and quantitative research share the same values where the quality of the process is emphasised [146]. In quantitative research, an emphasis is placed on standard measures, replicable findings, successful predictions and minimisation of bias [142]. Qualitative researchers emphasise the need for field journals, prolonged immersion, discussion with

experts in the field and exploration of changes in the investigator's point of view [142]. When deciding which approach is more appropriate, the pros and cons of both types of data should be considered in relation to the specific research question posed and resources available, rather than on a general abstract level [147]. Questions of rate, magnitude or prevalence yield to quantitative methods while those exploring questions about meaning, value or understanding are more suited to qualitative methods [142].

3.2.1. Implications for this research

The aim of this research was to understand the key issues faced by older people and carers when using/administering oral solid dosage forms and how these issues impacted adherence and acceptance. When considering adherence, objective measures where quantitative data is collected such as pill counts, electronic monitoring and biochemical measures, provide data on whether a medication has been adhered to, without providing data on causes for non-adherence [148]. Subjective measures, where qualitative data is collected, can identify individual patient concerns, allowing for the intervention to then be tailored appropriately [149]. A qualitative approach would provide an insight into human emotions and perspectives [150] which is particularly important for investigations in older people where complex circumstances, such as the presence of caregivers [151] should be considered. This approach was considered more appropriate for the research question, which requires an understanding of individual preferences on formulation characteristics and why certain characteristics may be more or less preferred.

The importance of a qualitative approach was further highlighted by the systematic review in Chapter two, where preferences for characteristics were found to be dependent on a number of factors. The presence of dysphagia, for example, determined preferences for capsule size [106]. Factors such as patient age, ethnicity, medical conditions and setting and how these may impact preferences were therefore important to consider and this would again suit a qualitative approach. There was, from the outset, an understanding that there was likely to be no "single truth" when discussing patient centric medicines but that each participant would have their own reflections based on their individual experiences. Using a qualitative approach would further help increase understanding of the patients' experiences when making decisions about whether to adhere to medication [152].

3.3 Methods

Participant observation, qualitative surveys, interviews and focus groups are common modes of collecting qualitative data [153]. The choice of single or combined methods depends on the research

question and an assessment of whether the chosen method can answer the question effectively, i.e. the fit between question and method [154].

Participant observation is a method that is particularly employed within ethnographic research [155]. It is used to investigate the naturally occurring routines, practices and interactions of a group of people in their social environment [153]. The extent to which the researcher engages in the setting being observed may vary between studies. “Participant as observer” involves the researcher being part of the observed setting, helping them to gain insider views and subjective data, while “observer as participant” involves the researcher having minimal involvement and taking notes from a distance [156]. Participant observation is one of the more time-intensive data collecting strategies, as persistent engagement in field is essential to ensure the complexities of situations are adequately explored [153] and this can lead to increased costs. There is also the potential for the Hawthorne effect, where the subject’s behaviour is altered due to an awareness of being under observation [157]. This method was deemed not appropriate for the research question, as an understanding was required of participants’ experiences with taking oral solid dosage forms which would be better achieved through a verbal discussion.

Interviews are the most common form of data collection [158]. They aim to explore the views and experiences of individuals on specific matters and are particularly helpful when participants may not want to discuss sensitive topics in a group environment [159]. Interviews are appropriate when little is known about the study phenomenon; the researcher is able to listen attentively to the respondent in order to acquire more knowledge about the study topic [160]. There are three fundamental types of research interviews: structured, semi-structured and unstructured [159]. The advantages and disadvantages of each type are summarised in Table 3.1. In this study, a focus on the topic of interest was required while also giving participants the opportunity to respond to questions comprehensively [158]. Semi-structured interviews were therefore deemed the most appropriate type of interview and were used as the primary method of data collection.

Focus groups are a form of interview in which the group interaction is a means to explore the research issue being studied [153]. The discussion is monitored, guided and recorded by a facilitator or moderator [161]. The optimum size is six to eight participants; however, they can work successfully with as few as three and as many as fourteen participants [153]. Too few participants can lead to a limited discussion while larger groups may be chaotic and hard to manage for the moderator [162]. Potential limitations of focus groups include the potential for conflicts to arise leading to problems managing interactions, the need for skilled moderators, and the potential for shallow or poor quality data [163]. Poor data may arise as a result of “groupthink,” where group members involved in a

cohesive group strive for unanimity rather than a more realistic appraisal [164]. However, focus groups are helpful in generating information on collective views, and the meanings that lie behind them [159]. They provide a rich understanding of participants' beliefs and experiences [165] and are particularly helpful when used to clarify or extend data collected through other methods [162]. A focus group was considered as a potential method to expand on data collected during the initial semi structured interviews. During these focus groups, 3D models could be presented and the group interaction would provide useful information on the extent to which the models match a patient centric dosage form for older people.

Table 3.1: Advantages and disadvantages of the three types of interviews [153,159,166,167]

Type of Interview	Description	Advantages	Disadvantages
Structured	A "verbally administered questionnaire." Pre-determined questions are asked with no variation and no scope for follow up questions.	Relatively quick and easy to administer.	Only allow for limited responses and therefore not helpful if depth is needed. Unable to explore interesting leads
Semi-structured	A dialogue between the researcher and participant, guided by a flexible interview schedule and supplemented by follow up questions and comments.	Provides participants with some guidance on what to talk about. Allows for elaboration and discovery of information that may not have previously been thought of as pertinent by the research team.	Difficulty interviewing participants can affect novice researchers. Problems can arise when the interviewer does not effectively ask follow-up questions or listen attentively. Extensive resources required for recruitment, transcription and analysis.
Unstructured	Conducted in an everyday conversational style with little or no structure. Participants take the lead in telling their stories rather than the	Useful when significant depth is required. Helpful when virtually nothing is known about the subject area.	Very time-consuming, often lasting several hours. Extensive resources required for recruitment, transcription and analysis.

	researcher directing the interview.	Can be difficult to manage due to the lack of pre-determined questions which many participants find difficult or unhelpful.

3.3. The use of data triangulation in qualitative research

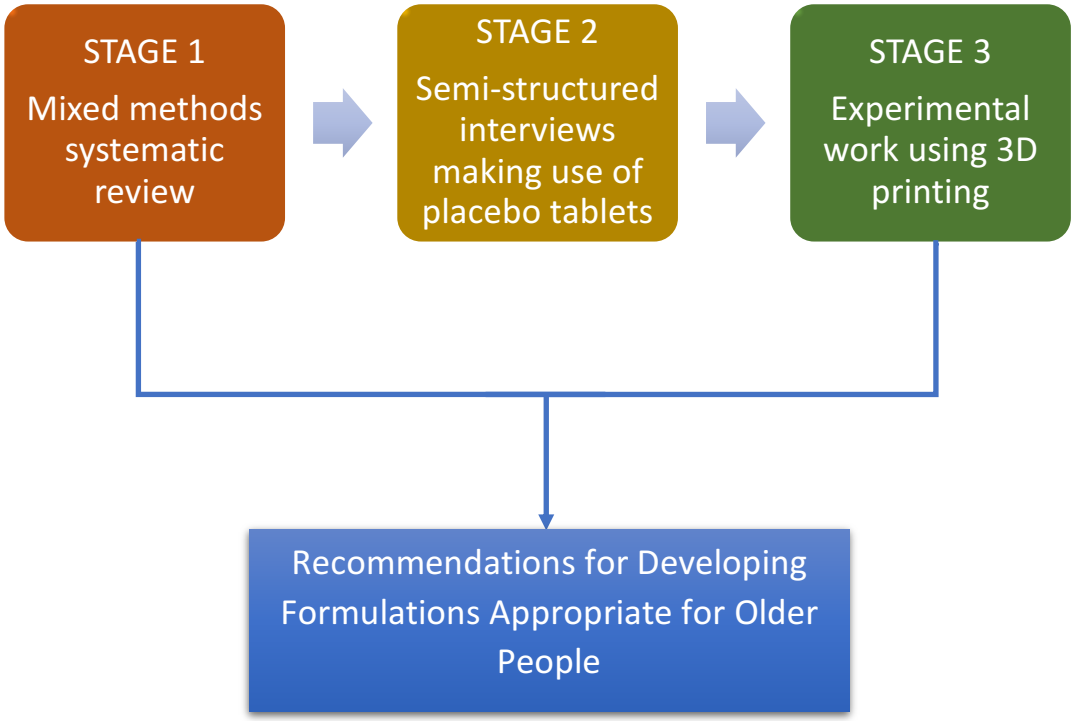
Triangulation is a research strategy that can be used to enhance the rigour of research [168]. It involves the use of multiple methods or data sources to develop a comprehensive understanding of the phenomenon of interest [168]. Four types of triangulation have been identified: method triangulation, investigator triangulation, theory triangulation and data source triangulation [168,169]. Method triangulation involves the use of multiple methods to collect data in relation to the same phenomenon, while investigator triangulation involves the use of more than one researcher to review findings [168,170]. Different theories can also be used to help support or refute findings (theory triangulation) and data can also be validated through the collection of data from multiple sources using a single method (data source triangulation) [170], for example pre and post intervention questionnaires or data collected from multiple settings.

Method triangulation is a helpful tool to increase the validity of study findings [170]; inconsistencies or variation in the data collected from different methods can provide a deeper understanding of the phenomenon of interest [168]. The present study aimed to adopt method triangulation by conducting the study in three stages, each of which used different methods to collect data in relation to patient centric dosage forms for older people. The first stage, a mixed methods systematic review, would provide a detailed understanding of previous work in this area and would highlight areas that need targeting in future research. The next stage, semi structured interviews, would explore the key issues faced by older people and their carers in further detail and would be used to inform the development of 3D printed tablets. The final stage, experimental work, would aim to develop 3D printed models based on findings from the semi-structured interviews.

Future work in which these models are presented to participants in the form of a focus group would further complement the initial findings from the semi-structured interviews. Previous studies using method triangulation through the use of interviews and focus groups have found that the nature of data collected by these two methods differs. Interview participants are more likely to discuss sensitive topics [171] whereas the “dynamic and interactive exchange” between focus group participants can lead to the expression of “multiple stories and diverse experiences” [172]. Focus groups and interviews

therefore can provide different perspectives and the two approaches are complementary [171]. The potential to use focus groups in follow up, postdoc work will be discussed further in Chapter 7. The proposed programme of work for this PhD has been summarised in Figure 3.1. The mixed methods systematic review was covered in detail in Chapter 2. The following section will focus on the details in regards to the semi-structured interviews.

Fig 3.1. Proposed programme of work



3.4. Semi-structured interviews making use of placebo tablets

3.4.1 Interview schedule and placebo tablet development

Development of the interview schedule is an important first step in the construction of the interview process [173]. The interview should start by asking easy questions, such as demographic information, followed by essential questions which concern the main focus of the study [173]. The interview schedule should be tested either with other researchers or people familiar with the topic in question so that unclear or inappropriate questions can be identified [174] and also on the target population.

In this study, the interview schedules for older people, carers and health and social care practitioners were developed through informal discussions with patients and care staff, the researcher's experience as a practicing pharmacist and through discussion with supervisors (see Appendix 6). Interviews

started by asking basic demographic questions before going on to discuss the characteristics of oral solid dosage forms. The schedules were pilot tested with a pharmacist and with an older person to refine the questions and also to identify any specific methodological issues. The interview schedule was used as a guide, however there were planned supplementary questions and these were asked based on the responses of participants. The primary aim of these interviews was to provide an insight into the issues experienced by older patients and informal/family carers when using/administering oral solid dosage forms, and to also compare these views to those of health and social care professionals.

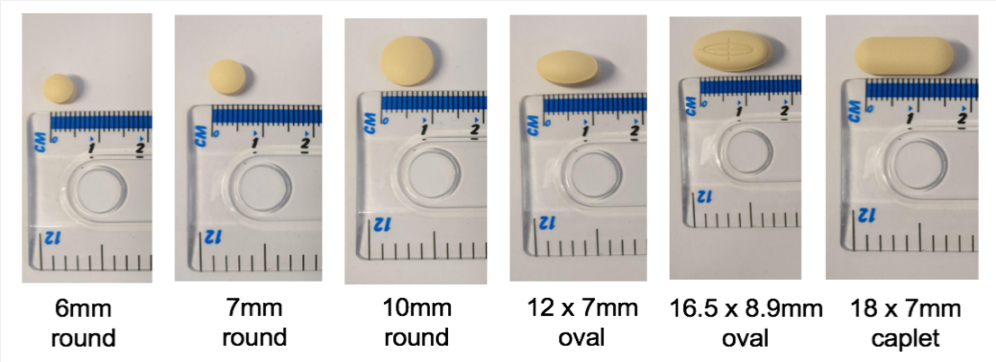
In addition to the interview schedules, the study made use of placebo tablets to provide participants with a point of reference to communicate their ideas. While participants also had the opportunity to refer to medications that they were currently taking, these placebo tablets were used to provide some consistency to the results. The placebo tablets were made in partnership with Colorcon who co-sponsored this project. Colorcon is a pharmaceutical manufacturing company supporting the development, supply and technical support of formulated coatings and other excipients for the pharmaceutical industry. They provide formulation development assistance and have experience in safety by design to target patient adherence [175].

The placebo tablets were monochrome in colour (yellow). The colour was chosen following a discussion with colleagues at Colorcon who highlighted that this shade is most commonly used (after white) and is a neutral option that would help trigger a dialogue around the use of colour in oral dosage forms. Members of the team at Colorcon also advised on the most commonly used shapes in their experience. These were chosen so that patients would be familiar with these from taking their own medication. Round and oval are two of the most commonly used shapes and so the majority of tablets created were round and oval.

In addition to using the expertise from the team at Colorcon, the characteristics of the placebo tablets were informed by the literature. Previous studies in adults have found that tablet sizes greater than approximately 8 mm in diameter are associated with an increase in the number of patient complaints [176]. This included retention of tablets within the oesophagus and the need to wash down tablets with a further drink after they were retained for five minutes [176]. Furthermore, studies in healthy volunteers (under the age of 65) have found that oval tablets are easier to swallow than round ones, especially if they are large [132]. In order to explore this further in the older population, placebo tablets of sizes both greater than and less than 8 mm were made available to participants alongside oval, caplet and round shaped tablets.

The placebo tablets that were used in this stage can be found in Figure 3.2. The tablets were not tasted or swallowed; rather they were used as a reference point so that participants could illustrate their answers. All placebo tablets were presented to participants.

Figure 3.2. Placebo tablets presented to participants in Stage 1



3.4.2. Sampling and recruitment process

Concerns with sampling in qualitative research centre around the importance of discovering the scope and nature of the "universe" to be sampled; qualitative researchers aim to explore what the various components of the universe are so that they are able to provide a valid representation of it [177]. This is in contrast to quantitative research, where a greater emphasis is placed on numbers and how many cases or observations are required for a valid representation [177]. The most common approach in quantitative studies is to use random, or probability samples; all members have an equal chance of selection and the larger the sample size, the smaller the likelihood of a random sampling error [178]. However, this approach would not be suitable for a qualitative study: values, attitudes and beliefs form the core of qualitative studies and these would not be normally distributed across a population [178]. The three broad approaches that are more suitable for qualitative studies include convenience sampling, purposeful sampling and theoretical sampling [178].

Convenience sampling is a sampling strategy in which participants are selected based on their accessibility [179]. While this strategy is the least time intensive and least costly, a clear limitation is the difficulty to generalise results to any target populations, with characteristics such as sociodemographic variation being unaccounted for [180]. Purposeful sampling is a commonly used method within qualitative research in which information rich cases are selected for study in depth [181]. These information rich cases are those from which details on the phenomenon of interest can be collected. Patton suggests that all types of sampling in qualitative research is purposeful and details 15 strategies for selecting information rich cases [182]. These include sampling methods such as

maximum variation sampling and snowball sampling [182]. The final approach, theoretical sampling, allows for flexibility during the sampling process; sampling is directed by an emerging theory and data is collected that can elaborate and refine this theory [183]. This is the principal sampling strategy used within grounded theory [184].

The sampling approach taken in this study used a combination of convenience and purposive sampling. There is an element of convenience sampling in all qualitative studies [178] and this approach was partly used to recruit participants that were easily accessible to the researcher, for example NHS trusts and CCGs (Clinical Commissioning Groups) were selected that were in or around the West Midlands. Maximum variation sampling, a form of purposeful sampling [185], was also used in order to identify patients and carers with a range of characteristics that may affect their responses. As the sample was not limited in terms of the clinical condition, ethnicity, location or socio-economic grouping, participants were actively sought that represented a diverse population in order to aid the generalisability of the results. The sample of older people was not limited by the number or class of medications being taken, rather there was an aim to include as wide a range of clinical conditions as possible. There was also an aim to include older people and their carers from a range of ethnic backgrounds and from a range of settings to include community, hospital and care homes. Purposive sampling was used to target these areas to aid generalisability of the results. Health and social care professionals were also recruited using maximum variation sampling so that participants were recruited from a range of settings (including care homes and secondary care again) and had varying degrees of experience to aid generalisability of results.

The NHS Organisations that were involved in identifying participants included NHS Birmingham and Solihull CCG, University Hospitals Birmingham NHS Foundation Trust, University Hospitals of North Midlands NHS Trust, NHS Dudley CCG and NHS Southern Derbyshire CCG. Care Homes enrolled with ENRICH (Enabling Research in Care Homes) and those registered with the RMBI (Royal Masonic Benevolent Institution) were also used to recruit older people in care homes as well as social care professionals. The study was advertised on recruitment websites, including Join Dementia Research and People in Research, and participants were also recruited who contacted the research team as a result of PPI (Patient and Public Involvement) activities such as social media activities.

The research was advertised to potential participants using recruitment material and/or NHS and other link staff. The recruitment material included a template email that was sent out to help recruit potential professionals (Appendix 7). A poster and newsletter were sent out by NHS organisations to recruit patients and carers and these were also advertised on the recruitment websites (Appendices 8 and 9). [The newsletter was updated later in the study and sent to participants from Stage 1 who

were interested in taking part in the focus group (Appendix 10)]. Participants were invited to contact the researcher should they be interested in taking part in the study. Participants who expressed an interest in taking part were provided with a copy of the Participant Information Sheet (see Appendix 11). They were asked to contact the researcher after having read the information sheet should they be interested in taking part. Participants who were recruited by NHS/other link staff were also first provided with an information sheet prior to confirmation of participation.

3.4.3. Sample size

The number of participants within a qualitative study requires careful consideration; too large a sample size can lead to superficial or unmanageable volumes of data, whereas too few participants can risk adequate depth and breadth [186]. Qualitative researchers should justify the sample size on the grounds of quality data and this should be reflected within the study's findings [187]. The sample size is therefore decided following data collection and is dependent on "redundancy of information" or "saturation" [146]. This approach involves sequentially conducting interviews until no new concepts or themes are discovered [188,189]. In this way, the stages of data sampling, collection and analysis are combined rather than treated separately in a linear process [190].

The concept of data saturation has, however, led to much critical discussion [189]. Braun and Clarke state that coding is a reflexive, organic process and analysis can never be truly complete [191,192]. It is therefore necessary for the researcher to make a situated, interpretative judgement about when to stop coding and move to theme development, and when to stop theme development and move to the final written report [191]. Previous qualitative studies in this area recruited between 11 and 59 participants [82,118]; however, this sample size included only patients. The present study aimed to recruit patients, informal/family carers and health/social care professionals, therefore a larger sample size would be more appropriate. A sample size of 75 participants was estimated split as 30 older people, 20 informal carers and 25 health and social care professionals. However, the data was regularly analysed to determine the extent to which new data repeated what was expressed in data previously collected [189]. Based on this information, the researcher, in discussion with supervisors, made an interpretative judgement on whether saturation was reached in relation to the purpose and goals of the analysis [191]. A total of 52 interviews were conducted; 18 older people, 7 informal carers and 27 health/social care professionals. The characteristics of included participants can be found in Chapter 4 and more detailed information on the characteristics of older people has been included in Appendix 24.

3.4.4. Conducting the interviews

The interview location should be quiet, private and provide minimal disruption [166]. Often the participant's home is the best location [193]; participants may not be as open in their answers in a strange environment in the presence of many outsiders [194]. In this study, interviews largely took place at a mutually convenient location, such as the patient's home, where the researcher was able to gain a unique insight into the difficulties they face when taking their medication. This further provided the opportunity to illustrate these difficulties with photographs, subject to consent provided by the patient and with the removal of any patient identifiable information. Where it was not convenient to conduct the interview at the patient's home, interviews were conducted in a private room within a public library or at Aston University. Interviews with health and social care staff were also conducted at a mutually convenient location, such as the health/social care professional's workplace. One healthcare professional interview was conducted virtually.

Prior to the interview, the researcher reconfirmed that the participant had read and understood the Information Sheet and provided the opportunity to ask any questions. Once any potential concerns and questions were addressed, participants were given a hard copy of a consent form to read and sign (see Appendix 12).

Throughout the interview, the researcher aimed to build rapport with the participant by listening attentively to the information shared. This is an essential component of semi-structured interviews and includes establishing a safe and comfortable environment for the interviewee to share their personal experiences [195]. As the interview progressed, planned and unplanned follow up questions were used that invited the participant to further clarify, explore or elaborate on their responses [166]. Probing techniques, including repeating the participant's words, remaining silent after asking a question, and using affirming words [196], were used to encourage participants to continue talking. The researcher had experience of using these techniques as a result of conducting qualitative interviews as part of her Masters project and also as a result of attending internal training days on this topic.

3.4.5. Data Handling, Storage and Processing

An Olympus DS-9000 Dictaphone was used to record the interviews and audio files were uploaded as soon as possible to a password protected University laptop. Each interview was re-named with a unique participant identifier number. The interviews were uploaded via a password protected electronic platform to The Typing Works; a professional transcription service that has a contract with Aston University. Following transcription, each interview was checked by the researcher for accuracy.

During the interview, participants often pointed to a placebo tablet in their response and therefore the tablet being referred to was often not picked up by the recording. Field notes were key to updating transcripts with the shape and size of the placebo tablet being referred to in each interview. Once checked and updated, all recordings were deleted from the Dictaphone.

3.5. Data analysis

3.5.1. Choice of thematic analysis as a data analysis tool

The data analysis method should be chosen based on the goals of the research itself [197]. Sandelowski and Barroso offer a useful framework that can be used to compare and contrast qualitative analysis methods [198]. They contend that data analysis methods fall along a continuum that is defined by the extent to which data is transformed during analysis; at one end lie methods in which data is not significantly transformed (resulting in a purely descriptive analysis) and at the other end of the continuum are highly interpretative analyses in which there is a significant transformation of data [198]. Grounded Theory, for example, results in data interpretation and transformation to the point of developing theory [184]. The aim of this research was to connect elements of the data using some data interpretation. Thematic analysis was chosen as the most appropriate data analysis tool; this method most naturally lies near the centre between the two poles of the continuum engaging in more than data description but not extending as far as to develop theory [197].

Thematic analysis is a powerful tool for understanding a set of experiences, thoughts or behaviours across a data set [199]. It is a highly flexible approach than can be modified according to the needs of the study, providing a rich and detailed yet complex account of data [200,201]. Thematic analysis also requires the researcher to take a well-structured approach to handling data and therefore helps in the production of a clear and organised final report [201]. However, this flexibility can also lead to a lack of consistency and coherence during theme development [202]. Researchers who use thematic analysis should therefore provide a sufficient description of the analysis process [200].

3.5.2. Three approaches to thematic analysis

Thematic analysis is used to identify, analyse, organise, describe and report themes [200]. A theme can be defined as “a patterned response or meaning” that is derived from the data and informs the research question [200]. In contrast to a category (in which the manifest content of a data set is described and organised), the development of a theme involves a greater degree of interpretation and integration of data [203]. Braun and Clarke have recently offered three approaches to conducting thematic analysis each of which can be used to develop themes from a data set [204].

The first approach, coding reliability, is a more structured approach to coding and theme development [205]. Analysis begins with theme development and the process of coding involves correctly identifying material relevant for each theme [204]. A pre-determined codebook or coding frame is usually used to guide the coding process and multiple coders help to ensure "reliable" or "accurate" coding [204]. In contrast to this, the reflexive approach is one in which coding is an organic process that is flexible, exploratory and iterative in nature [204]. Themes are interpretive stories about the data actively created by the researcher, produced at the intersection of their theoretical assumptions, analytical resources and skills and the data themselves [204]. The final approach, codebook thematic analysis, lies between the two previous approaches; a structured coding process is used with themes being developed early on; however, these can be refined during the coding process [204]. This approach does not require multiple coders and is more influenced by a qualitative paradigm. Examples include framework analysis [206] and template analysis [207].

The approach used in this study was largely informed by the codebook approach, namely framework analysis [206]. Themes identified from the Systematic Review in Chapter two were used early on in the analysis process as an initial template and the researcher's experience alongside that of supervisors also informed the initial themes. However, the coding process was iterative in nature, and the themes constantly evolved throughout the analytical process. This was also the case when considering the role of healthcare professionals in the provision of patient centric medicines. The final question within the semi-structured interview schedule for professionals explored how health and social care professionals can ensure characteristics are appropriate for individual patients. As the analytical process proceeded, the themes developed to focus on both barriers and facilitators in this area, as explored further in Chapter 5.

The approach chosen will lead to either an inductive or deductive approach towards the identification of themes. The reflexive approach is more inductive, in which themes are derived from the data, similar to the approach used in Grounded Theory [208]. As themes are data driven, they may not mirror the questions asked of participants and are not necessarily reflective of the researcher's own beliefs or interests [200]. Deductive approaches (such as the coding reliability approach) conversely use a pre-existing framework, theory or researcher-driven focus to identify themes [199,208]. In this study, both an inductive and deductive approach were taken towards the identification of themes. While the foundation for some themes was developed early on, these evolved as the data analysis process continued. It is also important to note that the process of conducting a thematic analysis can never be purely inductive; the researcher's prior training, skills, assumptions will influence the creation of themes [204].

3.5.3. The six steps of thematic analysis

Braun and Clarke outline six steps towards conducting thematic analysis however state the approach to coding and theme development should be adapted based on the requirements for each individual project [200]. Studies can take an inductive, deductive or a "hybrid" approach to coding [209]. The present study followed the six steps towards conducting thematic analysis and the process for generating initial codes (Step two) was adapted so that it was both data and theory driven, following the principles of a codebook approach to thematic analysis. These steps have been summarised below:

- Step one- data familiarisation. The researcher read and re-read the transcripts to become intimately familiar with their content.
- Step two- integration of both inductive and deductive coding. Themes developed from the systematic review provided an initial framework. This was used to label features of the data that were relevant to answering the research question. However, as coding continued, it was necessary to develop new codes that were more data driven. The transcripts were read line-by-line and appropriate codes generated so that the entire data set was coded.
- Step three- examining the codes and collating data to generate initial themes. The initial theme maps developed used the themes from the systematic review as a starting point, i.e. the dimensions, palatability and appearance of oral solid dosage forms. These theme maps can be found in Appendix 13. However, as the analysis progressed, adopting a more inductive approach led to the development of further themes that were more patient focussed, such as the importance of the patient's background, age and disease characteristics. The theme map illustrating these themes can be found in Appendix 14.
- Step four- reviewing the themes to ensure that they answered the research question. As the entire data set was coded, this involved discarding some themes that were not relevant and often combining themes that had a shared meaning. There was much overlap between; for example, the dimensions and appearance of the dosage form that had the common shared concept of being able to identify a medication.
- Step five- determining the scope and focus of each theme, and deciding on an informative name for each theme. This step led to the development of a new set of themes that was more focussed on the patient's experience of the medication taking process rather than the formulation of the drug product (which was the main focus of the themes developed from the systematic review). The three themes identified included medication identification and memorability, medication handling and swallowability.

- Step six- writing up. The analytic narrative and data extracts were weaved together [200]. This write up is the focus of Chapters four and five.

3.6. Trustworthiness in qualitative research

Qualitative research is increasingly becoming recognised and valued and it is imperative that it is conducted in a rigorous and methodical manner so that meaningful and useful results are generated [210]. Recording, systematising and disclosing the methods of analysis can provide evidence that a robust methodology was followed [210]. Trustworthiness, a term introduced by Lincoln and Guba, is a key concept that can assure researchers and readers that their research findings are worthy of attention [146]. Research should satisfy four key criteria to ensure trustworthiness: credibility, transferability, dependability and confirmability [146]. These criteria are widely accepted and easily recognised. The following section will define these criteria in more detail and will go on to describe attempts to ensure trustworthiness in the present research.

The first criteria, credibility, addresses the "fit" between the respondent's view and how they are represented by the researcher [211]. It poses the question of whether the research findings represent a plausible representation of the participant's original data and is a correct interpretation of the participant's original views [212]. Strategies proposed by Lincoln and Guba to ensure credibility include prolonged engagement, member checks, persistent observation and peer debriefing [146]. However, not all strategies may be suitable for all studies and therefore this must be taken into account during the study design [212].

Transferability, comparable to external validity, is the generalisability of inquiry [211]. In qualitative research, this relates to case-to-case transfers; there is no single or "true" interpretation as qualitative research is specific to a particular context [211,213]. By providing "thick descriptions," the reader is able to assess whether the findings are transferable to their own setting [212].

Dependability is key to ensuring that the process is described in enough detail to allow another researcher to repeat the work [213]. The research process should be logical, traceable and clearly documented; this can be achieved through an audit trail in which decisions made throughout the research process are recorded, e.g. reflective thoughts, sampling, research materials, and information on data management [211,212,214]. Reflexivity is key to the audit trail, where researchers record a self-critical account of the research process and themselves [211].

The final criteria, confirmability, is concerned with establishing that all interpretations and findings are clearly derived from the data [203]. This is comparable with objectivity or neutrality [211].

According to Guba and Lincoln, confirmability is established once dependability, transferability and credibility are all achieved [215].

Table 3.2 below outlines the steps taken to meet the trustworthiness criteria outlined by Lincoln and Guba. It is important to note that the processes of data collection, analysis and report writing are not always in distinct steps when undertaking qualitative research; they often occur simultaneously throughout the research process [143]. The data analysis process may therefore not be entirely distinguishable from data collection [216]; therefore, while the table below details steps taken during the analysis of data to ensure trustworthiness, these can also be applied to the data collection process itself. Furthermore, data analysis was an iterative and reflective process involving a constant movement between different phases.

Table 3.2: Steps taken in this study towards achieving trustworthiness

Criterion	Steps towards achieving trustworthiness
Credibility	• Prolonged engagement with data: participants were encouraged to provide examples to support statements. The researcher asked follow up questions to ensure long-lasting engagement in the field with participants. • Peer debriefing: regular meetings were held with supervisors who examined transcripts, reports and the general methodology. • Persistent observation: The use of placebo tablets provided a focus point that was relevant to the phenomenon being studied. All participants were provided with placebo tablets of different shapes and sizes as a reference point so that all participants had a similar "baseline" in regards to their exposure to certain characteristics. These preferences were then evaluated and reported during data analysis to ensure the findings matched the participants' descriptions. • Familiarity with the topic: a systematic review was undertaken to investigate previous research in this area and provide the researcher with a detailed understanding of the topic prior to undertaking data collection. The researcher also had practical experience in this area.
Transferability	• A thick description was provided in which details including the age, ethnicity, setting and current medications of participants were recorded to provide sufficient detail for the reader to assess whether the specific findings are relevant for other settings. • Quotes and experiences were related to the context within which they were provided.
Dependability	• Details in relation to the research process including the sampling approach, setting, sample size, development of topic guide, recruitment process and data analysis methods were all recorded.

	• Reflective notes were recorded during the data analysis process that reflected the researcher's thoughts while collecting and analysing the data.
Confirmability	• Reasons for the theoretical, methodological and analytical choices made throughout the study were reported. • Direct quotes from participants were used to illustrate findings. • Photos of tablets were taken in field where relevant to illustrate any particular challenges.

3.7. Research ethics

The study received NHS HRA approval and approval from the Social Care REC (18/IEC08/0047). An initial assessment was provided by the HRA via email in December 2018 and responses to queries were provided (Appendix 15). An initial assessment from the Social Care REC was also received in December 2018 (Appendix 16). Responses were again provided to the queries raised (Appendix 17), following which final approval letters were received in January 2019 (Appendices 18 and 19).

A Letter of Access was also issued for both Primary Care (Appendix 20) and Secondary Care via the University Hospitals North Midlands NHS Trust (Appendix 21).

Key ethical considerations that were considered during the ethics application have been summarised below.

3.7.1. Possible distress

This is a non-interventional study and therefore the risks associated with it were low. However, during the course of the interview, there was the potential for participants to discuss sensitive information such as personal experiences in relation to illness and medication. This may have caused some level of distress to some patients. The researcher therefore made it clear prior to commencing the interview that the participant has the right to refuse to answer any question they may not feel comfortable answering, and also has the right to withdraw from the study at any point during the interview. There was also a procedure in place to terminate the interview if there were any signs to suggest the participant was upset or distressed; however, it was not necessary to implement this during any of the interviews.

The researcher was trained to conduct qualitative interviews and conducted qualitative interviews previously as part of a Masters project. The researcher also completed a face to face training session on Good Clinical Practice in February 2018. The researcher's co-supervisor (IM), who has extensive clinical experience in this area and led three funded qualitative research projects in older people [217-

219], provided mentorship and directed the researcher in providing any support to participants if required. After the first interview, a meeting was conducted with the supervisor to discuss any concerns and after this, regular de-briefing sessions were conducted as required.

3.7.2. Use of placebo tablets

The potential risks associated with the use of placebo tablets were low. This is because the participants were not left alone with the tablets at any point and a clear audit trail was recorded in which tablets were counted before and after the interview. Furthermore, all patients had capacity. Patients were also advised to base their answers on the appearance and feel of the tablets in the Participant Information Sheet, and this was emphasised again during the course of the interview.

3.7.3. Data protection and confidentiality

The researcher complied with the requirements of the Data Protection Act 1998 with regards to the collection, storage, processing and disclosure of personal information. The research was conducted in line with the General Data Protection Regulation (GDPR) and the recommended wording was incorporated into the Participant Information Sheets (See Appendix 11).

Participant's identifying information was replaced by a unique participant identifier number to create coded depersonalised data. Hard copies (e.g. consent forms) were archived in accordance with Aston University Archiving Policy. Only the researcher had access to participant's personal data, and consent was obtained for access to personally identifiable information. For monitoring and auditing purposes, individuals at Aston University and regulatory organisations may look at research records (including consent forms and recordings) to check the accuracy of the research study. Details of this were included in Appendix A of the Participant Information Sheet- Transparency Statement.

3.7.4. Amendments

Two non-substantial amendments (Appendices 22 and 23) were submitted for this study, both of which were approved in May 2019 and March 2020.

3.8. Chapter Summary

Due to the paucity of qualitative research in this area, as well as the importance of gaining a detailed understanding of preferred characteristics of oral solid dosage forms, a qualitative approach was deemed most appropriate. Semi-structured interviews were undertaken with older people, informal (family) carers and health and social care professionals. Results were analysed using thematic analysis informed by the codebook approach. The resulting themes will be discussed in Chapters 4-5. Chapter

4 looks in more detail at the preferred characteristics and how these have an impact on the medication taking process, while Chapter 5 discussed the role of health and social care professionals in this area.

Chapter 4- Findings from Semi-structured Interviews: Characteristics of Oral Solid Dosage Forms that Improve Adherence and Acceptance in Older People.

The work in this chapter has been published in the following publication: “Shariff, Z.; Kirby, D.; Missaghi, S.; Rajabi-Siahboomi, A.; Maidment, I. Patient-Centric Medicine Design: Key Characteristics of Oral Solid Dosage Forms that Improve Adherence and Acceptance in Older People. Pharmaceutics 2020, 12, 905.”

4.1. Introduction

The mixed methods systematic review in Chapter 2 highlighted the paucity of qualitative studies that consider the views of all those involved in an older person's therapy when designing a patient centric drug product. The following Chapter discusses the findings from the semi-structured interviews conducted with older people, informal carers and health and social care professionals, specifically in relation to the characteristics of oral solid dosage forms that impact patient acceptance and adherence. Participants were asked how characteristics such as the shape and colour of oral solid dosage forms affect their ability to take their medication as directed and what changes would make their medication easier to take. The aim was to use these responses to evaluate the current challenges experienced and to make recommendations for age appropriate medications for older people. Due to the open-ended nature of the questions asked, there were a range of themes generated from the thematic analysis. Findings specifically related to the characteristics of oral solid dosage forms are presented in this Chapter.

For a detailed description of the methods, please see Chapter three. A total of 52 semi-structured interviews were analysed and respondents varied by age, medical conditions, and the setting in which they were based. Details on respondent demographics are provided in Table 4.1. A more detailed table, detailing the medications being taken by older people and the setting in which they were based has been provided in Appendix 24.

Table 4.1 Participant characteristics

a) Older People

Code	M/F	Age	Ethnicity
P1	M	69	A
P2	M	66	A
P3	F	71	A
P4	F	80	A
P5	F	81	A
P6	F	66	A
P7	M	74	A
P8	F	69	J
P9	F	81	A
P10	F	74	A

P11	M	77	A
P12	F	97	A
P13	F	94	A
P14	M	72	A
P15	M	92	A
P16	M	93	A
P17	M	94	A
P18	F	67	A

b) Informal Carers

Code	M/F	Age	Ethnicity
C1	F	69	A
C2	F	64	A
C3	F	48	A
C4	F	61	A
C5	F	63	M
C6	M	51	J
C7	F	70	A

c) Health and Social Care Professionals

Code	M/F	Role	Period of time in Current role
HCP1	M	GP	6 years
HCP2	F	Health Care Assistant	14 months
HCP3	M	Trainee GP	7 months
HCP4	F	Consultant Pharmacist	16 years
HCP5	M	Prescribing Advising Pharmacist	4 years
HCP6	F	Clinical Lead Pharmacist/Practice based pharmacist	3 years/15 years
HCP7	M	Specialist in Pharmaceutical Public Health	17 years
HCP8	F	Older Person's Specialist Pharmacist	9 years
HC9	F	General Adult Nurse	4 months
HC10	F	Chief Nurse	3 years

HC11	F	Nurse for Safeguarding in Adults	7 years
HCP12	F	Clinical Nurse Specialist/ Continence Service Manger	23 years
HCP13	F	Practice based Pharmacist	1 year
HCP14	F	Community Pharmacist	8 years
HCP 15	F	Medicines Management Technician	6 months
HCP16	F	Pharmacy Technician	2 years
HCP17	F	Hospital Staff Nurse	15 years
HCP 18	F	Deputy Ward Manager	5 years
HCP19	F	Locum Senior House Officer (Non-Consultant Hospital Doctor)	5 weeks
HCP20	F	Staff Nurse at Nursing Home	3 years
HCP21	F	Senior Care Support Worker	10 years
HCP22	M	Care Support Worker	3 years
HCP23	M	Care Support Worker	3 years
HCP24	F	Senior Care Worker	5 years
HCP25	F	GP	10 years
HCP26	F	Clinical Lead at Nursing Home	7 months
HCP27	F	Care Team Leader at Nursing Home	2 years

Key:

A: White British

J: Asian/Asian British: Pakistani

M: Black/Black British: Caribbean

Three key themes were extracted from the data, all of which explored the impact of the medication's characteristics on different stages of the medication taking process: 1) medication identification and memorability; 2) medication handling; and 3) swallowability. These themes have been summarised in Table 4.2.

Table 4.2 Summary of themes and subthemes – the impact of medication characteristics on the medication taking process

Theme	Subtheme
Medication Identification	Colour

and Memorability	
	Dimensions and markings
	Impact of changes in appearance on identification and memorability
Medication Handling	Difficulties handling and removing
	Dimensions and scoring to improve handling
Swallowability	Dimensions - Size: A Balancing Act - The relationship between size and shape Palatability - Coating, texture and mouthfeel - Taste

4.2. Medication Identification and Memorability

4.2.1. Colour

The usefulness of colour to aid visual identification of tablets was dependent on setting; some older people within care homes had fewer preferences for colour and described the colour as "incidental". These residents had medication managed for them and administered by care professionals, therefore often the colour was described as irrelevant as they just "take what I'm given:"

"I think it's totally irrelevant what colour they are or shape." (P11)

In contrast, older people living alone within the community described the importance of using bright colours to ensure tablets are easily visible, especially when they were accidentally dropped on the floor. Healthcare professionals in particular also referred to the importance of brighter colours due to a decline in visual acuity as a result of macular degeneration or cataracts:

"But people when they're obviously, they can't see, they're a little bit, losing their eyesight, colour's very important" (HCP2)

"Is there something that maybe needs to be brighter because they've got, maybe, macular degeneration or they've got problems with cataracts. I suppose, for me, it's about, and I'm no expert, but are those the things that people need to consider around their eyesight, that need to link into how they're managing to take their medication." (HCP11)

Brighter colours were described as being particularly important for people living with dementia, who require "visible" and "appealing" colours. Older people agreed and in general had a preference towards brighter colours to aid medication identification:

"I think colour and I think bright colour. I would say bright colour. If they're wishy-washy pale pink, pale yellow and white, they're all a bit similar. I think colour would be good and reasonably bright colour" (P5)

Colour was also a useful tool to differentiate between medications, especially for patients taking a large number of tablets. Older people and informal carers often described the difficulties encountered when tablets were all white and this was highlighted as a deterrence to using pill organisers. P7, for example, was taking 7 different tablets (Fig. 4.1) and described them according to their colours. The capsules were described as being particularly useful as their colours tend to remain constant:

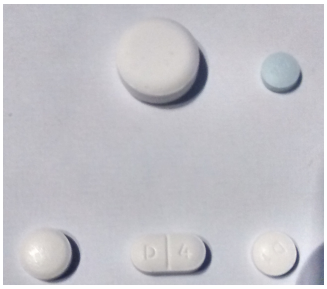
"So the blue and a pinkie and a Simvastatin, this sort of colour, you know they're that sort of colour, as I said the capsules are really quite good… they're fairly constant and irrespective of the manufacturer, so they're quite good" (P7)

In contrast, P18 had tablets that were mainly white (Fig. 4.2) and described these tablets as being "just small white tablets, boring as anything." In order to overcome difficulties that arise when taking a large number of medications, participants suggested the use of the same colour for groups of medications that had similar indications:

"But different colours and combinations that are, I suppose, unique to that particular tablet when there are likely to be similar ones in the group, a bit like the Paracetamol, Solpadol, combinations I was telling you about, because they're both white and they're both oval" (P3)

Fig. 4.1 Different coloured tablets and capsules taken by participant (P7)

Fig. 4.2 Majority of white tablets taken by participant (P18)



Informal carers agreed, with one carer suggesting colour would be helpful to differentiate between tablets but highlighting that this would be difficult due to the different medications that are often prescribed together. The dossette box that this carer was referring to in the quote below can be found in Fig. 4.3.

"Possibly colour, you know, to have different colours but then you can't, you don't know what tablets are going together so you might still end up with all white tablets, but obviously you know, when you're taking seven in the morning and they're all white apart from one, you know, maybe different colours would, would assist." (C5)

Fig. 4.3. Majority of white tablets in a dossette box administered by C5

A patient living with dementia further suggested the use of colour to differentiate between the timing of different medications. The colour was described as the most important characteristic for this patient, highlighting the importance of considering individual healthcare conditions when optimising characteristics:

"To me the colour is the most important one of all, so I take the yellow pill today, I'll take it 9 in the morning… And even if you know, sometimes it's what is it, it's the yellow one. Oh, you know I've got to take it first thing in the morning and take it first thing in the morning, that's the most important thing in it really." (P2)

Using colour to explain and differentiate between medications was described by informal carers as being particularly important for older people who do not understand English. Healthcare professionals agreed, suggesting overall understanding and, therefore, adherence could be improved if colour could be used for groups of medications when counselling patients.

"If there are a few tablets that are really important, for example anticoagulants… if they have a specific colour maybe it's easier even, even for the clinician to say "you know the brown tablet or the red tablet, you need to take." (HCP25)

There was also the need to consider the psychological importance of colour for patients with disabilities; for these patients, the colour is also an important identification tool and incorrect colours can therefore lead to a refusal to take the medication. One nurse described an example of this and suggested colour is therefore important for these patients:

I think the other one, we have had where a lady with disabilities she doesn't like certain colours she doesn't like, so she won't take her tablets. So, that's a problem because they are not the right colour…She won't take the tablets. So, colour is another thing that is probably quite important. (HCP12)

Colour was also seen as helpful to improve memorability of medications; healthcare professionals, older people and carers all referred to the use of colour as a tool to remember which medications were being taken. Distinctive colours were useful to remind patients whether they had adhered to a certain tablet and this was especially important due to the number of tablets being taken.

"It just helps them, I guess, remember what product they might be taking if it's a distinctive colour" (HCP3)

"It's easier for them to, I suppose, remember because the colour sort of, it pops out." (HCP14)

Older people and informal carers further suggested that, based on previous experience, preparations with two colours were especially easy to remember:

"Now, these particular ones, without opening it, I think are only white, though I have had some that are white and red, and that, actually, would be a lot better because then I would remember better, I think, when it comes to relating what I've done with the Paracetamol… if there was a query in my head I might be able to remember better if it had more of a distinctive combination." (P3)

"Well I think the thing that perhaps reminds me of the, of that I haven't taken this is the distinctive colour. So the blue and white being different to all the other medication that I take, I think that probably springs in my head in a way that perhaps a white tablet wouldn't spring in my head" (C2)

4.2.2. Dimensions and Markings

The size of tablets was also important to aid visual identification. Smaller tablets (similar to the 6 mm round) were described as difficult to see and often led to unintentional non-adherence. This was a significant concern for informal carers, who reported concern over whether smaller tablets (such as Folic Acid and Glimepiride) could be seen by the person they care for:

"I find the smaller ones, which are smaller than that (6mm round), I'm concerned that he doesn't see them to take them" (C7)

The very slight discrepancy between smaller sizes, such as the 6 mm and 7 mm round tablets, was also described as having the potential to cause confusion, and medication errors were reported as a result of difficulties differentiating between tablets.

"You and I are fine but if it's very similar to these (6mm and 7mm round) [looks at tablets] and really for an old person looking at that they think, because they are, it is only a slight discrepancy… But they could actually think they are taking same…" (HCP12)

Informal carers took on the responsibility of weighing up the importance of the tablet and discussed the need to ask for an alternative from the doctor if "more important" medications were of a small size to ensure patient adherence. There was a general preference towards larger tablets amongst this group to help ease the medication administration process; however, this was balanced alongside the ease of swallowing for the patient (Theme 3):

"The larger they are, the easier. I mean I'm not sure about how that would be for my dad, he doesn't seem to have any problem swallowing them but in terms of, you know, seeing them and making sure that they're there in his hand" (C5)

Shape was also an important tool to differentiate between medications and aid memorability. Unusual shapes were easier to remember and could be associated with the name of the drug:

"… I always recognise the Amlodipine… because it's sort of got one, two, three, four, about six or eight sided it is. It's quite small but it's an interesting shape, so I do notice that" (P5)

Participants further referred to the potential to use shape to associate a tablet with the time of day it needed to be taken; for example, the use of a star shape for tablets to be taken at night. While not unusual, the common use of an oval shape for statins led to participants associating these together and patients used phrases such as "the little oval one that I have at night time" when describing these tablets to health care professionals:

"Sometimes they do describe the shape because there's some of, like Atorvastatin for instance is usually like an oval shape and they might say, "it's the little oval one that I have at night time," but then again that depends on which brand you're using because that can always change" (HCP15)

When shape, colour and size are all similar, some participants suggested the use of markings to help differentiate between medications. Informal carers, in particular, highlighted this would improve acceptance, as it would reduce the worry when administering two tablets which look similar. There was an emphasis on the need for these markings to relate to the name or strength of the drug rather than the name of the manufacturer:

"This, I notice, has got a G on, which, I presume, is the maker, but, as I say, it would be a lot better for me if it said something like 25 and I'd know better what it was if it was round and not that shape and not in the calendar pack" (P3)

Pharmacy technicians working in secondary care also highlighted the importance of markings that represent the name of the medication, but suggested that this characteristic would be more beneficial for healthcare professionals as older people within secondary care often "get given" their medication and therefore do not pay attention to these characteristics:

"It (markings) might be for some people but same as I say, that like especially in the elderly care, I don't think they even, don't think sometimes they even look at what's on them, they just swallow them, get given them" (HCP15)

As well as the need for markings to relate to the name or strength of the drug, healthcare professionals identified the importance for them to be easily visible due to visual deterioration in older age. One healthcare professional referred to their experience with a medication error due to the shape, colour and size of the tablets being similar and due to the imprint not being well defined:

"I am just thinking, for instance, sort of like a Statin and a Doxazosin, the imprint on the tablet's not very defined. And that's where some mistakes have actually happened." (HCP12)

4.2.3. Impact of changes in appearance on identification and memorability

The appearance of oral solid dosage forms is an important identification tool; however, challenges can arise when different brands of the same medication are dispensed. This was a significant concern when patients associated specific shapes with certain medications, for example oval shaped statins were sometimes changed to a circular shape:

"*My only ability is I recognise them by their colour and shape, now as I say what throws you is when you get Simvastatin which is a very distinct sort of small yellow shaped tablet and you get it from a different manufacturer and it comes as a round as opposed to a whatever" (P7)*

These changes can also be especially difficult for patients with conditions such as Alzheimer's Disease, which impact cognition, who thus rely on the appearance of tablets; one patient described the confusion that can arise when different brands of Memantine (a drug used to treat moderate to severe Alzheimer's) were dispensed:

"They're quite difficult sometimes because when I get my medication, it's obviously generic so a different manufacturer will give a different colour, or no colour at all for that matter or a different size and you know if you're taking, like I say, Memantine, if it changes colour you think, well I wonder what that is I've got there." (P2)

Changes in appearance in general were not explained to patients or informal carers by healthcare professionals, and older people described the anxiety that this often led to. One older person described the distress caused by the possibility they had received the wrong dose, while another described the confusion that can arise caused by the fear they had received somebody else's medication by mistake:

"The only problem I did get, which I've made a note of, I clicked one out, they were a different colour, and do you know they drive me potty… Yeah [laughs], and I looked, I usually take that early morning and I looked yesterday morning, I thought they've altered the colour, instead of it being yellow and it's white and I panicked because I thought, oh god, it's the wrong dose, but it isn't. I wish they wouldn't do that" (P4)

"And yes, and they do, sometimes somebody gives, I think "well this isn't mine" and then you realise it is yours because it's got your name on it and it's the right drug." (P5)

Informal carers also rely on the appearance of medication to ensure they are administering the correct tablet. When using the dossette box, this would sometimes involve using the Medication Administration Record (MAR) sheet, which has a designated space for pharmacy professionals to fill in details in relation to the appearance of the medication. One informal carer described the difficulties caused when different brands were dispensed and the sheet was not updated with the new characteristics. The dossette box being referred to and associated MAR sheet can be found in Figures 4.4 and 4.5 respectively.

"No, this one has been altered but I did ask the pharmacist once when they changed it and she hadn't changed it up here because I realise this is a print-off every, you know, repeated... but if they change the tablets you should change that, you know." (C1)

Fig. 4.4 Dossette box referred to by C1

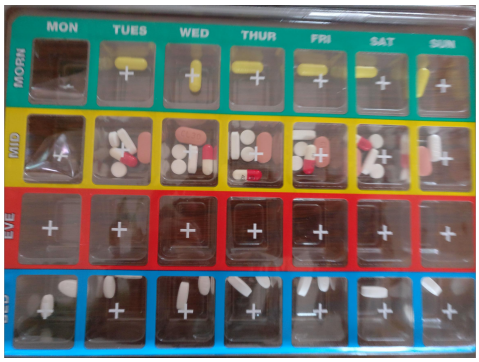
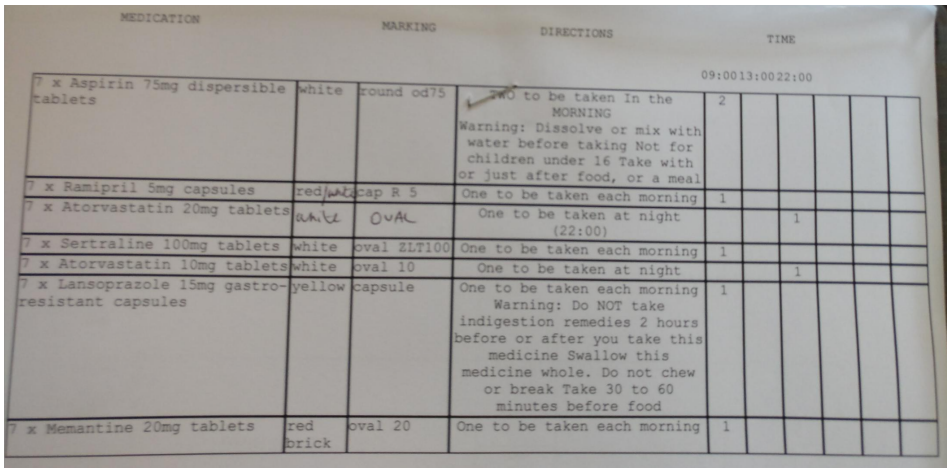


Fig. 4.5. Updated MAR sheet following a request from the informal carer to ensure the marking description column matches the brand dispensed in the dossette box



MEDICATION	MARKING		DIRECTIONS	TIME					
				09:00	13:00	22:00			
7 x Aspirin 75mg dispersible tablets	white	round od75	TWO to be taken In the MORNING Warning: Dissolve or mix with water before taking Not for children under 16 Take with or just after food, or a meal	2					
7 x Ramipril 5mg capsules	red/white	cap R 5	One to be taken each morning	1					
7 x Atorvastatin 20mg tablets	white	OVAL	One to be taken at night (22:00)			1			
7 x Sertraline 100mg tablets	white	oval ZLT100	One to be taken each morning	1					
7 x Atorvastatin 10mg tablets	white	oval 10	One to be taken at night			1			
7 x Lansoprazole 15mg gastro-resistant capsules	yellow	capsule	One to be taken each morning Warning: Do NOT take indigestion remedies 2 hours before or after you take this medicine Swallow this medicine whole. Do not chew or break Take 30 to 60 minutes before food	1					
7 x Memantine 20mg tablets	red brick	oval 20	One to be taken each morning	1					

4.3. Medication Handling

4.3.1. Difficulties removing and handling

Older people, carers and healthcare professionals described the difficulties associated with smaller tablets (6mm round) when trying to remove these from blister packs. Examples referred to by older people included Codeine Phosphate and Amitriptyline tablets:

"These are the Codeine Phos, and I shoot those all over, and my hubby, I don't know, it doesn't matter whether I have them over something or what, I don't know" (P4)

"No, the Amitriptyline is blue, and I find great difficulty in getting them out of the package" (P9)

In addition to difficulties with blister packs, informal carers also described difficulties removing tablets from both dossette boxes and weekly pill organisers. This led to the need to double check that all medications were taken and the additional concern on how the patient would take their medication if they were not available to administer it:

"I mean it'd make it easier for her if she ever needed… couldn't have a blister pack, and there wasn't somebody to administer them, if they're easier to get out of the packaging, because some aren't" (C3)

Healthcare professionals were aware of the difficulties removing smaller tablets from their packaging and referred to the challenges removing tablets from a Monitored Dosage System (MDS) due to "dexterity issues." Again, they referred to the 6 mm and 7 mm round tablets as being difficult to remove:

"Yeah, I'd move away from those (6mm and 7mm round) unless there's a clinical reason why they need an extra small tablet like that. You can just imagine your patient with dexterity issues trying to manage that (6mm round) or trying to pop it out of the MDS box" (HCP5)

Participants referred in particular to rheumatoid arthritis, stroke, neuropathy and carpal tunnel syndrome, all of which affected older peoples' ability to remove and handle smaller tablets. In order to overcome these challenges, some healthcare professionals suggested the possibility of assessing an older person's ability to remove medication from the packaging prior to dispensing using samples of tablets:

"It's about asking about them…do you feel that you can take it, can you pick it up, and it might be even asking, you know, samples, so can you show me whether or not you can pop it out of the blister pack or out of the packaging." (HCP11)

Following removal, difficulties were also highlighted by older people, carers and healthcare professionals when handling small, round tablets prior to administration. Again, both the 6 mm and 7 mm round tablets were least preferred and healthcare professionals referred to the potential for these to be dropped on the floor, resulting in distress for the patient:

I'm looking at the very little ones, (6mm round) they're perhaps fiddly, they're going to be easy to swallow but, you know, older person with arthritis, how many are going to get dropped down the side of the sofa? (HCP1)

Informal carers within the community often took on the responsibility of finding tablets that had been dropped; however, this was dependent on the appearance of the tablet and how easily visible it was (Theme 1).

"I mean we, I suppose we're used to them now and the fact that they are usually on a table or if they fall they're on a dark carpet then they are easily spotted, apart from there's a little tiny one here, there's a little tiny white one in the morning so that could, you know, present some difficulty" (C5)

"Well when I'm here I make sure he takes it because I have found them on the floor because he hasn't been able to pick up so…" (C7)

"Whilst it might be easier to swallow, to actually pick that (6mm round) up and then perhaps see it when you've dropped it, is actually really difficult, and if it's a brighter colour, if they did drop it on their patterned carpet they might be more likely to see it" (HCP4)

While informal carers can often take on the responsibility of finding smaller tablets that had been dropped, older people living alone or who were responsible for self-managing their medication described the difficulties associated with finding missing tablets. Healthcare professionals were aware of these difficulties and were also concerned that many may not be reporting problems to their GP or pharmacist, which may have a further impact on adherence:

"I guess some patients don't (deal with difficulties). Just as, if they drop the medicine, they're just like 'well I've dropped the medicine' They'll either pick it up from the floor and take it I guess, which is a concern in its own right, or contact the GP or pharmacist. If they do. If they do. Big question mark over that" (HCP5)

4.3.2. Dimensions and scoring to improve handling

A significant number of the difficulties associated with handling tablets were related to small, round tablets, and healthcare professionals highlighted that, in their experience, these difficulties were present regardless of age. There was a general preference, therefore, for oval shaped tablets and the caplet shape, which healthcare professionals highlighted would be easier to handle. Informal carers agreed and had a preference for tablets with a "pillow shape:"

"And I think if they can make them so that they don't roll all over the place if you drop them. And those are the tinier ones obviously, they're the flat-sided ones. The pillow ones, they're fine, it's just the tiny ones seem to roll" (C4)

Preferences for the oval and caplet shapes were often largely related to their relative thickness in comparison to the 6 mm and 7 mm round tablets. Participants described the need for tablets to be "chunkier" due to the loss of fine finger movement in old age:

"I, personally I think the tablets need to be more chunkier (referring to 18 x 7mm caplet). I think because the fine finger movement, they lose that as they get elderly through arthritis or neuropathy or anything like that" (HCP12)

Although larger in diameter, the 10 mm round tablet was again relatively thin compared to the oval shapes and this was picked up by healthcare professionals; the 12 x 7 mm oval, for example, was preferred over the 10 mm round due to the thickness and ease of picking when on a flat surface:

"If that was on the table it would be a bit, so that's the 10, even the 10mm round. Whereas these ones (12 x 7mm oval), the oval ones are slightly easier to pick up because they're a bit thicker" (HCP19)

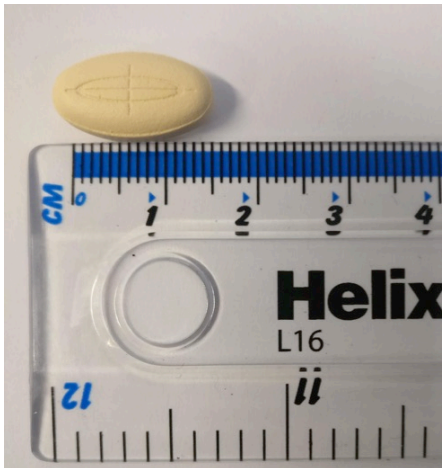
However, the majority of participants referred to the difficult compromise between ensuring tablets were easy to handle and the swallowability (Theme 3):

"Well, this is going to sound like a double-bladed sword here, in a way you don't want them to be so tiny that if you do have arthritis that they are difficult to manage but on the same side, you don't want them so big that you're going to need to drink a full glass of water just to get one down" (C4)

One healthcare professional suggested that the potential to modify larger dosage forms may help to overcome the need to balance the ease of handling a large tablet with the difficulty of swallowing larger dosage forms. Others picked up on the markings on the placebo tablets (Fig. 4.6) and discussed the ease of handling tablets with an indentation:

"I think I quite like, is it one of these? The indentations actually. Quite like those (16.5 x 8.9mm oval). [Looking at tablets] You can get hold of those, easily can't you? and they are not going to slip out" (HCP12)

Fig. 4.6 Indentation on placebo tablets that may help handling



The potential to use markings as a "mechanical grip" with which to hold the tablet was highlighted by a further healthcare professional, who this time used the example of how a score line can make it easier for older people to handle the tablet:

"The scoring, yes, it's a marker to actually cut the tablet, however it provides that grip that's needed to control the tablet. If you think of it operationally, mechanically, you know, having that grip there you know, it's, you're more likely to get that kind of grip they needed to administer that medicine" (HCP5)

4.4. Swallowability

4.4.1. Dimensions

4.4.1a. Size: A Balancing Act

As discussed in Theme 4.3.2., participants identified the need to balance ease of swallowing dosage forms with the ease of handling, and the priority placed on each stage differed according to the setting. One older person in a care home suggested that size was the most important characteristic and "the smaller the better." Healthcare professionals were aware of the importance of setting, and a locum senior house officer working in secondary care described the differences in priorities between inpatients in hospitals and older people who were self-managing medications within their own homes:

"*Obviously whilst in hospital we tend to give them in a pot and sort of almost spoon-feed them to patients, whereas I imagine in their homes maybe the very small tablets if they've got poor manual dexterity or poor eyesight, it's difficult for them to see" (HCP19)*

The importance of setting was also highlighted by a community GP, who again suggested a smaller size would be more important for older people in care homes where medication could be administered and therefore swallowability would have a greater priority over medication handling:

"If they're in a care home and they have swallowing problems then I think the smaller version is easier because they can, the staff can administer and they can swallow it easily" (HCP25)

When discussing the small size of tablets, healthcare professionals would often refer to the theoretical ease of swallowing that would need to be balanced against the difficulties handling the tablet. However, older people living within the community often described smaller tablets as being more difficult to swallow and were further aware of how this may seem contradictory to expectations

"They're very small. Yeah, which in theory it should be easier to swallow but it's not, the very small's not so easy." (P2)

"Sometimes, you know, you sort of take one gulp of water and sometimes that's not enough, you've got to have two or three more to make it sort of go down, but those tend to be with the smaller tablets, with the Amitriptyline." (P9)

"And then the Amitriptyline I take just before I go to bed, and that's the one that sometimes I feel it hasn't gone quite down, despite the fact that it's a tiny little tablet." (P18)

Informal carers were also aware of the difficulties in relation to swallowing smaller tablets and internally tried to justify why this may be the case. *S*ocial care professionals further discussed the difficulties ensuring that the tablet had been completely swallowed when administering smaller sized tablets:

"He talks about also, the small tablet, which I think is the rivaroxaban, he talks about that as being difficult for him to swallow and I wonder if it's because he can't really feel it in his mouth." (C2)

"Sometimes they can get lost in their mouth and you don't even know if it's gone in… But then eventually it does go but then you really do have to keep an eye on it." (HCP23)

"I know obviously large are trouble but also small because they can lose them in their mouth" (HCP26)

Patients were therefore more aware that they had swallowed the medication if the tablet was larger in size and this can further be related to the importance of mouthfeel when enhancing swallowability. However, a balance is required when determining the most appropriate size, with larger tablets also leading to difficulties swallowing and the need to modify tablets by breaking them in half. Other management techniques included re-positioning the head when swallowing, drinking more water and sometimes "ignoring it" because "it's going to go down eventually." Calcium and Vitamin D preparations were often referred to as being difficult to swallow due to the large size; one older person described the need to take "a lot of water" with these tablets, which were described as being similar to the 16.5 x 8.5mm oval.

"Swallowing is a bit difficult because they are quite a big tablet so I don't have to break it, but I have to swallow it with a lot of water" (P8)

An example of a "Multi-Vite" preparation that was described as being particularly challenging can be found in Fig. 4.7. While this was described as being difficult to take, the older person suggested that it was her "choice" to take this medication and therefore it would be classified separately to prescribed medications. Other medications that caused difficulties due to the large size included metformin, paracetamol, antibiotics and co-codamol; quotes in relation to the difficulties taking these formulations can be found in Table 4.2 below. Metformin was described as being "bigger than" any of

the placebo tablets presented. Both the standard release and slow release metformin were referred to as being difficult to swallow, and healthcare professionals were aware of the potential for the large size to result in unintentional non-adherence:

"We come across patients on Metformin, they're big tablets, they say they get GI problems so we give them a slow-release preparation, then as we titrate the dose and put them on higher strengths, they end up being like horse pills and the patients are like 'it's not that I don't want to take them, it's just I can't swallow them'" (HCP6)

Multiple tablets would therefore be prescribed to avoid non-adherence, adding to the overall pill burden for the patient:

"I mean if you get up to 1g tablets then they're a, there's a larger group of people that can't take them so, you know, your Metformin 1g for example would be, there'll be a group of people who are on 500mg, two tablets, because they just simply can't get the pill down" (HCP1)

Fig. 4.7 A Multi-Vite preparation (a) and (b) alongside 18 x 7mm caplet and 12 x 7mm oval placebo

4.4.1b. The relationship between size and shape

Both older people and healthcare professionals described a relationship between size and shape when considering the difficulties swallowing some tablets. Difficulties swallowing large round (>10 mm) preparations, including co-codamol and paracetamol, could be overcome by changing to a "bullet" or caplet shape; quotes highlighting this relationship have been asterisked in Table 4.2. There was a general preference for the caplet shape over the round; however, the thickness and size of these shapes are important. This was especially true for paracetamol caplet formulations, which were preferred to the round formulation but which were sometimes nevertheless modified prior to administration to patients:

"So if I tell you, it, older people, they really struggle taking the medication like in this size (18 x 7 mm caplet) … so like in this (18 x 7 mm caplet) we can get a Paracetamol I think and when it's come they will ask us to break it in two and take it one by one.. otherwise they always complain that they are stuck in the throat if they take the one full size." (HCP17)

16 of the 27 healthcare professionals referred to difficulties associated with swallowing the 18 x 7 mm caplet. One healthcare professional was aware of the preference for caplet shapes, but highlighted that this particular size may cause patients difficulties:

I'd say this one (18 x 7 mm caplet) runs a risk of, even though some people prefer caplets, if they get lodged in there in a real awkward way then it could be quite distressing (HCP5)

An informal carer also expressed her concern in relation to the thickness of the tablets, this time referring to chronic conditions which impact swallowability for older people in general:

"But these (12 x 7 oval and 18 x 7mm caplet) that have a thickness to them, I do think you know especially for older people. I mean you've got to think as well that there may be people with really chronic mouth problems, even mouth cancer" (C2)

The thickness of the tablet was also perceived to be the main disadvantage of the 12 x 7 mm oval shape tablet. In general, older people and healthcare professionals both highlighted the ease of swallowing oval tablets in comparison to round tablets, with some also highlighting a preference for the oval shape in comparison to the caplet:

"The shape that I prefer is the oval. For me that seems to be quite easy to swallow. It doesn't matter if it's a big or a small but the big... Oh, I don't know what you call that, that shape (caplet)… I find that can be a little bit more difficult" (P2)

Table 4.3. Illustrative data extracts in for preparations that are difficult to swallow due to the size and shape

Medication	Illustrative Data Extract
Metformin	I think if it (metformin) was any bigger it might be a bit difficult (to swallow) because it is fairly big. It's bigger than any of the ones that you've got there (P1)
	These are big buggers, these Glucophage ones… And they're dry, and they would go down a lot easier with a coating or something I would think, and maybe you know, a pillow or whatever shape (P7) *
	Well the Metformin are more difficult because they're quite a big round tablet, I mean they're much bigger than the ones you've got

	here. So they're circular like that (10 mm round), but quite a bit bigger and thicker. So that's more difficult. (C3)
	You have to drink a lot, you have to make sure you know, you drink before, during and after really. (C4) (In reference to Glucophage)
	I mean if you get up to 1g tablets then they're a, there's a larger group of people that can't take them so, you know, your Metformin 1g for example would be, there'll be a group of people who are on 500mg, two tablets, because they just simply can't get the pill down so (HCP1)
	if like for example, we come across patients on Metformin, they're big tablets, they say they get GI problems so we give them a slow-release preparation, then as we titrate the dose and put them on higher strengths, they end up being like horse pills and the patients are like 'it's not that I don't want to take them, it's just I can't swallow them' or you know, like 'I have to psyche myself up because of the gag reflex' (HCP6)
	If they could all, I don't know how you would do this but I know that the size puts a lot of people off, so if they could compact like a, like whatever that is, I mean that (18 x 7 mm caplet) looks like the kind of shape a Metformin would be. I don't know like how you'd be able to make a Metformin that sort of size (6 mm round)? (HCP15)
Paracetamol	Apparently, this oesophageal problem I've got I… I mean you'll laugh at this, yesterday I was trying and I thought I'm sick of not being able to swallow them (paracetamol), and do you know I can put one in the back of me mouth and I've two glasses of water and it's still there, it never goes down. Is that just me? (P4)
	I'm just thinking that for instance like, you're not asking, I'm going to say it's with the Paracetamol, I find like I don't normally take painkillers from one week to the next to be quite honest but I have been taking them and I much prefer the caplets of Paracetamol. I do break them in half but I do find them very much easier to swallow than, I always, on the odd occasion that I've taken the round Paracetamol, I think those are quite difficult to swallow to be quite honest. (P5) *
	I think these ones (caplet) they are a bit easy to take, but the other round ones sometimes it's hard to swallow them and I have to sip lot of water with it (P8) *
	Paracetamol I find is very large… (I break it) in two, two I can just about get down but it's a bit of a swallow (P10)

	Although I do have trouble with Paracetamol. Unless that goes in straight... I find it very hard to swallow but I think they made them that size to deter people from... (P11)
	So occasionally it (paracetamol) seems as if it might be getting stuck…But I'm not 100% certain. (P18)
	They're (paracetamol) like that (18 x 7 mm caplet) but they're like a caplet, a coated one, but that shape, perhaps a little bit deeper than that. He doesn't find them easy to swallow at all. And really weird just getting them down him (C2)
	And the Paracetamol are similar to these ones, (18 x 7 mm caplet) they're relatively long, and fairly thin, but they're still harder than for example the Simvastatin that's more that shape (12 x 7 mm oval) (C3)
	Paracetamol, is that (bulkiness) just because of the amount of active ingredient, is that? … Because that's the one medication usually patients complain about. (HCP3)
	We can see some of the, some Paracetamol in this shape isn't it, so people, usually they'll ask us to break the caplet. The caplets, usually elders ask to break it in two so they can make it more easier. (HCP17)
	Sometimes they are big and very round, like round Paracetamol, they are quite difficult as well… (HCP18)
	If we changed, because some of them, if we changed the size, like, paracetamol's quite big, instead of changing the size, the best thing is just to like to prescribe in soluble form. (HCP20)
	Yeah. There have been a few instances where for example some Paracetamol tablets, they prefer the caplet sometimes because it's easier to swallow (HCP25) *
Co-codamol	I go for the sort of bullet shape rather than the round ones. But, I mean, these are small enough for it (the shape) not to matter, but when you get into bigger pills, it's easier, things like the Co-… Solpadol, yeah. (P3) *
	What you haven't got here, which I was expecting you to have is the thick round one. That type of paracetamol. Or the co-codamol which I take. And it's round and it's thick. And I struggle with that, it can make me feel like vomiting. Sometimes I wretch when I take that tablet. And I was expecting to see that one here, because it's bigger than that one (10 mm round) sometimes with the co-proxamol… what is it? Co-codamol (C2)
Calcium & Vitamin D (including Adcal)	Swallowing is a bit difficult because they are quite a big tablet so I don't have to break it, but I have to swallow it with a lot of water

	(P8) (In reference to 16.5mm x 8.5mm oval calcium and vitamin D tablets).
	The Adcal are a bit sizeable (P9)
	Many times we'd see that a lot of patients would just not take their calcium, Vitamin D tablets, they're large tablets (HCP14)
	On a, probably the only stuff that we've had complaints about are Adcal and Metformin, I think is Adcal massive, it's a gram isn't it, so? (HCP1)
	So do I chew it? Do I dissolve it in water? This is a massive tablet and we worked out that it was a, I think it was an Adcal-D3 or something like that, calcium and vitamin D which he was to chew (HCP7)
	I mean Adcal-D3 is a really good example of one that it's very poor adherence because they don't like the size of it and they don't like the taste of it (HCP8)
	Yes. I mean certainly with the big round Adcal we've quite often gone to a soluble version or a caplet, which I believe are actually slightly bigger than that one (18 x 7 mm caplet) but because of the taste and the size of the tablet (HCP8)
Antibiotics	I mean if you were looking at Azithromycin 500mgs, they're massive aren't they? And you might think "oh they're bloody big tablets so let's think about either the formulation or another macrolide maybe" (HCP7)
	I think it's whether they're going to be able, because there are certain antibiotics capsules which are really big, you know, for example Metronidazole and Flucloxacillin, even I at times have struggled, you know, to sort of take those and I think God if I've struggled then, you know, an older person, you know, some older people probably would really struggle with trying to swallow some of those (HCP9)
	I'd probably go that one (16.5 x 8.9 mm oval). [Shows interviewer]. Because that's probably about the size of a Co-amoxiclav and a lot of patients can't take them ones because they say they're too big (HCP16)
	Yeah, that is one and sometimes when they prescribe antibiotics as well for them, some of them come in big, which you need to break about 2/3, even though the one they normally swallow on its own won't swallow it, he will tell you "it's too big I will choke", so you need to break it in 2 or 3 pieces for her to drink it (HCP24)

	Yeah, we always face that issue with antibiotics. Whenever they prescribe antibiotics here it's always a problem because it's always big. (HCP24)
	I know antibiotics are and they're generally big. (HCP26)

** Indicates quotes illustrating relationship between size and shape*

However again, in order to optimise swallowability of this shape, the thickness needs to be considered. One informal carer described the ease of swallowing statin tablets that were similar in size and shape to the 12 x 7 mm oval, the only difference being the thickness of the tablet:

"The Simvastatin that's more that shape (12 x 7 mm oval), but and that size really, but smaller, it's not as thick so it's easier" (C3)

The size of the 16.5 x 8.9 mm oval was also perceived to be a concern for participants and health care professionals often compared this to the size of antibiotics with which patients often have difficulties:

"I'd probably go that one (16.5 x 8.9 mm oval). [Shows interviewer]. Because that's probably about the size of a Co-amoxiclav and a lot of patients can't take them ones because they say they're too big" (HCP16)

One patient in a care home who had suffered a stroke spoke about the need to modify tablets if they were any larger than this size:

"If I had to take any larger than that one (16.5 x 8.9 mm oval), they'd break them in two for me." (P13)

There are however potential issues associated with modifying dosage forms. Social care professionals including formal carers in care homes were more aware of the potential for the tablet to crumble when modifying the tablet due to a poorly functioning score line.

"Sometimes they can crumble, yeah, which obviously you don't want to happen do you?" (HCP26)

The optimum dimensions therefore must consider the relationship between the size, shape and thickness of tablets. In general, oval shape tablets were preferred but the size of these must be optimised to enhance swallowability.

4.4.2. Palatability

4.4.2a. Coating, Texture and Mouthfeel

The coating of tablets was described by most participants as being a helpful tool to aid swallowability, and various different types of coating were often referred to. Older people and informal carers referred to coatings that made tablets appear "shiny," referring to the ease of swallowing these tablets:

"Well probably I would say the two that have a fairly shiny coating, which I think would be the amlodipine and the telmisartan, are easier to swallow."(P1)

"I mean some of the tablets in the past that she's had for I think it was indigestion problems, were a different texture, so they weren't, like the ones you've got here, they were more sort of shiny really, coated. So those were slightly easier, or less formidable than these." (C3)

"Shiny" tablets are often associated with a sugar coating, which can also make the tablet seem "slippery." This was again referred to by older people and healthcare professionals

"The ones that are coated, I don't know if they coat them in sugar solution or what, they seem to swallow a lot easier." (P2)

"I definitely think the slightly slippery coating is helpful" (P18)

"Sugar coating, that's the, I think sugar coating might possibly help, again they seem to be a bit slippier don't they?" (HCP7)

Whilst the sugar coating in general aids swallowability, one carer in a nursing home highlighted that this benefit can only be appreciated if patients are willing to take the tablet initially. While sugar coatings can be white, colours are often used as part of the sugar-coating process. This can deter people from taking the tablet and therefore the advantage of the improved swallowability is lost. This was the case for one patient in a nursing home (caring for those with mental illness) who refused to take ibuprofen which had a bright pink sugar coating, highlighting the importance of considering palatability alongside the visual aesthetics of the medication (theme 1):

"If I've not tasted it I wouldn't have known that the purpose of you making that coating is for me to have the sugary part of it. But if I look at it without tasting I might say what is this, I don't like it. And you say, oh try it, it's a nice taste but you are trying to convince me to take it but my eyes have already said that is not right, why is it pink instead of white." (HCP24)

A further functional coating referred to by participants was that of an enteric coat, however this is usually used to optimise drug delivery to the intestine by reducing degradation in the stomach acid rather than enhance palatability. One healthcare professional referred to the possible "placebo

effect" this may have, with patients often asking for an enteric coated tablet when they have not been prescribed or recommended by a medical provider:

"They do have this thing about enteric coated tablets which they tend to prefer, even with like the Aspirin, although there's very limited evidence, they like to have the enteric coated for that, and the enteric coated for the Prednisolone. I think it's, and you can explain to them about the evidence and lacking evidence, but they'll still prefer, it's more like, I don't know if it's a placebo effect, they just think it's better for them, and they have some type of gastric protection because it's coated, or there's just this general perception amongst elderly patients that enteric coated tablets are better for them, safer for them." (HCP13)

Another healthcare professional therefore referred to the importance of a coating that aids swallowability, and again highlighted that this does not necessarily need to be an enteric coating, but rather one that helps the oesophageal transit of the tablet:

"I mean, I suppose something that's quite soft and feels easy, so if you've got some medication that sometimes can feel quite rough or it sticks at the back of the throat, so not necessarily something enteric coated, but something that's quite easy and feels as if it goes down quite quickly, so it doesn't feel as if they're lodging, you know, in their throat." (HCP11)

The final coating referred to by participants was that of a film coating, often used for aesthetic purposes. One healthcare professional referred to the difficulties with tablets that were not film coated, as patients don't always take their medication with a full glass of water:

"Some of the non-film coated tablets tend to, patients sometimes complain they feel like they're getting stuck in their throat and despite you saying to them that they need to take a glass of water with them, some of them choose not to, and so we do have to think about what options are available for them" (HCP8)

In general, participants perceived tablets that were coated to be more expensive and one older person went on to state that this may be the reason why coated tablets are not more widely used:

"If it's got a coating which makes it easier. Oh, it's more expensive mind you..."(P2)

"When I was taking Ibuprofen more regularly, I used to ask for the white ones, because I thought the red ones upset me. Now, I don't know what the difference is, but at one point I think a pharmacist said to me that the white ones are more expensive. Now, if they're more expensive that perhaps suggests that they had a coating" (P3)

"I definitely think the slightly slippery coating is helpful. Is that a lot more expensive for them to produce, is that why they don't use it?" (P18)

Tablets that were uncoated often had a negative impact on the texture of the dosage form, which has a subsequent effect on mouthfeel. Some tablets were described as having the potential to disintegrate in the mouth prior to swallowing and one informal carer of a person with dementia described her concern that the person she cared for may experience the same difficulties as she does with gliclazide tablets, but that these may not be communicated

"Sometimes they're soft, they melt in the mouth" (P12)

"The gliclazide and sometimes they kind of break up in my mouth, and some goes down and some stays in my mouth, and that's a bit of a concern to me when that happens… So I think that's another factor to be borne in mind, but my uncle hasn't talked to me about that" (C2)

Uncoated tablets were also described as being "chalky," again leading to difficulties swallowing the tablet:

"And they're (Glucophage) not coated so they're chalky you know, you need a good swallow of water to be able to get them down" (P7)

"I mean what about the chalkiness of it? Is that a word to describe tablets? I mean my co-codamol and when I've had paracetamol in that form as well, there's sometimes white stuff comes off isn't it, and you don't know whether you're getting the whole of the tablet anyway because some's kind of coming off in your hand" (C2)

A pharmacist also referred to the difficulties associated with "powdery" tablets and went on to associate this with taste:

"I think sometimes they're powdery, if they're really powdery and bitter, you might not want to take those" (HCP4)

The plastic texture and mouth feel of capsules can sometimes overcome the difficulties associated with uncoated tablets, and many participants referred to the ease of swallowing capsules such as Lansoprazole in comparison to uncoated tablets:

"I find some tablets can be, um, that it's not a plastic coating but it can look like plastic, I find that they're easier to take than some which are perhaps a little bit drier" (P6)

"The plasticy ones, torpedo, they are not too bad, they seem to go down as well better" (P10)

One healthcare professional agreed with this, and stated that the gelatine material often used to make these capsules could lead to ease of swallowing compared to conventional tablets:

"Is it gelatine-based, is it, the capsules? I've forgotten, what are they made out of?... Gelatine-based, yeah, so I'm not sure if that might be a little bit easier to swallow than a tablet because there's an increased risk of them getting stuck" (HCP3)

However, another GP described the importance of considering each patient's culture/religion when prescribing medication, especially when considering the use of gelatine capsules. This highlights the importance of considering individual patient needs when optimising formulation:

"Some of our Muslim patients will refuse capsules on the ground that they feel it's not Halal, that's, and that happens even if we, you know, look in some of your product characteristics and say, you know, it's, you know, a vegetable gelatine or a beef gelatine not pork, you know, even then they'll say well not sure and I have a feeling, you know, we would make an effort to prescribe tablets rather than capsules for Muslim patients." (HCP1)

Other healthcare professionals were also hesitant about the use of capsules that have a plastic feel, however this was related to the theoretical ease of swallowing. Many voiced their concern with these dosage forms based on their personal experiences administering them to older people, again highlighting a need to consider individual preferences:

"I think you know some of the textures can make you gag, like the plastic coatings and, so if you've got a smooth coating, it's just easier to swallow" (HCP2)

"I think the capsule forms are more difficult for them, they will stick up there… So most of the time we find difficulty with the capsules" (HCP17)

"But I know we've had to stop one of our patient's capsules because she can't swallow them and she just spits them out" (HCP19)

One of the main concerns with capsules referred to by healthcare professionals was the large size of some capsule formulations, highlighting again the relationship between dimensions and palatability, and the overall impact on swallowability:

"Generally you find that like tablets like this size (6mm and 7mm round) they're okay with but anything sort of bigger than that (18 x 7mm caplet) and in a capsule form I think is when they would struggle with" (HCP9)

In general, the application of a coating (rather than the use of capsules) was perceived to be help improve the swallowability of larger tablets:

"I honestly think regarding my swallowing problem, if they're coated. What do they put on it?" (P4)

"These are big buggers, these Glucophage ones… And they're dry, and they would go down a lot easier with a coating or something I would think" (P7)

4.4.2b. Taste

The taste of solid dosage forms was described by participants as having a significant impact on the acceptance of tablets and this in turn had an important effect on adherence. Healthcare professionals were aware of the increasing importance of acceptability, and the need to ensure optimum taste so that patients are able to take their medication as directed:

"I think increasingly it's becoming more important to patients' like acceptability of dosage forms and palatability as well. I think some cases they don't like the taste of something or they can't actually take the medication, then that's a big barrier to compliance." (HCP13)

A community pharmacist expanded on this, and referred to the unpleasant taste of chewable formulations which can again lead to non-adherence. This is a key issue which requires discussion between healthcare professionals so that problems can be identified and addressed:

"Many times, we'd see that a lot of patients would just not take their calcium, Vitamin D tablets, they're large tablets. The chewable formulation, it's a chalky taste and perhaps they haven't really discussed other options with the professionals, so it's at that point when you notice that patients aren't adherent, to pick it up, find a reason and offer solutions and offer options, and even offer those options to GPs because I think that's where maybe the lapse is." (HCP14)

The taste is especially important for chewable formulations, which spend longer in the oral cavity. Calcium and Vitamin D preparations were commonly referred to as having poor rates of adherence by healthcare professionals. Formulations which do not take the taste into account can therefore lead to the need to change to an alternative route of administration due to non-adherence, which can be costly and also have further safety considerations:

"I mean Adcal-D3 is a really good example of one that it's very poor adherence because they don't like the size of it and they don't like the taste of it" (HCP8)

"I know like with the chewable things they don't like the taste so they don't take it, so they end up going from having a chewable tablet to being injected every three months" (HCP16)

One older person taking a chewable calcium and vitamin D preparation referred to her hesitance to take the tablet should she find an issue with the taste, and again used the word “acceptable” to describe the current palatability of her tablets:

“I mean I guess if the chewable one tasted disgusting then I wouldn’t want it, but no, it’s fine… I mean it’s not the nicest, but it’s acceptable” (P18)

While taste is significant in determining the acceptance and adherence to chewable formulations, the acceptance of standard tablet formulations was also found to be largely impacted by taste. Participants used the term “bitter” to describe tablets that were more difficult to take, with codeine phosphate and paracetamol formulations both being described as having a particularly bitter taste:

“One that I get a horrible taste with is Paracetamol…You get a taste and it’s quite... It’s a little bit of a bitter taste.” (P2)

“They’re (Codeine) bitter and horrible and I don’t like them, they’re very bitter, and I mean if as long as I have a good glass of water they’re okay.” (P4)

“Co-dydramol does, sometimes when it’s a bit difficult to swallow it, and it’s left in the mouth, then it’s very bitter taste” (P8)

Whilst in general bitter tasting tablets were perceived to reduce acceptability, one older person (who referred to her friend’s experience with bitter tasting sleeping tablets) suggested that the bitter aftertaste could act as a reminder that the medication had been taken. This highlights the difficulties associated with taking a large number of dosage forms, and the strategies older people may resort to in order to help aid their memory of taking each tablet:

“Well, a friend of mine who had sleeping pills said they didn't like to take them, and I've forgotten what it was called now…It was blue, and they said it was a terribly bitter aftertaste. Now, I think if I wanted to sleep I'd put up with the aftertaste, but it would at least alert you to the fact that you've taken one, so you shouldn't be taking any more… I mean, it might seem odd at first to think, ooh, why have they made it so horrible to take, but I think, when I think about it, I can see there's a logic there, because it persists.” (P3)

In addition to bitter tasting tablets, one older person referred to difficulties swallowing amitriptyline, which she associated with having a “perfume” taste:

“Yeah. Well that is the Amitriptyline, it’s a yellow one and it tastes very much like you’ve swallowed some perfume, which isn’t very pleasant. I know other people with the same problem” (P10)

This older person went on to compare the amitriptyline tablets with indomethacin capsules, and referred to the ease of taking the capsules due to the lack of taste. Whilst the indomethacin capsules were larger in size compared to the amitriptyline (7mm round), improved palatability was a greater concern than the size of the tablets, highlighting the importance again of considering both size and taste when optimising swallowability:

"*And the Indomethacin and they're like a sort of torpedo, in between those two but they've got like a plastic and I think one side blue and one side is white but there's no taste in that because it's plastic which is quite a bonus really. I would prefer something that didn't taste than something tinier that did taste" (P10)*

The preference for tablets that did not taste was also highlighted by another older person within a nursing home, who did not have any current issues taking his medication:

"I don't taste them at all… They don't taste at all, and I don't want them to. I just swallow them." (P16)

Healthcare professionals were aware of the importance of ensuring that the taste did not interfere with the patient's acceptance of the medication, and therefore referred to the importance of the use of a coating, such as a sugar coating, to overcome this difficulty. Older people also referred to the association between the coating and taste of tablets:

"I think sometimes the coating, so, and that might reflect in the taste" (HCP4)

"Coated tablets, sweeter, sweeter tablets, they might be more likely to take those tablets than a bitter sour tasting tablet" (HCP14)

"Now some pills that are not coated taste horrible" (P2)

The potential to use a "sweeter" taste to help improve acceptance was also referred to by an older person, who described the potential to use flavouring to help improve an older person's willingness to take their medication. However, this is again dependent on individual preferences with certain flavours being more or less acceptable:

"If people were, didn't like taking medication, if there was some neutral but pleasant flavour that they might have, I don't know how easy or difficult that is in terms of not interfering with the medication. But, and it would have to be something very neutral, because obviously different people like different things. I mean maybe they could be slightly minty or something, or slightly, I was going to say vanillary, but I don't know, not everybody, I mean I love it, but not everybody does" (P18)

There is, therefore, a need for palatability to be considered alongside the dimensions, appearance and individual needs of each patient.

4.5. Discussion

4.5.1. Main findings

This study found that the formulation of oral solid dosage forms has an impact on an older person's ability to identify, handle and swallow oral solid dosage forms. Figure 4.8 illustrates the relationship between key characteristics and each stage of the medication taking process. The characteristics can be classified into three main categories: dimensions, appearance and palatability [220]. The dimensions have an impact on all stages; in general, small round tablets (≤ 7 mm) are least accepted amongst older people and their carers and were perceived to have a negative impact on all stages. The size and shape alongside the use of bright colours can make tablets easy to identify, distinctive and memorable. Markings can be used to aid identification; however, this is largely resorted to when all other characteristics are similar. Palatability, while useful to enhance swallowability, also has an impact on the visual appeal and memorability of the tablet. Several other factors also determine preferences for formulation characteristics, as summarised in Figure 4.9, and there is a need to ensure these are also considered when designing an older person's patient centric drug product.

Fig. 4.8. The relationship between key characteristics and each stage of the medication taking process

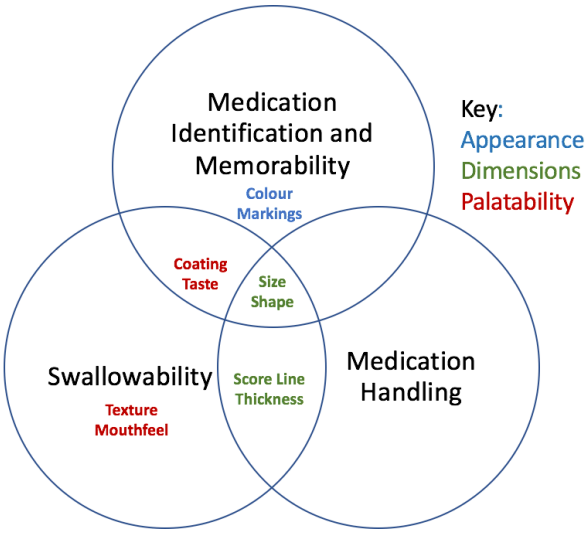
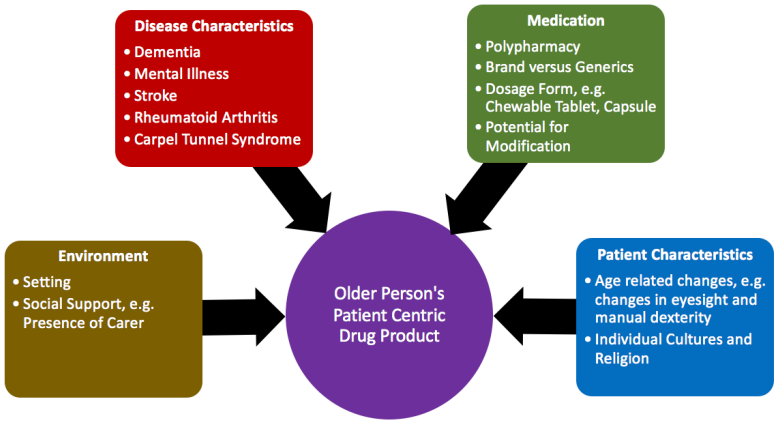


Fig. 4.9. A holistic approach towards the design of an older person's patient centric drug product- four key areas have an impact on preferences for formulation characteristics



There are parallels between the factors illustrated in Figure 4.9 and the International Classification of Functioning Disability and Health - a model that defines health by considering the interaction between a number of different components [221]. One of these key components includes environmental factors, such as the physical and social environment, support and relationships. These can all act as barriers or facilitators to a person's functioning [221]. Environment is a key area illustrated in Figure 4.9, as the setting and presence of support was found to influence an older person's ability to take medication as directed. Body function is another key component of the model, and includes physiological functions such as sensory functions. This relates to both patient and disease characteristics as illustrated in Figure 4.9; age related changes and specific conditions such as dementia and stroke both have an impact on body function which in turn influences the patient's adherence and acceptance to medication.

4.5.2 Comparison to other studies

Medication identification is complex for older people who are taking a greater number of medications [5]. Studies in polypharmacy patients (aged 29-80 years) have highlighted the importance of formulation characteristics for these patients; the use of white tablets was described as "boring" and innovative shapes such as a heart for cardiovascular medication can further improve medication recognition [222]. Older people are also more likely to suffer from visual impairment [223] and, therefore, commonly recognise oral medications based on their size, shape, colour and embossing, rather than reading the product label [3]. In particular, tablets with two colours result in faster detection times [102]. This study supports these findings and further highlights the importance of colour alongside coating and taste to make tablets easy to identify and memorable. However, changes in appearance that arise as a result of different brands and generics can significantly increase the odds of non-persistence, which may have important clinical implications [224]. Advice from GPs and pharmacists is key to improve the use of these tablets [225]; however, the present study highlights

that changes are often not explained to patients, which can result in increased anxiety and reduced acceptance.

The dimensions also have a significant impact on the removal of medication from packaging and handling. Findings from the study highlight the difficulties associated with small round tablets (≤7 mm), especially due to the flat side, which can make picking difficult. Previous studies in the general adult population (aged 18-45 years) have used 3D printing to create a tilted diamond shape in order to tackle dexterity issues; the shape remains on a tilted position while on a flat surface, thereby allowing for easy picking [226]. However, despite being specifically designed for ease of picking, this shape scored lowest during the picking session [226], highlighting the need to involve patients when optimising dosage form characteristics. Healthcare professionals in the present study discussed the potential to assess the patient's ability to handle medication prior to dispensing. However, the findings highlight the need for this to be broadened to include informal carers, who are often responsible for handling and administering medication. Informal carers often find the role of medication management challenging [219] and the present study highlights some difficult decisions they need to make as part of the medication administration process, such as asking for alternative brands due to the potential for non-adherence.

The use of larger tablets to aid handling requires a balance alongside the swallowability. Previous studies in healthy adult males (aged 24-33 years) have found that swallowing larger tablets (greater than 8 mm) requires significantly more swallows and more effort than smaller tablets [227]. Patients use management techniques to overcome difficulties, including drinking more water, splitting/crushing tablet or mixing it with food [83]. Similar management techniques were reported in this study, with participants using characteristics such as the break mark to modify dosage forms; however, this can affect the stability, safety and efficacy of the drug [134]. Consideration of the shape may help to overcome some of these challenges as the oesophageal transit of tablets is dependent on both shape and size [132,133]. Oval shapes have a faster oesophageal transit time compared to round tablets [132] and the study supports older peoples' preferences for oval and caplet shapes in comparison to large round formulations of paracetamol and metformin.

Smaller tablets (≤ 6 mm) can also present their own challenges. These tablets are difficult to feel in the mouth and can therefore lead to the perception they have not been completely swallowed, highlighting the importance of mouthfeel when optimising swallowability. Similar findings were reported in a study investigating patients' willingness to pay for oral solid dosage forms; older patients were less negative about larger sized tablets, partly due to the difficulties seeing and swallowing smaller sized pills [228]. Difficulties swallowing as a result of tablets being "too small to sense" have

also been reported within the general adult population [229]. Optimisation of swallowability with a sole focus on the dimensions of the dosage form is therefore challenging, and the present study highlights the need for a more holistic approach, taking into account the palatability to overcome some of these difficulties.

Palatability has been defined as "the overall appreciation of a (often oral) medicine by organoleptic properties, such as vision (appearance), smell, taste, aftertaste and mouth feel and possibly also sound (auditory clues)" [77]. Optimisation of taste, mouthfeel and texture can all be achieved through the use of a coating; uncoated tablets require more water to swallow, take longer to swallow and cause tablets to lodge within the oesophagus [123]. The results in this study support these findings, with older people in general highlighting the superior mouthfeel, texture and swallowability of coated preparations. Preference for taste is often more personal and can differ between individuals; a previous study (in participants over 18 years of age, n=300) found that while the majority (55%) had a preference for a dosage form that did not taste, some (40.7%) preferred a sweet taste while others (4.3%) had a preference towards a bitter tasting tablet [230]. Similar results were found in the present study, with preferences for taste varying between participants; patients taking a large number of tablets described the potential for taste to improve memorability, while those within care homes had a preference towards no taste at all, highlighting the need for a personalised approach when considering this aspect of palatability.

4.5.3 Strengths and Limitations

The qualitative design of this study was based on findings from a systematic review, which highlighted the paucity of qualitative research in this area [220]. The study involved older people, informal carers and health and social care professionals, providing the perspectives of all those involved in an individual's therapy. The use of placebo tablets provided participants with a point of reference to communicate their ideas. Purposeful sampling was used to target participants from a range of ethnicities; however, these participants were particularly difficult to recruit, despite the lead researcher having a South Asian heritage. Older people unable to provide informed consent were excluded, although swallowing difficulties are commonly seen in patients with cognitive changes [231]. The study did, however, include the views of health and social care professionals who are often responsible for administering medication to these patients.

4.5.4 Future work

The present study highlights the impact of external factors (Fig. 4.9) on preferences for formulation characteristics and future work should aim to explore these in further detail. Further exploratory work

on the impact of conditions such as dementia is particularly important, due to the progressive nature of these diseases, leading to a shift in responsibility of medication management to informal carers [219]. Further work is also needed in Minority Ethnic groups; future work can help determine whether factors such as language barriers may result in greater emphasis being placed on certain areas of the formulation, such as the appearance. Previous studies both within paediatrics and the general adult population have explored the use of 3D printing to improve acceptance [226,232]; further work should explore the use of this technology in the older population, taking into account the recommendations made in this study. In order to ensure patient centric medicine design, future work in this area should also include working in collaboration with the pharmaceutical industry, so that recommendations can be incorporated into the Quality Target Product Profile for specific drug products.

4.6. Conclusions and Implications

Medication adherence in older people is challenging and a key determinant of this is acceptability. Characteristics of oral solid dosage forms are key for ensuring acceptability and, therefore, adherence. There is a need to consider the medication taking process as a whole when optimising these characteristics. Tablets must be visually appealing and memorable, be easy to handle and have optimum swallowability (by considering the dimensions and palatability side by side). The identification and memorability (including the size, shape, colour, markings and coating) and handling (including the size, shape and thickness) of oral solid dosage forms, in particular, is of greater importance for older people and informal carers self-managing multiple medications.

A further key finding from the results is the importance of considering individual preferences; each person is different and patient centred care is therefore key. In particular, environmental, patient, medication and disease characteristics may lead to a greater emphasis being placed on certain stages of the medication taking process, and these factors therefore also determine preferences for formulation characteristics. Overall, developing an age appropriate dosage design for older people requires a holistic, patient centric approach to improve acceptance and adherence.

Part of this holistic approach also involves considering the role of health and social care professionals in the provision of patient centric medicines. The current study highlighted the importance of advice from GPs and pharmacists to improve adherence to medication, especially when different brands are dispensed. However, the systematic review in Chapter two found that there is a need for further research that defines the role of health and social care professionals in this area. The following Chapter will therefore explore this role in more detail, looking in particular at the facilitators and barriers towards the increased involvement of health and social care professionals in the provision of patient centric medicines.

Chapter 5- Findings from Semi-structured Interviews: Facilitators and Barriers Towards the Increased Involvement of Health and Social Care Professionals in the Provision of Patient Centric Medicines

5.1. Introduction

The findings from Chapter four highlight the characteristics that need to be taken into account when considering an older person's patient centric drug product. However, a key finding from the systematic review in Chapter two is the need for health and social care professionals to ensure these patient centric drug products are then prescribed and dispensed appropriately so that patients receive the most suitable formulation. This includes a need to consider the formulation alongside the active ingredient prescribed [82]. Healthcare professionals should take steps towards understanding the patient's experiences and attitudes towards their treatment as well as engage the patient in shared decision making [82,233]. Information can be used to select a medicine that has the most appropriate characteristics for a certain individual, such as a dosage form that causes fewer swallowing difficulties [84,117].

This Chapter will discuss the findings in relation to the role of health and social care professionals in this area. Thematic analysis of the results led to the development of two key themes: 1) Barriers towards the increased involvement of health and social care professionals in the provision of patient centric medicines and 2) Facilitators towards the increased involvement of health and social care professionals in the provision of patient centric medicines.

The barriers have been split into three sub-themes: a) knowledge based barriers b) the availability of patient centric medicines and c) gaps in communication.

The facilitators have been split into four sub-themes: a) proactively encourage the reporting of issues surrounding formulation b) identify individual patient needs c) implement shared decision making and d) a collaborative, multidisciplinary approach between health/social care professionals. These themes and subthemes have been summarised in Table 5.1.

Table 5.1 Summary of themes and subthemes – the role of health and social care professionals in the provision of patient centric medicines

Theme	Subtheme
Barriers	Knowledge based barriers - Ease of access to details on the formulation - Knowledge of patient needs
	Availability of patient centric medicines - Inconsistencies in the characteristics of the formulation - The need to modify formulations and the consequences of these modifications
	Gaps in communication

Facilitators	Proactively encourage the reporting of issues surrounding formulation
	Identify individual patient needs
	Implement shared decision making
	A collaborative, multidisciplinary approach between health/social care professionals

The present Chapter will explore these themes further; each of the themes and sub-themes will be discussed and illustrated with quotes from participants. These participants include health/social care professionals, patients and carers. The discussion will then focus on the wider implications of these findings and how this work is an important part of answering the thesis question. It will also discuss the strengths and weaknesses of the study and suggest topic areas for further research. Finally, this Chapter will conclude with how findings in relation to the role of health and social care professionals in combination with previous findings led to the work carried out in Chapter six.

5.2. Barriers

5.2.1. Knowledge based barriers

5.2.1.1. Ease of access to details on the formulation

Healthcare professionals who directly handle medication either in the dispensing or administration process are more likely to be aware of the formulation characteristics and therefore be able to adopt a patient-centric approach. All three GPs interviewed working in community highlighted that when prescribing medications, they very rarely will have any information relating to the physical characteristics of the medication itself, making it difficult to ensure patients are receiving a formulation that is tailored to their needs:

"I'd say GPs and probably doctors in general don't have great experience of the tablets themselves, you know, we're not dispensers here. Even in a dispensing practice it won't be a GP that does the dispensing so, you know, if I prescribe a pill I'm aware of the milligrams, I'm not really aware of whether it's big or small and, you know, the excipients or the capsule shape" (HCP1)

"I think having an idea of the type of medication that you're prescribing is always beneficial. I think the problem is, the issue is that when prescribing, you almost never know what the actual product looks like. And then, I think, if you are more aware of the actual physical characteristics, that might help guide the prescription" (HCP3)

"I think as clinician I've never seen any tablet, apart from Warfarin which we know the obvious colours, it's really I've never had a look at tablets. So I think it's a bit difficult that way, yeah." (HCP25)

This was further picked up by a patient, who questioned whether GPs would be aware of characteristics when prescribing and identified this as a barrier towards their further involvement in this area:

"I mean will GPs for example, know what that tablet is there? Will they know the shapes and sizes of the tablets they're prescribing? Unless they're actually on them themselves" (P7)

In order to access information about formulation characteristics, there is a need to access resources such as the Summary of Product Characteristics (SPC). However, the time associated with checking these characteristics resulted in GPs delegating this task to pharmacists instead, who often have easier access to the characteristics of a dosage form:

"And also easy access isn't it? Because I'll probably spend a few minutes to find out what shape or colour it looks and you'll have to go through the SPC and everything. So I would normally get the pharmacist to have a look and advise if they're having any problems." (HCP25)

While pharmacists, pharmacy technicians and dispensers have easy access to details on the formulation, discussions in relation to these characteristics rarely took place. Community pharmacists suggested that they rarely have an "opportunity to have that type of detailed conversation with patients" and that instead there is a current focus on dosage and side effects when they do have consultations with patients. They further highlighted that these conversations currently do not take place at the point of dispensing, as often the characteristics are not something the pharmacist actively thinks about discussing with the patient. As a result of this, identifying issues with formulation is dependent on the patient reporting problems:

"Maybe we do not discuss that in terms of when you're dispensing medication to a patient that it might be difficult to swallow, or 'let me know if you're having trouble swallowing this or if you're not happy taking this particular formulation'. We never really go down that route, we probably just speak about well, the side-effects if they're very significant, bring those up and how many times to take it, if ever we get an opportunity to have that type of a detailed conversation with patients. But hardly ever I think in a conversation do we bring up the ease or the hardship the patient might face in actually swallowing the tablet, that's something we don't talk about and I suppose if it is, then the patient themselves takes that responsibility to bring it up as a problem." (HCP14)

While easy access to characteristics is therefore important, there is also a need to actively ask about issues in relation to formulation and this is discussed further in Theme 5.3.1. The difficulties arising from easy access to formulation characteristics amongst certain healthcare professionals was also identified within secondary care. A locum senior house officer, for example, stated that as nurses

often administer medications within these settings, they are more likely to be aware of characteristics and the difficulties that arise as a result of these:

"I think we are quite prone to prescribing medication not really knowing what form it comes in, so the size of the tablet or the capsule. And then it's usually the nursing staff who will highlight if a patient is struggling to take the medication. So if it's too large or difficult to swallow for them" (HCP19)

There is therefore a need for effective communication and collaboration between healthcare professionals due to the differences in accessing information on formulation characteristics. This was identified as a potential facilitator and has been discussed further in Theme 5.3.4.

5.2.1.2. Knowledge of patient needs

Similar to 5.2.1.1., health and social care professionals responsible for dispensing or administering medication were often more aware of individual patient needs and therefore more able to ensure a patient centric dosage form was provided. Pharmacy technicians working within secondary care suggested that while it should be a team effort to change a formulation, the nurses would most likely be the ones who are aware of the need for this change:

"It would have to be like a complete team to try to change it or alter it or, but the nurses deal with the patients more closely than the doctors and the pharmacists." (HCP15)

Community pharmacists are ideally placed to discuss how the patient's healthcare conditions may impact their ability to take their medication as directed; however, while they had an appreciation for the condition itself, often this was not linked to the patient's ability to take their medication as directed. One reason for this suggested by a pharmacist was the lack of experience visually seeing patients taking their medication. This results in a lack of appreciation for the problems that may arise:

"I think sometimes as pharmacists we, because we're not there when they're taking tablets we don't always appreciate or experience the difficulties people have" (HCP7)

An older person's specialist pharmacist, in contrast, had experience of seeing older people taking their medication, and was much more aware of the individual needs of older people, and was therefore able to provide more detail on what may constitute an older person's patient centric drug product:

"I mean I think from my perception of seeing older people take medicines, that kind of size (12 x 7mm oval) is ideal because it's oblong and it's medium. With the smaller round tablets (6mm and 7mm round), obviously they're easier to swallow but there's dexterity issues isn't there? Picking them up and actually manually handling them" (HCP8)

Social care professionals working within care homes also had more information on the preferences that individual patients had, and highlighted the need for this to be communicated back to the GP and pharmacist to ensure a patient centric medication was then prescribed and dispensed:

"For instance the pharmacy we are using, we are the ones that pass the information to them to say, this is what we can do, this is what we cannot do, because they are doing medication generally, they don't know who is who, they don't even know the names of the service users, they have not even seen any of them." (HCP24)

This again highlights the importance of effective communication between health and social care professionals, and also highlights the need for professionals such as pharmacists to actively enquire about any difficulties the patient may be experiencing. These important facilitators to overcome the barrier arising from the ease of access to information have been discussed further in Themes 5.3.1 and 5.3.4.

5.2.2 Availability of patient centric medications

5.2.2.1 Inconsistencies in the characteristics of the formulation

The inconsistencies in the characteristics of a specific formulation can pose a further barrier towards the provision of patient centric medicines. A practice based pharmacist highlighted that while it was possible to phone community pharmacists to check availability of formulations of a certain shape or size, they "might just be dispensing what they get in." Often, the characteristics of specific drug products would change, and another practice based pharmacist highlighted that unfortunately this was a common occurrence that made it difficult to ensure the products supplied to patients had a consistent appearance:

"It's the way that the pharmaceutical industry is funded that we have…what would be ideal would be that you had the same box with the same colour tablets in, every single time that you got them, but the reality of the way the system works is how would that happen?" (HCP6)

An older person agreed, and suggested that ensuring patients receive patient centric medicines would be difficult due to the range of manufacturers that produce a single drug product:

"I think, you see it's very difficult, I mean are you looking to ask the world to make say Candesartan 2mgs all the same size, shape and colour? I mean that's one of the problems isn't it? The changing you see… But again I don't see how anyone could do anything about that because different firms make them all over the world. (P5)

Another older person also agreed with this, and suggested that to receive patient centric medicines, companies manufacturing the medications would require "more guidelines:"

"It would be nice if the companies manufacturing the drugs… if they had a bit more guidelines, like in this case colour or size or shape and they had similar, if they have their own stamp on it it doesn't really matter, show that it's theirs and not someone else's but to me the colour is the most important one of all" (P2)

The inconsistencies between different formulations of the same drug often arose due to various generic preparations being available for dispensing when drugs came of patent. This can result in the same drug having multiple different formulations, and patients receiving a different formulation each time their medication is dispensed. One patient highlighted the need for the pharmacist to make a written note about the importance of a caplet shaped paracetamol formulation, rather than the circular shape:

"I said to (the pharmacist) one day, "I'm having a problem," and she said, "I'll put on your sheet, you know," that I think it probably is on here actually, and I'm sure she put it on that I've got to have caplets" (P4)

While in this case the pharmacist took an active role to ensure a consistent, patient centric formulation was provided, healthcare professionals highlighted that this was not always possible and that the formulation dispensed would often depend on what is the cheapest available preparation on the day. One practice based pharmacist highlighted that patients are not always accepting of generic versions especially when they have previously received a brand, but that their priority is to ensure the most cost-effective treatment is dispensed:

"Yes, you had Lipitor for 20 years and now we have Atorvastatin, and you don't like Atorvastatin… But actually, at £26 a month we can't afford to give you the Lipitor, we used to give it you because there wasn't a choice and now there is a choice, we have to go with what's cost-effective" (HCP6)

This can also result in changes to the formulation of dosage forms provided to patients during a stay in hospital. Prescribing policies within secondary care can often differ to those within the community to maximise cost effectiveness, resulting in patients often receiving a different brand and difficulties ensuring that these are patient centric:

"Sometimes the colour can even change, the shape, and obviously the hospital, they have to buy in whatever's like, whatever deal they're getting, so it's not maybe what they've been used to having in community" (HCP15)

While these barriers may be difficult to address without significant input from regulatory bodies and the pharmaceutical industry, healthcare professionals have an important role to explain any changes in the appearance of a medication to the patient. This can help overcome some of the confusion that arises when patients receive different brands and can help ensure a patient centric approach is taken where any significant difficulties with certain brands can be identified and addressed. The importance of shared decision making has been explored further in Theme 5.3.3.

"They're quite difficult sometimes because when I get my medication, it's obviously generic so a different manufacturer will give a different colour, or no colour at all for that matter or a different size and you know if you're taking, like I say, Memantine, if it changes colour you think, well I wonder what that is I've got there, is it Memantine or not, so there might be a slight confusion." (P2)

5.2.2.2. The need to modify formulations and the consequences of these modifications

Certain formulations available on the market were identified as being inappropriate for the needs of individual patient groups. There is sometimes a need to modify dosage forms, and healthcare professionals may need to search guidelines to check which formulations can be modified safely:

"My pharmacist colleagues contact me about issues around their medicines and inability for patients to swallow, they've had to refer to the NEWT guidelines to look at alternative mechanisms to ensure that the patient's able to swallow a tablet, capsule or a liquid." (HCP5)

"I think, when someone does have an issue… it's all about them trying to find out if it can be crushed or not. So I can remember using a particular website to find out if it could be crushed." (HCP3)

However, the modification of medication often had to be balanced against the necessity of providing an unlicensed product. Healthcare professionals highlighted that often, there are no suitable alternatives available and that there is a need to therefore modify a dosage form which may require "bending the rules." The dilemma of balancing the greater responsibility associated with providing an unlicensed product would have to be balanced against the needs of the patient:

"*If you've got a capsule opening it might happen if there's, you know, if there's limited alternatives, so you're always trying to act in the patients' best interests and sometimes the rules aren't flexible enough for each patient" (HCP1)*

"Sometimes you might consider whether a capsule can be broken in two and sprinkled on food. Crushing tablets is something else that people probably do and in certain cases that's not a good idea, as I'm sure you know probably better than I do. And actually, arguably if you start crushing stuff you're actually making a new product in sort of regulatory eyes, unless it's in the SPC." (HCP7)

Healthcare professionals therefore highlighted the need to constantly re-assess and balance the need to modify formulations and patient safety. This is especially true for residents in care homes, for whom medications were constantly modified to ensure patient acceptance and adherence. This required effective communication with GPs and pharmacists, and all care professionals described the importance of ensuring that there were appropriate approvals in place before tablets were modified:

"No, we're not allowed to break them in half. If we've got the letter from the doctor, we can either give them covert which is put in food and drink and if we've got the doctor's signature we've got a specific, it's like a little crusher, and certain tablets, not all tablets, can be crushed" (HCP27)

Clinicians may therefore need to work outside guidance with medicolegal consequences or risks. There is a need for healthcare professionals to take an individualised approach when considering the most appropriate formulation. The risks associated with modification can sometimes be overcome by effective communication and collaboration between healthcare professionals. Participants identified, for example, the potential to sometimes change to an alternative formulation such as a soluble formulation, or the potential for an alternative class of medication to be prescribed:

"I mean certainly with the big round Adcal we've quite often gone to a soluble version or a caplet, which I believe are actually slightly bigger than that one (18 x 7mm caplet) but because of the taste and the size of the tablet" (HCP8)

"I mean if you were looking at Azithromycin 500mgs, they're massive aren't they? And you might think "oh they're bloody big tablets so let's think about either the formulation or another macrolide maybe"" (HCP7)

"If they've got a problem with taking a particular tablet, well do they have a liquid version? I mean I don't easily go to liquids, but you know, if we really needed to." (HCP6)

These solutions can be reached when problems with a formulation are identified and then communicated between professionals involved in the care of a patient: a facilitator discussed in further detail in Theme 5.3.4.

5.2.3. Gaps in communication

The potential for healthcare professionals to be more involved in providing patient centric medicines requires effective communication between all those involved in an older person's therapy. However, the frequent lapse in communication was identified as a barrier towards implementing this. This was two-fold- the lapse between professionals, and the lapse between patient/informal carer dyads and professionals. When considering communication between professionals, a key area that was required

attention was the communication between pharmacists and GPs. Pharmacists highlighted the need communicate further with GPs when doing reviews, especially when non-adherence due to formulation characteristics was identified. One community pharmacist suggested that this is currently where the lapse is and by highlighting more appropriate formulations, non-adherence issues could be addressed:

"It's at that point when you notice that patients aren't adherent, to pick it up, find a reason and offer solutions and offer options, and even offer those options to GPs because I think that's where maybe the lapse is." (HCP14)

The communication between healthcare professionals and patients/ informal carer dyads is a further barrier to consider. Older people suggested that they did not report difficulties as they never thought it was a "sufficient problem" that required reporting:

"I haven't really thought that there's a sufficient problem. I mean, this one was [laughs] well the Ibuprofen thing will stay in my memory for ever more, but the others I just regard as well, just temporary, you know, a temporary blip, oh, well, it was a bit difficult to swallow last night" (P3)

Many older people instead described management techniques used to overcome difficulties, such as modifying tablets by breaking in half, taking with food and drinking more water. Patients were, in general, more accepting about the need to take medication; they viewed it as a necessity and were therefore less likely to voice any issues:

"Nothing is important to me. If I'm told to take them, I take them. I just think they're not giving me to take them because of anything else, they're giving them because I need them." (P17)

"I'm quite sort of, matter of fact about this stuff, you've got to take it, you've got to take it, just take it." (P18)

Because patients are accepting, they often develop workarounds for formulation issues which may not always be appropriate. One patient, for example, suggested that they would look into the literature of what modifications can be made to a specific formulation. While this may be helpful in some circumstances, a discussion with a healthcare professional would be more beneficial and would result in a more patient centric approach being adopted:

"Well I suppose I would look and see if it said anything about it either not to be broken in half or small pieces, I'd look to see what it said on the box" (P5)

Some informal carers suggested that if they had been asked about problems during the when the medication was initially prescribed, they may have been more likely to report a problem. However,

having taken the medication for so long, people often adapt and get used to it. Other informal carers also reported management techniques; a carer of a patient with dementia discussed her uncertainty over how to deal with concerns should they arise in the future. Rather than report these to a healthcare professional, she discussed her own potential management technique for dealing with the difficulty:

"But I don't know what to do about that, if he starts having any more problems, I think it might be an option to say well what about going, upgrading what you take them with, and taking them with milk, because he does always have fresh milk in the fridge. So that would be an option if things got more problematic I think." (C2)

As discussed in Theme 5.2.1.1., pharmacists often don't think about asking about these difficulties and therefore are often not aware of the issues patients and carers experience. There was a perception amongst some older people that healthcare professionals, especially community pharmacists, could do more to help ensure patient centric medicines were provided:

"We do have actually a new pharmacy attached to the doctors, the health centre, and they used an interview room and there is also a quiet booth with screens as well, so there's every opportunity for the pharmacist to talk to you, but 9 times out of 10 you don't even see the pharmacist, it's one of the girls just behind the counter, isn't it?" (P7)

Healthcare professionals agreed, and highlighted that while it should be everyone's responsibility to ask patients about difficulties they may be experiencing so that patient centric medicines can then be prescribed and dispensed, often this is not the case, resulting in gaps in communication:

"I'd like to say everyone. [Laughs] But in reality, does it happen? I would say probably not. It should be everyone's responsibility to actually ask if someone's been able to take that medication and that goes across primary care, secondary care and in community. However, does it happen? We know it doesn't." (HCP8)

There is therefore a need to improve communication between healthcare professionals, and also between healthcare professionals and patients. This was identified as an important facilitator, as discussed further in Theme 5.3.4.

5.3. Facilitators

5.3.1. Proactively encourage the reporting of issues surrounding formulation

As discussed in Theme 1.3., older people often do not report problems with the formulation and this can result in gaps in communication. Proactively ensuring that patients are aware of the need to report

any issues can help make sure that they are then involved in the most appropriate treatment option, and this was identified as a potential role for pharmacists:

"Perhaps it's also a responsibility of the pharmacist to inform the patients directly that they need to bring up any problems or issues" (HCP14)

Enhanced medication reviews were suggested as a tool to help encourage the reporting of any issues surrounding formulation. Pharmacists in particular suggested that these discussions can take place as part of the medication review process, during which they have the opportunity to ask patients how they are taking their medication. One pharmacist further suggested that it was their responsibility during these reviews to ask the most appropriate questions; however, as discussed in Theme 1.1.1., the extent to which this is currently implemented is limited:

"I think we probably do have a responsibility to refine it for the patient and to, when we're doing med reviews and things like that, ask those questions." (HCP7)

A prescribing advising pharmacist suggested that a template could be added to the current medication use review process to facilitate discussions surrounding the characteristics of tablets if patients do report having any difficulties taking their medication. This would enable pharmacists to easily ask the appropriate questions and ensure that the topic of formulation characteristics is explored in a more standardised way:

"I guess we could set up a kind of, during medication review process, maybe set up a template, that forms part of that medication review if we identified that there is a swallowing issue then it kind of kicks into this 'Well let's have a look at behaviours and adherence' in that you'll potentially move on to 'What size tablet would you prefer? What shape would you prefer?', bolt on to the review process" (HCP5)

An older person's specialist pharmacist agreed, and highlighted the need to ask the right questions during the medication review process. Rather than a sole focus on factors such as whether the medication works, this will enable a more holistic approach to determine whether the patient can take the medication initially:

"Well I mean for me it comes down to a good medication review and asking the right questions to get the information that you need. Because you can do a medication review and not actually find out what's the problem but you can do a good medication review and actually find out what is really the issue and it's sometimes not the medication as in what it does, it's actually they can't take it or they don't like to take it, or that particular one gets stuck or they can't see to pick it up, so I would say it's all about a good medication review" (HCP8)

In addition to asking the correct questions during the medication review, participants highlighted the importance of a close relationship with patients that would further encourage patients to report any issues. Whether or not older people voiced concerns over formulation characteristics was dependent on the relationship formed with healthcare professionals. If a community pharmacist could develop a close relationship then older people could be more willing to report difficulties as and when they were experienced:

"But I do, I mean the pharmacist's a lovely brilliant person, and if I have a problem anywhere, any way with pills I would always go and see the pharmacist." (P4)

"I'd report it back to the surgery, or to the pharmacist, they're very good at the pharmacy down the road" (P9)

Health care assistants and receptionists working within GP practices also had an important role in passing on any information in relation to problems with formulation characteristics. Their patient facing role meant that they could build up a rapport with patients and pass on any information as required. One health care assistant described this as an important part of her current role in this area, and informal carers also identified the receptionist as often being their first point of call if they had issues in relation to the formulation characteristics:

"I can build up quite a good rapport with them… that they are able to approach you, and perhaps sometimes when they don't always want to approach the doctor, they mention things to me if they're coming for a blood pressure check or you know, annual reviews for certain conditions and they tend to open up more to me, and I will then follow it up" (HCP2)

"Actually, my first port of call would be the receptionist" (C4)

As well as encouraging patients to voice concerns with formulation characteristics, building a strong rapport can also help healthcare professionals to identify the individual patient's needs (an important facilitator as discussed in Theme 5.3.2). Care professionals, for example, had a close relationship with patients which put them in an ideal position to notice issues in relation to formulation characteristics:

"We spend the most of the time with them and we actually, I think we know them better than the nurses and the management to a certain extent so, we are the ones who are actually in a better position to be able to make, to notice those things." (HCP22)

5.3.2. Identify individual patient needs

Patient preference and choice is important when considering a patient centric approach and there is a need to watch and work with patients to identify individual needs. Health and Social Care

Professionals were aware of the need to "know your patient" and highlighted the importance of first identifying individual patient needs so that patient centric medicines can then be prescribed appropriately:

"I think you need to know your patient don't you?" (HCP9)

"I think it has to be very individualised to that person" (HCP11)

"I think it will obviously vary patient to patient." (HCP19)

Identification of these needs can help to identify patients who struggle with formulation, and these conversations can potentially take place at the point of prescribing:

"So around that I think you've got to know your patient, you've got to understand your patient's needs haven't you? And also I suppose you've got to ask them before you whip off a prescription "are you going to be alright taking these?" And it's about having those conversations." (HCP9)

Identification of individual patient needs is particularly important in the older population due to the heterogeneity of this population. A nurse highlighted that care must be provided according to the level of support that individual patients required:

"It depends on the people actually, the people who are more active in their life or can do things by themselves, it's okay for them, but as the days go when they get older and older it is difficult for them to manage, so they need some support to deal with their medications" (HCP17)

A locum senior house officer within secondary care expanded on this, and highlighted the difficulties with a one size fits all approach by referring to the age-related changes which must be considered when providing a patient centric medicine, as well as the level of support individual patients may have. Consideration of all of these factors is an important facilitator towards providing patient centric medicines:

"I suppose that would be on a case-to-case assessment… where you establish what level of ability they have in terms of swallow. If they're alone, if they've, what sort of level of manual dexterity of fine grip that they might have. I imagine patients with rheumatoid arthritis with very deformed hands would probably struggle more trying to pick up small tablets and whatnot. And if they've got any visual issues, so we have quite a few patients who have poor vision" (HCP19)

The importance of identifying individual patient needs was also highlighted by healthcare professionals working within the community. There was an increased emphasis on the importance of building a strong relationship with patients by providing an enhanced level of care that is dependent

on knowing the individual needs of patients. This also relates to the need for improved communication and listening to the needs of the patient by showing empathy, as discussed in Theme 5.3.1.

"I think it's just caring about people. Rather than dismissing people and putting everybody into one category, it's important to treat people as individuals" (HCP2)

Pharmacists agreed, and highlighted the importance of considering an individual patient's lifestyle which will then impact what their individual needs and requirements are:

"The first thing is communicating with the individual patient, it's establishing exactly what their needs are and then what their individual requirements are based on the certain lifestyle." (HCP14)

Older people living within care homes can also represent a heterogeneous population. One care support worker suggested that there was therefore a need to assess residents on a "case by case" basis in order to ensure patient centric medicines are provided:

"I think they have to be assessed on it, one-by-one really and then the nurse has to take it from there really" (HCP23)

In addition to the heterogeneity of the population within care homes, different care homes work in different ways and this can be a further complicating factor. One social care professional therefore identified the need for research to be conducted within different homes, and recommendations to be made based on the way in which each home operates:

"I think... get information from different homes. You have been to this place, you have seen how we assess, we get it based on our own service users, so if you go to a different home there might be different answers compared to what you got here." (HCP24)

5.3.3. Implement shared decision making

Shared decision making was a potential facilitator identified by participants. Healthcare professionals may have a different opinion on what the most appropriate characteristics are compared to the preference of the patient. This can result in a barrier towards providing patient centric medicines and can be due to a lack of knowledge of the individual patient's needs (Theme 1.1.2). Participants therefore highlighted the importance of involving patients in decisions about treatment options:

"I think it's really important to involve your patients in the choice of medication, so having a concordant sort of approach to consultations" (HCP13)

"About the patient choice, so just because I feel, actually, you might be better with, say, I don't know, this middle one because it will be easier for you to swallow, but it might be too big for them." (HCP11)

Healthcare professionals need to be well informed about the characteristics of tablets to maximise shared decision-making and thus potentially improve acceptance and adherence. This will help ensure professionals have all the available information that can then be communicated back to the patient, helping the patient in the shared decision-making process:

"I think also possibly, having the information on each item, like if you can possibly have like a survey from patients themselves, just to find out which one they find easier to swallow. And then you can kind of help that, a new patient commencing on that medication, they can make a more informed choice." (HCP3)

Nurses also referred to the importance of shared decision making, again highlighting that while it is important for the patient to make a choice, healthcare professionals have the responsibility of ensuring they provide the patient with the necessary information:

"There's the health professionals, there's a degree of continuity, there's good information and helping people make shared decisions about, you know, what's right for them." (HCP10)

Involving informal carers in the decision-making process was also identified as an important part of providing patient centric medicines as they are often responsible for noticing whether patients experience difficulties taking their medication. HCPs needed to proactively ask both formal and informal carers about support need to empower the patient.

"I think it's about talking to, if people are in residential care, or supported living, is to talk to the family members or the carers to get their take on how they think we can empower people to take their medication, because we shouldn't just take it off them just because we think, oh well, actually, their eyesight's poor or their hands aren't particularly good or they've got dementia, I think we need to empower them to be able to do that." (HCP11)

5.3.4. A collaborative, multidisciplinary approach between health/social care professionals

The majority of healthcare professionals suggested that a multidisciplinary approach, involving all types of staff in addition to informal carers, must be taken to identify issues that arise as a result of formulation characteristics:

"*That ranges from healthcare assistant all the way up until GP, pharmacist, whoever. It needs to be everyone's problem, making every contact count, otherwise there's no point. Including the carers as well. If you miss anyone out of this jigsaw puzzle, then you've missed an opportunity to make that change and optimise that treatment" (HCP5)*

"It is obviously working with the Pharmacist's and the GP's and I think it's probably us all collaborating together to help our patients at the end of the day comply. People are living longer, and we want to help them live longer. But if they are struggling to take medication then we have got to try and come up with solutions to help them, haven't we really?" (HCP12)

"It's not just one particular healthcare professional, it will mean starting from prescribing to dispensing to administering it, to help the patient, carers, and everybody I think should be involved, you know, what it is and how we make those changes" (HCP25)

The team should also include social care staff:

"I think every one of us as a health care professional, if we're involved in that patient's medication, their social care or their, you know, if it's their mental health or their physical health, we've all got a responsibility that if we identify something that we do something about it." (HCP6)

Social care staff may be more able to identify any issues due to the strong rapport they are able to build with patients (Theme 5.3.1). All care professionals highlighted, however, that while they were able to identify any concerns in relation to formulation characteristics, these would then need to be reported back to the appropriate healthcare professional to ensure an appropriate formulation was prescribed. This highlights the need for collaborative practice to ensure the final preparation administered is patient centric:

"When they're prescribing for us, if we're receiving from the pharmacy, we now need to say oh, this particular service user, this is not going to work, we need to ring the doctor. So, we'll now ring the GP and say, oh we received this but it's not going to work for us, if you can change it in a liquid form or change it in a different form, this is the physical health issue that a particular service user facing, so they will now say, okay, we will change it to something better for them to swallow it." (HCP24)

The degree of collaborative practice can vary according to the setting. Within secondary care, a greater level of collaboration between healthcare professionals was reported, and this was key towards providing patient centric medicines. Hospital staff nurses and deputy ward managers all referred to the importance of collaborating with doctors and pharmacists when patients could not swallow preparations. A decision would then be made as to the type of formulation to be prescribed.

"In the hospital, if the patient is not tolerating with any kind of tablet, we refer that to the doctors… or we will refer that to the pharmacies" (HCP17)

A locum senior house officer within secondary care highlighted this as a part of their current role to ensure patients receive appropriate formulations. Communication with the wider team can help

identify and address any issues with inappropriate formulation characteristics, which in turn can help informal carers who are responsible for medication administration:

"We had a patient who had, who was a Parkinson patient and he was struggling with the tablets, so we just discussed it and they change it from the tablet to patches and it was really, really helpful for the, mainly for the patient family because they were helping him with his tablets" (HCP18)

Pharmacy technicians within secondary care also referred to the importance of collaborating with pharmacists to ensure patient centric medicines were provided. When there was a need to modify the dosage form, for example, pharmacy technicians would rely on pharmacists to endorse which medications could be modified and this would determine whether a liquid preparation would then be considered:

"So I know like I say that they always ask pharmacy to endorse the chart if things can be crushed or chewed, and that's our first step, if they can't be crushed or chewed then obviously we'd go for a liquid or a patch" (HCP15)

Healthcare professionals within the community suggested that improving communication and collaboration within this setting would be a key facilitator towards providing patient centric medicines.

"Just information sharing on what the patient's characteristics are" (HCP1)

Communication can determine the underlying problems, potentially identifying the need for alternative formulations and potentially overcoming the need for modifications which was identified as a barrier in Theme 1.2.2.:

"I think we need to first discuss with each other isn't it what the problem is? How it can be changed? We can issue or consider alternative preparation or any other alternative antibiotics or any medications that's required but I think we need to speak to each other and solve the underlying problem" (HCP25)

A community pharmacist gave an example of effective communication with a GP, which resulted in the formulation being changed to one that was more appropriate and at the same time more cost effective:

"We had a patient who, Quetiapine, she was prescribed Quetiapine in tablet form and was reluctant to take it saying that she's finding it difficult and she's gagging and as a result the GP prescribed her liquid formulation, which is a special… which for a month cost £850, as opposed to under £10, so a significant difference and as a result of that, the GP did contact us to see how we could help the patient, and the only way that I could suggest is to show the patient the different sizes of the tablets and to

perhaps get her to choose which ones she would want to try, even if that meant taking, let's say, four tablets instead of one to make up her required dose" (HCP14)

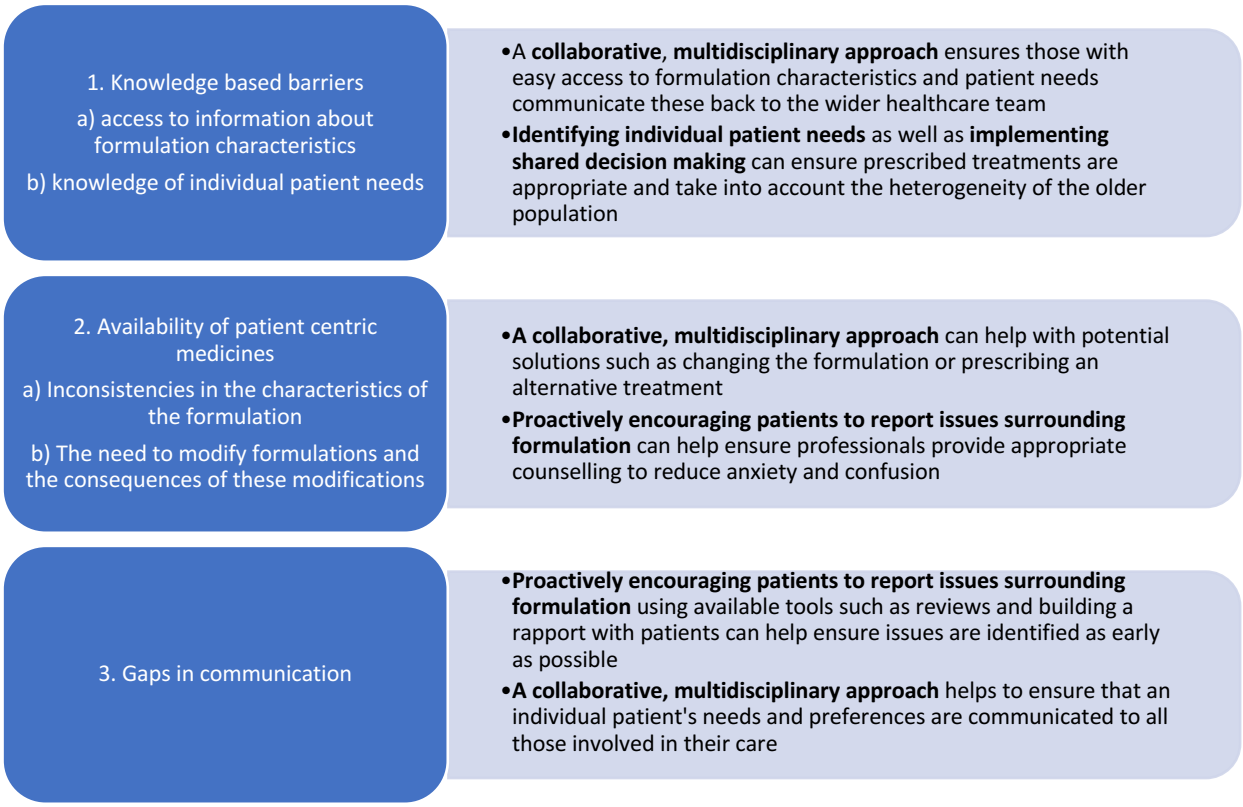
5.4. Discussion

5.4.1. Summary of key findings

This study has discussed several key barriers and facilitators towards the further involvement of health and social care professionals in providing patient centric medicines. The barriers were categorised into three areas; knowledge based barriers, barriers arising as a result of the availability of patient centric medicines, and barriers arising as a result of gaps in communication. Lack of access to details of formulation characteristics and a reduced awareness of individual patient needs can result in healthcare professionals not having the required level of knowledge to provide patient centric medicines. The characteristics of certain formulations may also change dependent on the brand, and there is also the need to sometimes modify formulations when a patient centric dosage form is not available. This can lead to a dilemma for professionals who must balance the risk of providing an unlicensed medication with the needs of an individual patient. Finally, gaps in communication both between professionals and between professionals and patients/carers can result in missed opportunities for identifying issues in relation to the formulation.

Four key inter-related facilitators were identified from the study. These facilitators can help to overcome the barriers identified in this study as illustrated in Fig 5.1 (text highlighted in bold corresponds to facilitators identified in the study). These facilitators are key towards enhancing the role of health and social care professionals in this area and ensuring patients receive age appropriate formulations.

Fig 5.1 Overcoming the barriers identified towards the provision of patient centric medicines



5.4.2. Comparison to other studies

Patient-centred and multidisciplinary approaches have previously been highlighted as important potential interventions to improve adherence in older people [234]. Patient-centred care has been defined by the Institute of Medicine as: "care that is respectful of and responsive to individual patient preferences, needs, and values" [235]. Prescribing, dispensing and administering patient centric medicines is a key part of delivering patient-centred care; there is a need to take into account the patients' individual preferences and values when healthcare professionals make a decision in relation to therapeutic options [236]. The present study has highlighted facilitators which can help improve the role of health and social care professionals in this area.

Proactively encouraging patients to report difficulties in regards to formulation is key to overcoming barriers that arise as a result of gaps in communication. Older patients who find medication a burden often don't report this to anyone and there is therefore a need for healthcare staff to ask questions to find out whether patients need extra support [10]. Older people are often unwilling to discuss issues with their physician for fear of being found to "be unable to care for themselves" and "for fear of appearing incompetent"[237]. This is also true in regards to formulation characteristics; previous

studies investigating the extent to which patients report problems with formulation characteristics found that only 13.7% of patients inform their doctor about the problems they experience [84].

To overcome these gaps in communication, there is a need the need to actively ask patients about difficulties with formulation characteristics. Such an approach would encourage patients and informal carers to raise any concerns. The limited number of GPs actively asking about swallowing difficulties has been previously recorded; only 70 out of 1,051 patients (6.7%) had ever been asked about swallowing difficulties by their doctor [84] and further studies found that only 2 out of 92 patients (2.2%) who had ongoing or previous swallowing difficulties said that their physician enquired about these [83]. A limited number of pharmacists enquired about difficulties; 43 out of 1,051 patients were asked about swallowing difficulties by their pharmacist [84]. The qualitative findings in the present study supports these quantitative findings and highlights the need for health and social care professionals to actively ask about problems with formulation.

Enhanced medication reviews were identified as a potential tool to ensure formulation characteristics are explored with patients in a standardised way. However, Medicine Use Reviews (MURs) were recently decommissioned in March 2021 and have been replaced by Structured Medication Reviews undertaken by pharmacists in general practice. When considering formulation, this shift is an important consideration; community pharmacists have direct access to the characteristics of a formulation but as they are no longer conducting medication reviews, alternative opportunities to discuss the issue of formulation must be identified. This may include checking suitability at the point of dispensing or during provision of services such as the New Medicines Service (NMS). Further work in this area is key to help defining this role for community pharmacists.

In addition to ensuring professionals are asking relevant questions about the formulation, there is also a need to ensure patients are comfortable reporting problems as and when they arise. There is therefore a need to build a rapport with patients and this was further identified in the study. Pharmacists in particular have an important potential role in this area, with findings from the present study suggesting some older patients form a strong bond with community pharmacists which facilitates reporting any issues. The role of pharmacists has evolved from a focus on dispensing to broader responsibilities of pharmaceutical care which require a more intimate and intensive relationship with the patient [238]. Therapeutic relationships with patients can lead to improved patient health outcomes and can also ensure patients are comfortable asking questions [239].

While pharmacists have an important potential role in identifying any issues with formulation, studies have found patients' perceived role of pharmacists can sometimes lead to few patients reporting difficulties with medication; patients would often only ask the pharmacist about minor problems as

they believed the pharmacist did not have their full medical history [240]. Informal carers have also focused on practical aspects of the role of pharmacists, such as supplying or delivering medication [219]. The tendency to define community pharmacies as premises where medications are dispensed can compound this view [241] and the present study supports the need to actively raise public awareness to ensure patients are aware of the importance of raising concerns.

The identification of the individual patient's needs is also key towards a patient centric approach. By considering the patients' preferences, needs, values and goals, a strong partnership can be formed between the professional and patient [242]. The extent to which this approach can be implemented is, in part, affected by the context in which the healthcare professional works [242]. The present study supports these findings and highlights the differences in access to information about a patient's needs based on the setting; professionals more directly involved in responsible for dispensing or administering medication are often more aware of individual patient needs. There is a need, however, to then use this information to provide the most appropriate formulation. While pharmacists are directly involved in dispensing medication, their primary focus is often centred around characteristics such as drug interactions and side effects [243]. The formulation of medication is often not explored, leading to further gaps in communication and a missed opportunity to provide a medication tailored to the patient's needs.

A further facilitator towards improved communication with patients identified from the study was implementing shared decision making. Previous studies in this area support these findings, with clinicians and nurses expressing a positive attitude towards shared decision making due to the potential to improve patient adherence [244]. However, problems with applying shared decision making have been reported, including a perception that patients do not want to be involved in making decisions about their care [244]. In general, however, older people are less involved in decisions about their care than they would prefer [245] and patients have reported feeling that their own expertise is undervalued by professionals [246]. The present study supports the importance of using the patient's expertise to ensure the most appropriate formulation is chosen; healthcare professionals often are unaware of the individual patient's needs and involving them in decisions about treatment options is key to overcoming this barrier. Where patients are less keen to be involved in decision making, a joint decision can be made that the professional will make the final decision [247]. When considering formulation, this would require professionals to ensure they have all available information so that the most appropriate, patient centric formulation is dispensed.

Communication between healthcare professionals can improve access to information that can help in providing patient centric medicines. A team approach is required: any formulation issues identified by

an individual clinician need to be communicated within the whole health and social care team. By sharing information on individual patient needs, healthcare professionals can work together to select the most suitable pharmaceutical drug product [60]. This is key to overcoming barriers arising as a result of the availability of patient centric medicines. Modifying dosage forms can have adverse clinical effects and there are also legal implications which can be minimised by following evidence-based practice [248]. Potential alternatives such as stopping unnecessary medications, finding an alternative commercially available dosage form and finding an alternative medication from the same class are all potential solutions that can be applied [248]. These solutions were highlighted by participants in the present study and require a collaborative approach so that inappropriate modifications can be avoided.

Improved collaboration between physicians, nurses and other health care professionals can also help to increase awareness of each other's knowledge and skills, leading to improved decision making [249]. The present study suggests effective communication in secondary care results in patients receiving an appropriate formulation. The results further highlight the importance of communication between professionals involved in the care of patients in care homes. The healthcare needs of patients within care homes are complex and unpredictable [250]. There is therefore a need for effective relationships between GPs and care home staff to improve the outcomes for residents [250] and the present study further supports the importance of establishing common goals in regards to optimisation of the formulation.

Improved communication between GPs and pharmacists in community is also key; as highlighted in the study, GPs rarely have access to details on formulation characteristics and improved communication with pharmacists can help overcome this barrier. Both professions need to work together to provide comprehensive patient care and this requires a greater awareness of each profession's competencies, working conditions and duties [251]. Effective, deliberate GP-pharmacist collaboration has the potential to significantly improve patient care, especially for patients with chronic illness or requiring regular medication reviews [252].

5.4.3. Strengths and weaknesses

Health and social care professionals from a range of settings were interviewed, providing important information about how their roles may differ according to the environment in which they work. The use of qualitative interviews allowed health and social care professionals to share information and experiences in their own words. However, this was dependent on their ability to honestly and accurately recall their experiences in relation to the provision of patient centric medicines which may be affected by social desirability bias [253]. This was partly overcome by pilot testing the interview

schedules and refining questions to ensure they were as open as possible. The open-ended questions were also useful in exploring the views of patients and carers on this topic; although older people and carers were not directly asked about the role of health and social care professionals, the open-ended questions and follow up questions (based on the answers given) gave a deeper insight into the importance of considering the relationship between health and social care professionals with patients and carers to ensure patient centric medicines are prescribed and dispensed.

Reflexivity must also be considered when conducting qualitative interviews; there is a need to take into account assumptions and values that may be subconsciously driving the interview [254]. This was especially important when exploring the role of health and social care professionals as my background in community pharmacy had the potential to subconsciously impact the questioning. The initial interview transcriptions were discussed with supervisors to identify any interview skills that required modification, such as inappropriate probing. A reflective approach was also taken when developing the codes from the interview transcriptions. Thoughts while analysing the interviews were recorded in a reflective diary, including references to the context in which answers were given and my thoughts on specific quotes. These were referred to when generating the codes to ensure the context in which answers were given was always maintained.

5.4.4. Future work

The facilitators identified in this study need further exploration; combining these facilitators together can provide a practical approach towards involving health and social care professionals in the provision of patient centric medicines. As highlighted in the study, community pharmacists have a key role in this area due to having easy access to details on formulation characteristics, their ability to form a strong rapport with patients and their convenience [255]. Further work exploring their role in this area is key; in particular their role in relation to that of primary care (practice-based) pharmacists (due to the shift in medication reviews), as well as in relation to that of GPs. Community pharmacy also involves a wide range of healthcare professionals, including medicine counter assistants, dispensers and pharmacy technicians. Patient facing professionals such as counter assistants have the potential to build a strong rapport with patients; further work exploring how these team members can be involved to ensure the most efficient delivery of a service focussing on improving access to patient centric medicines would therefore be helpful.

A key barrier identified from the findings in the present Chapter is the availability of patient centric medicines. Advancements in pharmaceutical technologies can be key towards overcoming this barrier. In particular, the use of 3D printing can provide personalised dosage forms on-site and on-demand; small batches of medicines each with tailored dosages, shapes and sizes can be produced [59]. The

potential of 3D printing in improving adherence in paediatric patients by modifying aspects such as the colour, flavour and form of solid dosage forms has previously been recorded [256]. Further work exploring the use of 3D printing to create a patient centric dosage form that considers the needs of the older population would therefore also be helpful and would help overcome barriers arising as a result of the availability of patient centric medicines.

5.5. Conclusions and Implications

The barriers towards the increased involvement of health and social care professionals include knowledge-based barriers, barriers arising due to the lack of the availability of patient centric medicines and gaps in communication. A number of facilitators were identified from the study to help overcome these barriers. There is a need to proactively encourage patients to report issues in relation to formulation using available tools such as reviews as well building a rapport with patients so that they are comfortable reporting issues as and when they arise. Due to the heterogeneity of the older population, an individualised approach is key, where the identification of patient needs is taken forward to inform the choice of formulation. Implementing shared decision making can also help to ensure the most appropriate formulation is then selected, empowering both patients and carers. A collaborative, multidisciplinary approach helps to ensure that professionals can share their knowledge and skills so that the most appropriate formulation is ultimately prescribed and dispensed.

The potential for 3D printing to address issues around the availability of patient centric medicines is explored further in Chapter six. Combining the potential use of this technology alongside the results from the previous Chapters in this thesis will provide a detailed understanding of the steps to ensure patient centric products are developed, prescribed, dispensed and administered appropriately to improve adherence and acceptance in older people.

Chapter 6- The Application of 3D Printing to Design an Older Person's Patient Centric Drug Product

6.1. Introduction

The findings in Chapter four highlighted the key characteristics that need to be considered when designing an older person's patient centric drug product. This Chapter will build on these findings and discuss the potential to use 3D printing as a tool towards achieving patient centric dosage forms. The Chapter starts by introducing the concept of 3D printing, with an evaluation of the advantages and challenges and a discussion of the main 3D printing technologies available. The Chapter goes on to discuss how the findings from Chapter four were used to create 3D printed tablet models in partnership with Colorcon.

Covid-19 had a significant impact on this stage of the work. The participants that took part in the semi-structured interviews were contacted to take part in a focus group in which the 3D printed models would be presented. A total of eight participants agreed to take part and the focus group was arranged for April 2020. Ethical approval for the study was obtained and the focus group was arranged to take place at Aston University. However, due to Covid-19, this was cancelled and the models could not be presented to participants. The following Chapter therefore concludes by discussing the potential to use these models in future work and this is explored in further detail in Chapter seven.

6.2. An introduction to 3D printing

There has been a shift in the pharmaceutical industry towards tailoring drug products to the needs of the individual and 3D printing – a process that involves the use of digital designs and a layer-by-layer process to produce 3D objects – provides an ideal tool to achieve this [226,257]; indeed, the first successful licensed 3D printed medicine, Spritam, was licensed by the FDA in August 2015 [258]. As such, the FDA aims to provide industry with a transparent and efficient regulatory pathway for 3D printed devices and further aims to work alongside manufacturers to ensure new and innovative products can be made safely and effectively [259], setting the precedence for the increased use of 3D printing in the preparation of drug delivery systems [260].

6.2.1. Advantages and challenges of 3D printed medicines

3D printing has been described as a revolutionary tool in the manufacturing of pharmaceuticals [261]; however, as with all manufacturing processes, there are advantages and challenges to using this technique. 3D printing distinguishes itself from other pharmaceutical manufacturing processes in three key areas: product complexity, on-demand manufacturing and personalisation [262]. When considering product complexity, 3D printing allows for the digital control over the structure of the final drug product. This provides the potential to create complex 3D printed shapes while maintaining control over the disintegration and dissolution times [262]. Geometry, for example, plays an important

role in defining the drug release profile and complex shapes such as a pyramid have a larger surface area to volume ratio, providing a much faster dissolution time [263]. On- demand manufacturing provides the opportunity to produce drugs that tend to degrade on storage (e.g. nitroglycerin) for immediate use [264]. The final area, personalisation, is the most relevant for this thesis and will be the focus of this Chapter. While personalisation can refer to the ability to tailor the dosage and drug release of a product for individual patients [265], the focus of this Chapter will be the potential to use personalisation to improve patient's adherence to their medication [262]. This includes optimisation of the dosage form in regards to characteristics such as the dimensions and appearance, which have been the focus of Chapters two and four.

While there are advantages, there are some challenges with 3D printing which have resulted in this technology not yet being fully exploited. One of the main challenges is in relation to the material used. The starting materials, including the drug and excipients, must be converted into a "curable ink" or a printable material [266]. This process will differ based on the type of 3D printer used, and the pharmaceutical formulation ink may take the form of a filament, binder solution, granule or paste [261]. This is especially challenging for fused deposition modelling, as filaments that have been prepared from pharmaceutical grade polymers and that contain active pharmaceutical ingredients are currently not commercially available [267].

A further challenge to consider is time; compared to traditional tablets, 3D printing takes longer to print a batch of tablets. The low speed of specific processes (e.g. Fused Deposition Modelling) and the time required for cleaning resulting 3D printlets can both increase the time of the procedure [268]. However, the rapidly improving technology may address this challenge in the future. The expense and risks of early adoption may also pose further challenges. The implementation of 3D printing is associated with a number of related investments, such as software, hardware and integrating the technology into an existing system [269]. The need to redesign the organisational structure and processes may lead to some wariness about adopting the technology, especially when there is uncertainty in regards to the demand for 3D printing [270]

A further aspect to consider is quality control. 3D printed medications must be manufactured in accordance with current chemistry, manufacturing and control standards [259]. There is a growing need for regulatory frameworks and while the FDA has released draft guidance for industry there are still some unanswered questions, such as how the FDA can ensure 3D printed products meet quality standards [271]. There are also no current regulatory pathways for bespoke 3D printed oral solid dosage forms; Spiritam, for example, is not considered bespoke as it is only available in four dosages [272]. There are also technical considerations and responsibilities that need to be defined. For

example, there is a need to consider who will be operating the printer; it can take one to two years to build confidence in using a specific process and printer [259]. The portability of 3D printers can lead to drug formulations being printed within industry, within hospitals, or within pharmacies; however, there is a need to ensure that regardless of location, the final product meets the set requirements [273]. This includes cleaning and sterilisation requirements, which can be a challenge for 3D printlets with small or complex structures and for printlets that require removal of residual raw material [259].

The 3D printing of pharmaceuticals is therefore still in the early stages of development and implementation. However, the potential to use this technology to create patient centric dosage forms has led to it gaining importance in the field of pharmaceutical and medical applications [267]. Significant progress has been made over the last five years and the evidence-base and investment into 3D printing has grown significantly, with over 3,700 academic papers published in this field since 2016 [274]. Oral solid dosage forms with complex geometries and varying release profiles have been successfully manufactured and 3D printing is increasingly being viewed as a promising alternative to classical manufacturing techniques [275].

6.2.2. Types of 3D printers

There are a number of 3D printing technologies available, with the most prominent approaches including powder bed inkjet printing, vat polymerisation based 3D printing (including stereolithography (SLA) and Digital Light Processing (DLP)) and fused deposition modelling (FDM) [276]. Elements to consider when choosing the most appropriate approach include accuracy, time and cost of fabrication [277].

Powder bed inkjet printing was developed in the 90s and was used in the manufacture of Spritam [258]. This process involves printing a binder solution onto a powder bed that contains the active pharmaceutical ingredient [276]. Following binding, a piston is used to lower the powder bed and the cycle repeated until the final product is complete [272]. Alternatively, drug loaded fluids can be printed onto an excipient powder bed; however, the bioavailability of the drug will be impacted by the ink solvent and drying rate [260] and this approach is often more challenging. Limitations of powder bed inkjet printing are often associated with the use of free-flowing powders; poor flowability can lead to incomplete layers being created and the particle size of the powder will determine the resolution, which can cause difficulties printing complex geometric shapes [278]. Key advantages of this technique include the wide range of materials available and the potential for large scale manufacturing [276].

FDM is an additive manufacturing technique in which filament is heated to a molten state and then extruded through the nozzle of the 3D printer [279]. Material is deposited layer by layer until the final

product is achieved [279]. Thermoplastic polymers are often used as the filament due to their relatively low melting point, with polyvinyl alcohol commonly used [280]. The drug can be loaded either by passive diffusion or incorporated by hot melt extrusion [266]. During passive diffusion, the filament is placed in a solvent containing the drug after which the drug loaded filaments are removed and dried [281]. This limits the risk of drug degradation, however highly concentrated drug solutions are required to incorporate very small amounts of drug resulting a low yield of drug loading [266]. Hot melt extrusion can therefore be used as an alternative in which the drug, polymer and additives are melted together and homogenised before being extruded [266]. However, this requires a high processing temperature and the additional step of hot melt extrusion can significantly increase costs [282]. Nevertheless, FDM is currently the most extensively employed 3D printing technique due to the wide availability, low cost and ease of storage of FDM 3D printers [282].

Vat photo-polymerisation based 3D printing includes both SLA and DLP [283]. This technique uses photo-polymerisation to solidify layers of liquid resin [284]. Either a digital light projector or a computer-controlled laser beam is used to focus a pattern onto the surface of a resin, causing solidification of the resin by photo-polymerisation [285]. The first layer solidifies and adheres to a support platform, which is then moved away from the surface so that the built layer is recoated with liquid resin [285]. A pattern is then drawn for the second layer, and this process is repeated until the final product is printed. The drug itself can be mixed with the photopolymer prior to printing and heating is not required reducing the potential for degradation [284]. Furthermore, complex geometries can be created due to the high printing resolution [272]. However, there are a limited number of photopolymer resins available and these materials are not currently regarded as safe [284].

6.3. 3D printing as a tool to create patient centric medicines

Previous studies have investigated the potential to use 3D printing to meet the requirements of individual patients. One of the first studies to be conducted in this area looked at the influence of shape, size and colour on patient acceptability [286]. The printlets in this study were made by hot melt extrusion and FDM 3D printing, and various unique shapes such as torus, sphere and pentagon were printed in addition to traditional shapes such as disc and capsule [286]. Shape, size and colour were found to have an impact on acceptability; while in general patients had a preference towards familiar shapes such as the capsule, the torus shape also scored highly for ease of swallowing and picking [286]. The study was one of the first to explore the development of patient centric medicines via 3D printing, however participants in this study were adults aged 18-45, making it difficult to generalise the findings to the older population.

Studies have also investigated the acceptability of 3D printed tablets amongst patients taking multiple medications, with studies showing the potential to use 3D printing to create a "multi-active solid dosage form" with 5 compartmentalised drugs [287]. In order to assess the perceptions of 3D printing amongst polypharmacy patients, FDM was used to create printlets in various shapes, colours and embossing [288]. Characteristics were again found to have an impact on acceptance, and factors affecting the participants' responses included aesthetics, practicality (e.g. handling medication) and physiological factors (e.g. swallowing) [288]. While polypharmacy patients are more likely to be representative of the older population, this was a small-scale study with only eight polypharmacy patients aged 29 to 80, again making the results difficult to generalise.

3D printing may be a useful tool to improving acceptance and adherence in the paediatric population, where optimisation of taste, shape and colour is key to ensuring treatment success [289]. 3D printing can be used to create unique formulations, such as chewable gummy formulations in different shapes and colours [290]. Taste-masking is a key challenge for developing paediatric formulations [291] and studies have therefore also investigated the potential to use 3D printing to create "sweet-like" chewable tablets [292]. The tablets were printed using Hot Melt Extrusion and FDM 3D printing in interesting shapes such as a bear, lion and bottle to improve patient compliance [292]. The results highlighted the potential to use 3D printing for taste masking bitter formulations, with participants (ten healthy volunteers age 18-25) reporting excellent taste masking with no bitterness or aftertaste [292]. Further studies are needed, however, that are more representative of the target population. Palatability is also key for improving acceptance and adherence in older people (Chapter 4), and their perceptions surrounding the use of 3D printing to enhance this characteristic is an important area for further investigation.

3D printing therefore has a useful potential application of bringing "the medicine closer to the patient," ensuring that personalised products are available and increasing the likelihood of adherence to treatment [273]. Previous studies have demonstrated the potential for 3D printing to create patient centric medicines; however, further studies are needed that investigate the use of this technology in older people.

6.4. 3D models developed from findings in Chapter four

The findings in Chapter four provide an important foundation on which to build 3D printed patient centric dosage forms for older people. The results highlighted the need for tablets to be visually appealing and memorable, be easy to handle and have optimum swallowability (by considering the dimensions and palatability side by side). By considering the preferences that were put forward by older people, their carers and health and social care professionals, models were made that provide a

useful starting point for creating patient centric drug products that aim to improve acceptance and adherence in older people.

As this is the first phase of creating patient centric dosage forms, including all areas discussed in the interviews would be challenging. In particular, palatability of the dosage form would be difficult to assess as the 3D printing process would result in models that cannot be tasted or swallowed. Nevertheless, a number of characteristics, such as the shape and size of the dosage form, can be manipulated using 3D printing. A wide range of shapes can be printed, providing an ideal opportunity to explore the potential of 3D printing in creating an older person's patient centric drug product using real world data as a starting point.

Table 6.1 below summarises the key themes identified from Chapter four and how these findings informed the design of the 3D models. Themes that are most relevant to the creation of the 3D printed models have been focused on, and while the models will not be tasted or swallowed, the theme focusing on swallowability has been included as patients' perceptions of how easy or difficult a model is to swallow will provide useful data on the development of future models.

Table 6.1 Key themes and their implications for the design of 3D printed tablet models for older people

Sub-theme	Summary of key findings	Implications for 3D printed models
	Theme 1: Medication Identification and Memorability	
Colour	• Need for visible, appealing and brighter colours • Two colours and distinctive colours help to improve memorability • Colour can be used to help differentiate between medications	• No specified colours were referred to but models should be bright and appealing in colour
Dimensions and Markings	• Smaller tablets, similar to 6mm round, were difficult to see • Balance required between identification and swallowability • Unusual shapes easier to remember • Oval shapes easy to remember and associated with statins	• Preference for sizes greater than 6mm for identification • Unusual shaped models may help identification and memorability • Potential for markings to be used but priority should be placed on optimisation of colour, size and shape.

	• Markings may help identification but used as a last resort	
Theme 2: Medication Handling		
Difficulties removing and handling	• Smaller tablets, similar to 6mm and 7mm round, difficult to remove and handle	• Preference for models of sizes greater than 6mm and 7mm for removing and handling
Dimensions and scoring to improve handling	• Preference for oval (pillow) shapes and caplet shapes to aid handling • 12 x 7mm oval shape preferred to round shape due to thickness and ease of picking • Potential to use markings/ indentations to aid handling	• Preference for oval shapes/ caplet shaped models due to ease of handling • Potential modification of round shape to aid handling and picking off a flat surface • Potential for models with markings/ indentations but a greater emphasis placed on optimising dimensions
Theme 3: Swallowability		
Size: A Balancing Act	• Difficulties swallowing smaller round tablets due to mouthfeel • Difficulties swallowing large tablets, including large round and large (16.5 x 8.5mm) oval	• Need for models to be presented in a range of sizes as preferences for size varies amongst participants • Need for modification to round shape to improve mouthfeel
The relationship between size and shape	• Difficulties swallowing large round (>10mm) tablets • Difficulties swallowing 18 x 7mm caplet shape • General preference for oval shape however dependent on size and thickness	• Preferences for size dependent on shape and therefore shapes should be printed in a range of sizes • Oval shape generally preferred but size needs to be optimised

6.4.1. Shape of models.

In summary, three key shapes were developed: a biconvex oval shape, a shield shape, and a biconcave disc that has been flattened at the centre. The oval shape was chosen as an example of a more traditional solid dosage form, which was commonly referred to throughout the interviews as being easy to swallow, memorable and easy to handle. Example quotes illustrating preferences for the oval shape in these key areas have been illustrated in Table 6.2. The importance of including a more traditional shape in the models presented to participants is also supported by the literature; previous studies investigating patient acceptability of 3D medicines found that patients had a general preference towards familiar shapes or shapes similar to conventional medications [286,288] and there is a need for further research on whether these findings can be generalised to the older population.

Table 6.2. Key quotes illustrating preferences for oval shaped table

Stage of Medication taking process	Key quote illustrating preference for oval shape
Identification and Memorability	I know what the Atorvastatin looks like because that's that shape of a drug, and sometimes, yes, I mean the Atorvastatin, I recognise that (P5)
	That to me is best for someone (16.5 x 8.9 oval)…I also think psychologically I feel they would know they've taken that (C7)
	These ones (12 x 7 mm oval) they can actually say 'yes, I have taken them'. It's a yellow one and it's oblong or whatever (HCP12)
	Sometimes they do describe the shape because there's some of, like Atorvastatin for instance is usually like an oval shape and they might say, "it's the little oval one that I have at night time," but then again that depends on which brand you're using because that can always change (HCP15)
Swallowability	The shape that I prefer is the oval. For me that seems to be quite easy to swallow. It doesn't matter if it's a big or a small (P2)
	They don't affect how I take them but I always find that that shape or sort of like the oval shape are easier to take than the rounder ones, especially if they're a big round. (P6)
	Well I think the small round ones, the oval, the oval type I think, I think they're preferable I think (P17)
	I think this shape is actually very good for taking tablets, I actually think it's in some ways better than the round ones, the sort of ovaly ones (P18)
	Round tablets often get stuck, so I think oval tablets may be better (HCP4)

	People do talk about bullets (16.5 x 8 mm oval), they like bullets and that does seem to be…I'm sure they're designed with ease of swallowing in mind (HCP7)
	Shape-wise I always think that the oval ones are easy to swallow (HCP16)
Handling	And those are the tinier ones obviously, they're flat-sided one, the pillow ones, they're fine, it's just the tiny ones seem to roll (C4)
	So maybe the optimum one, if I had to pick one would be that one there (12 x 7 mm oval), bigger than I would like, but probably at least I could pick it up if I had dexterity issues (HCP4)
	These ones (12 x 7 mm oval), the oval ones are slightly easier to pick up because they're a bit thicker (HCP19)

The shield shape was chosen as an example of a more unusual shaped tablet, that would help older people and their carers recognise and remember their medication. Key quotes illustrating the potential to use unique shapes have been illustrated in Table 6.3. A shield shape was deliberately chosen as it does not contain many sharp edges- a property which has previously been found to result in swallowing difficulties [293], and has a profile similar to the oval shape that was preferred during the interviews. Furthermore, participants referred to the potential to differentiate between medications based on the shape and previous studies have found similar results; for example, participants associated a heart shaped tablet with cardiovascular medication [288]. The shield shape provides a useful starting point to discuss the potential for certain shapes to be associated with different health conditions; for example, the shield shape may be associated with protective properties, and provides the opportunity for participants to provide more detailed feedback on the extent to which the shape should be unique or unusual.

Table 6.3. Quotes illustrating potential to use unique shapes

Stage of Medication taking process	**Key quote illustrating potential to use unique shapes**
Identification and Memorability	And then you see, but then the Amlodipine, I always recognise the Amlodipine because, well the one I'm taking at the moment, but it hasn't always been like that, because it's sort of got one, two, three, four, about six or eight sided it is. It's quite small but it's an interesting shape, so I do notice that (P5)
	I don't think I've seen any tablets in a square. That might be another idea to produce, you know, like tablet in square or make it like a star… I think that basically then if you make it like in a square, because it's something like a new, you know, nobody, I've not seen any tablet, I don't think you've think seen any tablet like that, so I think that could be probably, you know, if somebody said "I need to

	take this tablet probably at lunchtime" and then it's easier to remember that it's the square tablets I need to take (C6)
	So I'd say that actually colour and shape is useful for some patients because they recognise that, when I do medication reviews they refer to the little red one or the star-shaped one or the little white round one, so they recognise what medication they're taking based on the colour and the shape of it. (HCP8)

The final shape, a biconcave disc, was designed specifically in response to the numerous difficulties encountered with small round tablets. While patients often prefer traditional shaped medications [286,288], it was clear from the interviews that round tablets presented difficulties during all stages of the medication taking process. However, this shape is one of the most commonly used by the pharmaceutical industry, with patients consistently referring to their "small round tablets." In order to design a shape that would overcome some of the difficulties associated with round tablets, an initial proposal was put forward to design a torus, or "doughnut", shape that had been previously tested within the general adult population [286]. The drug release properties of a torus shaped tablet have been previously evaluated [263] and while it has a similar shape to a round tablet, the addition of a hole in the middle led to this shape previously scoring highest for ease of swallowing and picking [286].

While this shape has previously been tested for acceptability within the general adult population, there was a need to ensure printing and coating a torus shape would be a feasible and practical option. Previous studies have investigated the potential for creating torus shaped tablets using various different techniques. Prior to the use of 3D printing, torus shaped tablets were created by drilling a small central hole into the centre of compressed tablet [294]. There was, however, a lack of reproducibility with this technique, leading to the production of a compression-coated doughnut shaped tablet [295]. Specially designed punches were used to produce tablet cores and coats that could be compressed into a single, three layered tablet [295]. This technique still requires complex procedures and lacks flexibility, and therefore the use of 3D printing was viewed as a potential solution for producing dosage forms with complex design features [296].

Yu et al., created doughnut-shaped multi-layered 3D printed tablets which consisted of a drug loaded section with top and bottom barrier layers [296]. The release-retardant powder (ethylcellulose) was manually spread in selected areas before droplets of binder solution were deposited to form the top and bottom barrier layers [296]. More recently, taste masked doughnut-shaped formulations were printed using FDM printing paired with hot-melt extrusion, and this was highlighted as a potential approach for manufacturing patient centric dosage forms for the paediatric population [297]. SLA has

also been used to create 3D printed torus shaped tablets, with the drug release rate modified by amending the ratio of polyethylene glycol 300 (PEG 300) that was added to the printing solution [284].

Previous studies looking at printing a torus shape tablet largely focused on the release profile of the drug which was controlled during the 3D printing process, and it is clear that this shape provides the opportunity to tailor the release rate as required [294]. There are, however, other post-processing steps that require consideration and these are usually performed after removal of the product from the 3D printer. Primary post-processing activities must be done on all 3D printed products (e.g. removal of the support and cleaning) while secondary post-processing activities improve the performance or aesthetics [298]. Functions such as gloss, chemical resistance, and scratch resistance can be obtained by the application of another layer or coating [298]. Aesthetic properties in particular require attention when considering SLA printing, where the models produced are the same colour as the photopolymer solution [284,299]. When considering a torus shape, these post-processing activities may be difficult. The application of a coating in particular, which can enhance mechanical properties as well as improve the visual appeal of the tablet, is challenging; previous studies have manually coated this shape by inserting a rod in the hole and dipping and rolling the cores in coating solution [294], however, this is impractical and difficult to reproduce on a large scale.

In order to overcome the difficulties associated with post-processing the torus shape, an alternative shape, the biconcave disc, was developed. The shape of the disc was proposed as being unique enough to aid identification and memorability, while also being relatively similar to the round shape that patients are used to seeing when taking their medication. The disc shape also provides an indentation to aid handling of the tablet: a key challenge identified with round tablets. This shape would also be able to undergo post-processing and could therefore be coated easily alongside the other shaped models, resulting in visually appealing 3D printed tablets that could subsequently be presented to participants for evaluation.

In addition to these three shapes, a standard round tablet shape was also 3D printed. This shape is familiar to participants and can be used as a reference point when comparing the acceptability of the biconcave, shield and oval shapes.

6.4.2. Size of models

As illustrated in Table 6.1, there was a need to ensure each shape was printed in a range of sizes so that the relationship between shape and size could further be explored. A “standard” size tablet first needed to be printed, which could be used as a reference point from which other sizes could be printed. Previous studies evaluating the swallowability of 3D printed models used the dimensions of

a standard 500 mg paracetamol tablet. Geometries of each of the shapes were adapted to match the weight of the tablet, with the capsule shape resulting in dimensions similar to that of a size 2 capsule [286]. Capsule sizes range in size from size 000 capsules (26.1 mmx9.91 mm) to size 5 capsules (11.1 mm x 4.91 mm) [300]. A size 2 capsule (17.6 mm x 6.39 mm) lies in the middle of this range and is commonly used in pharmaceutical manufacturing [300]. A size 2 capsule was therefore used as the starting point in this study. The dimensions of a size 2 capsule were used to create a tablet using the same material that all other models would be printed with (Figure 6.1). This was weighed, giving a weight of 496mg (rounded up to 500 mg) and this was used as the reference standard; all tablet shapes were printed based on a weight of 500 mg. The weight was then increased and decreased in increments of 100 mg, giving models in a range of sizes that were comparable by weight. The full range of weights, sizes and the dimensions of the models created are shown in Table 6.4.

Figure 6.1 3D printed size 2 capsule

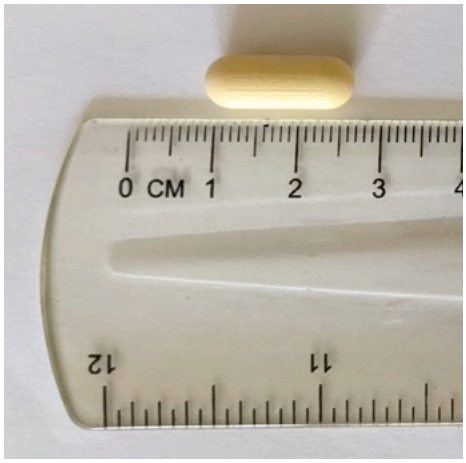
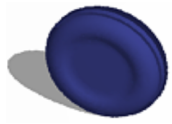


Table 6.4. Shape, size and dimensions of 3D printed tablets

Name	Shape	Weight (mg)	↔ (mm)	↕ (mm)	Depth (mm)
Oval		300mg	13.1	7.6	4.6
		400mg	14.4	8.3	5.1
		500mg	15.5	9	5.5
		600mg	16.5	9.6	5.8
		700mg	17.4	10.1	6.2
Shield		300mg	8.5	12.6	4.6
		400mg	9.4	13.9	5.1
		500mg	10.1	15	5.5
		600mg	10.7	15.9	5.8
		700mg	11.3	16.8	6.2
Biconcave		300mg	11.5	11.5	3.6
		400mg	12.6	12.6	4
		500mg	13.6	13.6	4.3
		600mg	14.5	14.5	4.5
		700mg	15.2	15.2	4.8
Standard Circular		300mg	10.3	10.3	4.3
		400mg	11.3	11.3	4.8
		500mg	12.2	12.2	5.1
		600mg	13	13	5.4
		700mg	13.7	13.7	5.7

6.4.3. Colour of models

The findings in Table 6.1 illustrate the importance of tablets that are bright and appealing in colour. Coating the models created by 3D printing in a range of bright and appealing colours was outside the scope of this study, however there was a need to explore the topic of colour further. It was therefore proposed that standard placebo tablets in shades of red, yellow and blue could be used as a starting point to discuss preferences for and against darker and lighter shades, and how the colour could be used further to aid identification and memorability. The placebo tablets that were chosen can be seen in Figure 6.2.

Figure 6.2. Placebo tablets in shades of red, yellow and blue.

6.5. 3D Printing Process

The 3D printing process starts by using Computer Aided Design (CAD) software to create the design of the models to be printed [301]. In this case, the CAD software used to design the tablets was Solidworks. The 3D models were then printed using a Digital Light Projector (DLP) 3D printer at Colorcon, Dartford. This process uses liquid resin that solidifies as a result of photo-polymerisation; however, rather than using a single beam of light, the DLP printer directly projects a whole print layer, leading to a whole layer solidifying at each exposure [283]. This significantly increases the print speed [283]. The resin used was an ABS (Acrylonitrile Butadiene Styrene) like tough white resin, which has high hardness and toughness that makes it suitable for printing rigid products. In order to ensure the models were aesthetically presentable, they were coated in a powder that was of the same colour as the models presented to participants during the semi-structured interviews. The O'Hara MX coating machine with a 12 inch fully perforated coating pan and a Schlick Anti-Bearding Cap (ABC) spray gun (nozzle size 1.2mm) was used to coat the tablets using Opadry II coating. The resulting models can be found in Figure 6.3 below.

Figure 6.3 3D printed tablet models produced at Colorcon, Dartford

A focus group to present these models to participants who took part in the semi-structured interviews was organised for April 2020 but unfortunately was cancelled due to Covid-19. Nevertheless, these models provide an important foundation for future work in this area. The potential to use these models in a focus group, alongside a potential interview schedule to use within the focus group, is discussed in more detail in Chapter seven.

6.6. Conclusions and Implications

3D printing provides an ideal tool for the pharmaceutical industry to move away from a 'one size fits-all' approach, allowing for the manufacture of personalised medication that can achieve the best therapeutic outcomes [302]. There are a number of 3D printing technologies available, including FDM, SLA and powder bed inkjet printing. Dosage forms can be produced in a range of shapes, sizes and textures that are difficult to produce using conventional manufacturing techniques [302]. However, there are a number of challenges which must first be addressed to allow for the rapid and significant growth of this technology. This includes addressing concerns over regulatory and quality control issues [303], as well as the availability of appropriate and compatible materials [302]. Defined regulatory guidelines, technological advancements and interdisciplinary work will all help to strengthen the potential for 3D printing to be used as a viable option in the manufacture of pharmaceuticals [304].

In order to recognise the potential of 3D printing to produce these patient centric dosage forms, there is also a need to work alongside patients and their carers. Patient-centred drug development is therefore likely to change the way the pharmaceutical industry operates; engagement and collaboration with patients and healthcare stakeholders is key for determining how best to improve patient outcomes [305]. Previous studies have taken the step towards involving patients in developing 3D printed patient centric dosage forms [286,288,292]; however, there is a need to further involve older people when determining the appropriateness of this technology in this important target population.

The results from the semi structured interviews provide an important foundation on which work in this area can build. This chapter used this data to create 3D printed tablet models in various shapes and sizes. The development of oval, shield and biconcave disc shaped models was based on the importance of tablets being easy to identify, handle and swallow. These models provide an important starting point towards creating an older person's patient centric drug product, and can be used in future work to help further define the characteristics which would help improve adherence and acceptance in this population. The use of 3D printing to create personalised medication alongside the improved role of health and social care professionals in providing patient centric medicines (Chapter 5) are two key steps towards ensuring older people receive medications that are tailored towards their individual needs, improving therapeutic outcomes and therefore helping to improve overall quality of life.

Chapter 7- Conclusions, Implications and Further Research

The work in this Chapter refers to the following associated publication, published in collaboration with the Patient Centric Medicine (PaCeMe) Initiative:

Stegemann, S.; Sheehan, L.; Rossi, A.; Barrett, A.; Paudel, A.; Crean, A.; Ruiz, F.; Bresciani, M.; Liu, F.; Shariff, Z., et al. Rational and practical considerations to guide a target product profile for patient-centric drug product development with measurable patient outcomes – A proposed roadmap. European Journal of Pharmaceutics and Biopharmaceutics 2022, 177, 81-88.

7.1. Overall aim of the thesis and how this has been answered

The aim of this thesis was to investigate the characteristics of oral solid dosage forms that contribute to age appropriate, patient centric medicines that help to improve medication adherence and acceptance in older people. The research design sought to address this aim via the following objectives:

1) To systematically review the available literature on how the characteristics of oral solid dosage forms impact adherence and acceptance in older people.

2) To collect data on the key issues faced by older people and carers when using/administering oral solid dosage forms and the characteristics that would help contribute towards a patient centric dosage form.

3) To explore the role of health and social care professionals in the provision of patient centric medicines.

4) To explore 3D printing as a potential tool to further understand preferences for characteristics.

A systematic review followed by a qualitative approach towards collecting data was undertaken (see Chapter three for full details and rationale behind the methodology). 3D printing was used to create model tablets of varying characteristics to further understand preferences. Numerous insights were generated from the analysis of data.

This study extends the literature on patient centric dosage forms for older people by:

a) Systematically reviewing the literature on this topic and categorising the key characteristics that impact adherence and acceptance in older people into three areas: appearance, dimensions and palatability (Chapter 2)

b) Determining the stages of the medication taking process that these characteristics have an impact on: medication identification and memorability, handling and swallowability (Chapter 4)

c) Identifying the key facilitators and barriers towards the further involvement of health and social care professionals in providing patient centric medicines (Chapter 5)

d) Discussing the potential to use 3D printing to further understand preferences for characteristics by using the data collected from semi structured interviews to create different shaped tablet models (Chapter 6)

7.2. Key findings

The findings from this thesis have important implications for the provision of patient centric medicines in practice. The key findings from all Chapters have been integrated to develop a four-step approach that can be implemented in practice to ensure the provision of patient centric medicines. This patient centric approach towards the provision of patient centric medicines has been illustrated in Table 7.1.

Table 7.1. A Patient Centric Approach Towards Providing Patient Centric Medicines

1. Take a proactive approach towards identifying the needs of the end user- Actively ask older people and their carers about factors that may influence their ability to take or administer a medicine as directed. Pay particular attention to patient characteristics (e.g. age-related changes), the environment (e.g. the presence of a carer), disease characteristics (e.g. difficulties handling medication due to rheumatoid arthritis) and the medication characteristics (e.g. potential for modification).
2. Understand how these needs impact preferences for characteristics by considering the formulation of the dosage form alongside the medication taking process- Consider each stage of the medication taking process (medication identification and memorability, medication handling and swallowability). Identify the key formulation characteristics (the dimensions, palatability and appearance) that require attention to optimise each stage.
3. Involve patients and informal carers in decisions about treatment options- Shared decision making and a concordant approach can ensure the most appropriate formulation is chosen. Where this may not always be possible, this should be communicated to the patient, and an action plan agreed in which any major difficulties are identified and addressed.
4. Proactively communicate any changes or specific patient needs to the healthcare team- Any underlying characteristics that may cause difficulties taking certain formulations should be communicated back to the healthcare professionals involved in the care for that patient

7.2.1. Take a proactive approach towards identifying the needs of the end user

The first step in this approach was developed from the findings in Chapters two, four and five. The systematic review (Chapter two) found differences in preferences for characteristics amongst older people with and without dysphagia. Dysphagia is a growing concern for the health of older people with multimorbidity; however, it tends to remain an under reported symptom [306]. 46% of patients with dysphagia do not inform their doctor about their condition, while 70.9% are not properly diagnosed [307]. Healthcare professionals must proactively question older people about their swallowing function so that the most appropriate dosage form can be provided [87].

The presence of dysphagia is one of a number of age-related changes that must be considered. Sensory changes including a deterioration in vision can impact patient adherence and acceptance, and the systematic review further highlighted the importance of this. Difficulties distinguishing between

different strengths due to similarities in appearance was found to lead to clinical deterioration [117]; and there is therefore a need for healthcare professionals to proactively question older people about their ability to see and differentiate between different tablets.

While the systematic review highlighted the importance of considering some age-related changes, a key finding was the lack of research directly investigating the formulation of oral solid dosage forms in older people. Detailed data on other factors that may affect the patient's/carer's ability to take/administer medication as directed were lacking and this gap was addressed in the next stage of the project. Findings from Chapter four are also therefore key for informing the first stage in Table 7.1. These findings highlighted the importance of a holistic approach, with patient, disease, environment and medication characteristics all impacting preferences for formulation characteristics (Fig. 4.9, Chapter four).

When considering the patient during step one, as well as age-related changes (including changes in cognition, motor function and sensory function [3]), results highlighted the importance of considering the individual patient's culture or Religion. This area was highlighted due to the potential for patients to refuse certain dosage forms such as capsules due to gelatine content. While this is a very specific example, it highlights the importance for healthcare providers to be increasingly mindful of how their recommendations intersect with the needs and beliefs of the population groups they serve [308]. For example, preferences for colour may vary due to colours having different meanings in different cultures [309]. Considering the patient as a whole and an individualised approach is therefore key during this first step.

The environment can also have an important role to play, especially the presence/absence of formal and informal caregivers. The systematic review (Chapter two), however, did not find any studies involving formal or informal caregivers. This gap was addressed through the semi-structured interviews and differences were found in preferences for characteristics depending on the availability of support. A large number of residents in care homes, for example, had fewer preferences for colour while those self-managing medication within the community highlighted the importance of colour to differentiate between medications. However, it is important to note that this finding was limited to those patients who were able to provide informed consent; patients in care homes suffering from more advanced stages of diseases (e.g. dementia) may have different preferences and further work is needed to explore this further.

In general, however, considering the presence/absence of support is important during this first stage. In particular, the presence of a family carer should be noted; family carers in the study were found to take on the responsibility of weighing up the importance of tablets and often only discussed the need

to ask for alternatives if “more important” medications were prescribed. Due to the reluctance of many informal carers to voice concerns [310], healthcare professionals have a duty to ask about any issues arising as a result of formulation characteristics. This was also a key finding highlighted in Chapter five. Addressing gaps in communication between patient/carer dyads and professionals was identified as a key facilitator towards providing patient centric medicines.

Particular disease characteristics are also key to consider during this first step. For example, patients suffering from stroke, dementia and Parkinson’s are all more likely to experience dysphagia [26], while those with arthritis have more difficulties handling or accessing medication [311]. However, a key barrier identified in Chapter five was healthcare professionals’ awareness of individual patient needs; while social care professionals and nurses within secondary care had a deeper understanding of the needs of each patient, other healthcare professionals especially within primary care were not aware of the difficulties patients may experience while taking their medication. Further disease specific research exploring preferences for characteristics amongst patients with specific conditions may help guide healthcare professionals to ask the most appropriate questions during this consultation.

Factors related to the medication itself should also be considered during this first stage. Findings from the semi-structured interviews found that changes in appearance of the medication when different brands were dispensed led to confusion for the patient. Specific shapes were often associated with certain medications and changes were especially difficult for patients with Alzheimer’s disease who relied on the appearance of tablets. The availability of patient centric medicines, especially due to changes in brands, was also a barrier identified by healthcare professionals in Chapter five. In order to overcome this issue, healthcare professionals can take a proactive approach in providing patients with counselling to help reduce patient anxiety associated with changes.

7.2.2. Understand how these needs impact preferences for characteristics by considering the formulation of the dosage form alongside the medication taking process

The systematic review resulted in formulation characteristics being classified into three key areas: i) Dimensions; ii) Palatability; iii) Appearance. The semi structured interviews found that these have an impact on three key stages of the medication taking process: i) medication identification and memorability; ii) medication handling; and iii) swallowability. The three themes identified from the systematic review were integrated with these themes to give a detailed understanding of how each category of formulation impacts each stage of the medication taking process. A summary of this integration has been illustrated in Fig. 4.8 (Chapter four).

The individual needs of the end user (identified during step one) will determine both preferences for characteristics and which stage(s) of the medication taking process require attention. When

considering the patient, for example, the presence of dysphagia may result in an increased emphasis being placed on optimisation of the dimensions and palatability to enhance swallowability. The systematic review found that both the size and shape determine swallowability. The findings from the semi structured interviews expands on this by highlighting the balancing act required to optimise the dimensions of oral solid dosage forms; larger tablets can lead to dosage form modification while smaller tablets can lead to difficulties feeling the tablet in the mouth and the perception they have not been completely swallowed. There is also a need to consider the taste, aftertaste, mouthfeel and texture all of which further impact swallowability. Preferences for palatability, specifically taste, are dependent on individuals' preferences and therefore a personalised approach is required when optimising this characteristic.

This second stage of the patient centric approach therefore requires an awareness of the individual patient's needs. While healthcare professionals can take a proactive approach towards identifying these needs, e.g. during consultations, there is also a need to ensure patients are comfortable reporting any problems as and when they arise. The results from Chapter five found that patients that had formed a strong bond with a healthcare professional such as a pharmacist were more likely to report any issues. Pharmacists are in an ideal position to form a strong rapport with patients and are able to therefore promote the importance of reporting medication taking difficulties rather than using self-management techniques. Promoting this advice, for example when dispensing medication, can help to ensure patients are more comfortable with reporting difficulties.

This second stage also requires an awareness of the characteristics of each individual formulation. However, a key barrier identified in Chapter five was healthcare professionals' access to formulation characteristics. Healthcare professionals who directly handle medication either in the dispensing or administration process are more likely to be aware of the formulation characteristics and therefore be able to adopt a patient-centric approach. GPs, however, rarely have access to details on formulation characteristics. Improved collaboration between physicians, nurses and other health care professionals is key to help increase awareness of each other's knowledge and skills and ultimately ensure a patient centric dosage form is selected.

7.2.3. Involve patients and informal carers in decisions about treatment options

Once any issues have been identified, there is a need for shared decision making and ensuring that the patient is involved in the discussion so that jointly agreed therapeutic options can be recommended (step three). Findings in Chapter five highlighted the importance of this approach, and the need for health and social care professionals to provide the patient with all the information they need to make an informed decision. According to the King's Fund report on shared decision making,

practitioners and patients bring different but equally important forms of expertise to the decision-making process [312]. The patient's values, experiences, preferences, social circumstances and attitude to risk all encompass the patient's expertise [312]. Clinicians have an expertise in diagnosis, prognosis, outcome probabilities, disease aetiology and treatment options [312]. Combining this expertise can ensure that the most appropriate, patient centric formulation is chosen.

There are instances when, however, an ideal formulation may not be available; the availability of patient centric medicines was identified as a key barrier in Chapter five. Where this is the case, this must also be communicated clearly to the patient, and an action plan developed that will ensure any difficulties are raised and addressed. This may involve, for example, setting a follow up appointment to discuss how the patient is finding the agreed formulation.

7.2.4. Proactively communicate any changes or specific patient needs to the healthcare team

All steps taken in this approach must be communicated back to the wider healthcare team and this is achieved during step four. Patients encounter multiple health and social professionals while receiving care; for example, during a 4-day stay in hospitals, patients can encounter 50 different employees including nurses, physicians, technicians and others [313]. Lack of communication between professionals can risk patient safety due to misinterpretation and overlooked changes [313]. In this case, the patient's preferences for a certain formulation may be overlooked if their needs and an agreed treatment plan is not shared with the wider healthcare team, e.g. GPs. The final step in this approach is therefore key to ensure patients continue to receive patient centric medicines. However, in order for this step to be carried out effectively, there needs to be a platform of established communication where the roles and responsibilities of each member of the healthcare team are defined. This area requires further work and is discussed further in Section 7.4.

7.3. Implications for the pharmaceutical industry

The findings presented in this thesis have implications for the way in which drug products are manufactured by the pharmaceutical industry. However, there are multiple drug product related decisions that must be made during the early drug product development process which often limits the extent to which patient centric design options are considered in the final phase. Randomised controlled trials often focus on the safety and efficacy profile of drugs and these are conducted on homogeneous populations that exclude patients with relevant co-morbidities, disabilities, and impairments [64]. The resulting drug product may therefore not provide the desired benefit to risk profile [40]. In order to effectively integrate the needs and perspectives of patients into this process, a rational approach is required that is implemented from the start of the drug development process.

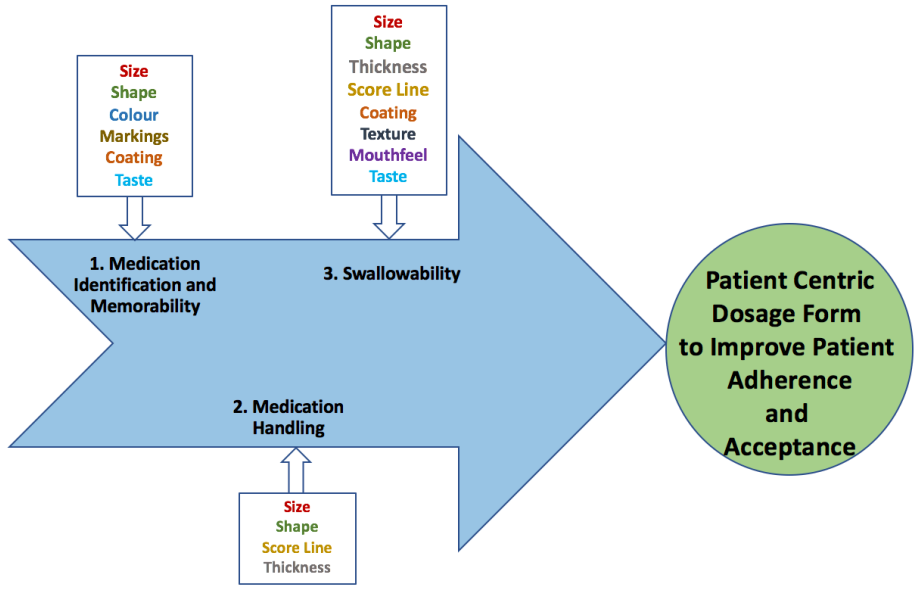
The author of this thesis has been involved in an initiative that aims to explore this further: the Patient Centric Medicines Initiative (PaCeMe In). This is a multidisciplinary stakeholder group with individuals from academia and industry that have expertise in various aspects of drug development and the patient/product interface. The group was set up in 2017 by Prof. Sven Stegemann and has had regular meetings and conferences where the theme of patient centric medicines has been explored. One of the outcomes developed from this group has been a proposed road map for patient centric medicine design that can be used during the early phases of drug development. A paper explaining the road map has recently been published [314] and highlights the three key areas that require exploration: 1) Drug characteristics (e.g. drug lipohilicity, pharmacokinetics); 2) Patient characteristics (e.g. retinopathy, co-morbidities); and 3) Product characteristics (e.g. acceptability, swallowability).

It is proposed that the road map is used to inform the QTPP, and that variables within each of the three areas are assigned a priority level (with 1 being low and 10 being high). A multidisciplinary approach is proposed to completing the road map, involving clinical, pharmaceutical, regulatory and industry representatives. The priority level is assigned by the relevant expert and will be defined using the benefit to risk ratio for a specific condition within a target population. The QTPP can then be modified, incorporating design outputs based on the priority level assigned for each variable.

For example, within the product characteristics, a key variable is the ability to differentiate the product from other products used for the same indication [314]. This would have consequences on the identification and acceptability of the product. The importance of this variable would be assigned a priority level but this is highly dependent on the individual drug product; for example, for a condition such as dementia, this particular variable may have a higher priority level. The design output as a consequence of the variable would focus on the product design, i.e., the colour, shape or imprint on the drug product. This would be incorporated into the QTPP.

The results from this thesis largely correspond to these product characteristics, specifically the formulation of the dosage form. There is a need for dosage forms to be easily identifiable and memorable, easy to handle and have optimum swallowability (as defined in Chapter four). The characteristics impacting each of these three stages have been illustrated in Fig 7.1. In general, small round tablets (<7mm) were least preferred and therefore should be avoided, while coated tablets were preferred by a large number of participants. The size and shape alongside the use of bright colours can make tablets easy to identify, distinctive and memorable. These characteristics summarise the general preferences of older people and can be used when defining the QTPP for oral solid dosage forms.

Fig. 7.1. Pathway illustrating how optimising formulation characteristics during the three stages of the medication taking process can result in a patient centric dosage form



However, while this summarises the general preferences, the results highlighted the need to consider a number of other variables early on in the drug development process to create a truly patient centric product. For example, patient characteristics such as co-morbidities can have a significant impact on preferences for formulation characteristics, with patients with multiple health conditions having a greater preference towards coloured preparations (Chapter four). Fig 4.9 illustrates how the disease characteristics, the environment, patient characteristics and medication characteristics can all have an impact on preferences for formulation. The results therefore support a holistic approach when defining the product characteristics for the QTPP and supports the need to include all those involved in an older person's therapy.

In order to ensure that this holistic approach is taken towards the development of patient centric medicines, the pharmaceutical industry must take steps towards collecting more detailed patient experience data. For example, more patient experience data on preferences for formulation characteristics in people with dementia may result in a QTPP where a greater emphasis is placed on identification and memorability, where the colour, size, shape, markings, coating and taste are optimised. An example of a patient centric medication for dementia could therefore be a brightly coloured, uniquely shaped (e.g. shield), sugar coated dosage form with the name of the medication or initials imprinted on the tablet. Further patient experience data can expand this further, and detail for example, how the presence of a carer, polypharmacy, and the setting in which a patient is based may all impact preferences for formulation characteristics.

The collection of further patient experience data requires a systematic approach that can be used to inform the early stages of drug development. The Food Drug Administration (FDA) has therefore recently developed a series of four methodological patient focused drug development guidance documents that provide a step-by-step approach towards collecting and submitting patient experience data from patients and carers [48]. These guidance documents aim to facilitate the use of systematic approaches to collect and use meaningful patient and caregiver input that can better inform the development of medicinal products [48]. The use of these guidance documents to collect further patient experience data to expand on the results from the present study will provide the pharmaceutical industry with a practical, holistic approach towards developing patient centric medicines.

This research therefore supports the need for the pharmaceutical industry to include a qualitative component to controlled trials. However, qualitative studies alongside controlled trials remain uncommon even when complex interventions are being evaluated [315]. This is despite the growing awareness of the role qualitative research can play when designing and evaluating interventions [316]. Poor access to relevant expertise or a lack of resources are some of the reasons provided for this [315]; however a deeper understanding of the industry's perspective on including qualitative components especially when considering patient centric medicines is needed. This is discussed further in Section 7.4. The use of a qualitative component to understand patient's perspectives on the use of 3D printing is particularly valuable; this can then be used to inform trials that explore the potential of this technique in creating patient centric medicines.

7.4. Future research

7.4.1. Evaluation of 3D printed models

The 3D printed models illustrated in Chapter six were developed based on the findings from Chapter four. A focus group using these models was planned, however could not go ahead due to Covid. These models can therefore be used in future work involving older people and carers and this would help further refine the characteristics of an older person's patient centric drug product. The initial semi structured interviews were a useful tool to gain a detailed understanding of which characteristics were preferred, and the factors that influence these preferences. The interactive nature of focus groups allows for participants to clarify or expand on contributions based on points raised by other members of the group, allowing for topics to be explored that may require further development [317]. In this case, the 3D printed models could be used within a focus group to further discuss the characteristics of oral solid dosage forms that would improve acceptance and adherence.

This method often makes use of a schedule or script that provides guidance for the focus group discussion [318]. The themes identified in Chapter 4 provide important discussion points to explore within the focus group. A potential schedule to follow that makes use of these themes can be found in Table 7.2. The use of group exercises within focus groups is common, where participants are given an activity to perform as a group [319]. Presenting the models to participants and asking them to, for example, rank the models based on preferences would provide useful information on the priorities that need to be focused on when considering an older person's patient centric drug product. The conversations that take place during this process would be particularly interesting, giving an insight into the thought processes that often take place when older people and their carers assess the acceptability of oral solid dosage forms.

Table 7.2. Schedule for future work involving the use of a focus group and 3D printed models.

1. Presentation of 500mg sized oval, shield, biconcave and round 3D printed models
2. Presentation of different sizes (400mg, 500mg and 600mg) of the most preferred shape. Followed by presentation of different sizes of the 2nd and 3rd most preferred shapes
3. Presentation of different colour placebo tablets
During all three stages, participants will be guided towards discussing their views on: a) identification and memorability b) handling c) perceptions of swallowability d) any other factors relating to the physical characteristics of the models presented.

7.4.2. Further evaluation of the role of health and social care professionals in the provision of patient centric medicines

The final step in Table 7.1 involves proactively communicating changes to the wider healthcare team. Three mechanisms allow team members to work together effectively: mutual trust, shared mental models and closed loop communication [320]. Shared mental models relates to a shared understanding of the tasks to be performed and each other's roles and responsibilities [320]. This is a key mechanism which requires further refinement for the provision of patient centric medicines. While GPs, for example, prescribe medications they are often not aware of the individual characteristics of each formulation. Community pharmacists have access to these characteristics; however, results highlighted that they often do not ask patients about the formulation.

Furthermore, medication use reviews have moved away from community pharmacy and have been replaced by structured medication reviews (undertaken by practice pharmacists). Community pharmacists have important access to key information about a drug product such as the shape, size and colour of a tablet, all of which can be checked prior to dispensing to a patient. Their role in this area should therefore not be underestimated and a partnership with GP practice-based pharmacists can be key towards optimising this role. There is also a need to define the role of healthcare assistants and dispensers, who are often patients first point of contact. Future work should help address these gaps by aiming to determine the role of each member of the healthcare team in providing patient centric medicines. Once defined, this can then result in the team working effectively together and a platform established for communication between each team member.

7.4.3. Further work exploring the role of the pharmaceutical industry in providing patient centric medicines

The shift towards a more patient centric approach is accompanied by increased pressure on costs, with a tension arising between providing individualised care and the larger economic considerations [305]. Some of the key challenges that need to be overcome before a patient centric approach is adopted by the pharmaceutical industry include scepticism about commercial success, a lack of understanding of qualitative research and internal habits of going back to established information sources such as clinicians [305]. Further research involving industry on their views in this area is therefore key; understanding what patient centricity means for the industry as well as their awareness of the current regulations and guidelines will help facilitate a more detailed understanding of the steps required for the industry to shift towards a more patient centric approach.

7.5. Strengths

7.5.1. Focus on the experiences of patients, carers and health and social care professionals from a range of settings

As far as we are aware, this is the first study that has looked at preferences for formulation characteristics from the viewpoints of patients, carers and health and social care professionals across primary care, secondary care and within care homes. The use of semi-structured interviews enabled the collection of detailed information from all participants and highlighted the complexities of providing patient centric medicines that arise especially when considering these different settings. The preferences of older people in care homes, for example, differ to those who self-manage their medications at home as the ability to identify and distinguish between medications is of more significance for these patients. By taking this holistic approach, these differences in preferences were highlighted and can be taken into account in future work in this area.

The experience of health and social care professionals from a range of settings also provided an important extra dimension to the findings. Care professionals from care homes, for example, had a very close relationship with patients and were therefore aware of each patient's individual preferences. They were aware of the colour of the medication that individual patients preferred and knew the exact foods to give medication with should they suffer from dysphagia. They could therefore ask for changes to medication if the incorrect formulation was dispensed. In contrast, some health professionals within the community and secondary care were often not aware of the importance of the formulation. This again highlights the complexities when considering the provision of patient centric medicines and supports the need for further research exploring the role of healthcare professionals in this area.

7.5.2. Integrated approach combining pharmacy practice with the pharmaceutical industry

This project was undertaken in partnership with Colorcon and this has enabled a practical, integrated approach towards investigating this topic area. The research team were able to produce a range of placebo tablets for presentation during the interviews based on the most commonly used shapes and sizes, and this helped provide an important reference point for participants during the interviews. The research team were also able to draw on the expertise of the team at Colorcon when considering the most practical shapes that can be produced via 3D printing. The difficulties, for example, with a 3D printed torus shape tablet when considering mass production and coating was discussed with the team at Colorcon, enabling the development of the more feasible, biconcave shape. The 3D printed models could also be printed on site at Colorcon, Dartford, providing models that are ready for presentation to participants. Furthermore, the findings from the study have been communicated back to the Colorcon team to help ensure a wide dissemination of the results.

7.5.3. Experience of the research team

The background and experience of the lead researcher and supervisors are relevant to this research. The lead researcher is a community pharmacist with experience of talking to older people, particularly about issues in relation to formulation (section 7.7 below). The lead researcher also has experience of conducting qualitative research, and conducted semi-structured interviews as part of her Masters project. The co-supervisors provide a multidisciplinary approach combining pharmacy practice and pharmaceutics and have extensive experience of conducting research in these areas. The external supervisory team at Colorcon provide further experience, and have previously funded and conducted research into patient centric medicines.

7.6. Limitations

7.6.1. Multiple coders were not used

The use of multiple coders when analysing qualitative interviews can provide multiple perspectives from researchers of different backgrounds as well as the opportunity to discuss coding disagreements [321]. However, key challenges can also include the resource needs to include multiple coders as well as the time demands [321]. Due to these challenges, multiple coders were not included in this project. However, the supervisory team were constantly updated with progress during the coding of interviews, and were involved in refining the key themes.

7.6.2. The characteristics of the sample

Despite the aim to use maximum variation sampling to gain a representative sample for the semi-structured interviews, it was challenging to gain a representative sample of all ethnicities. Only one Asian-British older person was interviewed, one Asian-British carer and one Black/Black-British carer. No participants with a Chinese ethnic background were recruited. This may limit the extent to which the results can be generalised and further research focusing on recruiting patients from ethnic minorities is needed. Participants were limited to those who could speak/understand English which may have further limited the sample. Furthermore, all participants were from England which may limit the extent to which the results can be generalised to other countries.

7.6.3. Socially desirable responses

Social desirability is a common limitation of qualitative research and refers to the tendency for participants to give answers that are perceived to be socially acceptable but not a true reflection of reality [322]. In this case, the lead researcher is a community pharmacist and this may have led participants to deliver socially desirable responses indicating complete adherence to medication. In order to address this limitation, participants were informed that all answers were confidential and their identity would remain anonymous at all times. Follow up questions and prompts were asked to gain a true, deeper understanding of any potential issues the patient may be experiencing. Personal experiences in particular were encouraged and follow up questions again asked on these experiences. Nevertheless, it is impossible to completely eliminate social desirability and it is therefore necessary to acknowledge this as a limitation of this research.

7.7. Reflective account

Reflexivity is an awareness of the researcher's role in the practice of research and how he or she affects both the process and outcomes [323]. It has been defined as "the process by which research

turns back upon itself and takes account of itself" [324]. Reflexivity recognises that the interpretation of data is influenced by the assumptions of the researcher including their values and pre-understandings [325]. There is a need to reflect specifically on how these assumptions inform the interpretation of qualitative findings [325]. Questions that can help during this process include motivations for conducting the research, underlying assumptions being bought forward, and how any connections to the research (including theoretical, experiential and emotional connections) may impact the approach taken [323]. The following section provides a reflexive account of my motivation for conducting this research and my experience of data collection and interpretation.

The aim of this study was influenced in part by my own experience in this area. I came into this project as a practicing community pharmacist with four years' experience within multiples and independent community pharmacies. During this time, I encountered patients on a regular basis who were non-adherent to their medication due to factors such as the shape and size. Tablets needed to be specially ordered that were of a specific brand to ensure adherence. These tablets were kept in a separate, designated area within the dispensary, as illustrated in Fig. 7.2. I therefore had a professional interest as a pharmacist to explore further how some of these tablets could be re-designed to ensure adherence and acceptance. From my experience of talking to patients, a patient-centric approach was deemed most appropriate; medicines need to be as patient centric as possible to ensure the target population were accepting of the need to take them.

The aim and research design of the study also considered an extensive review of the literature in this area (Chapter two). While my personal background was within community pharmacy, reviewing the literature identified the need to explore this topic within secondary care and care homes where preferences may differ to those of patients and carers within the community. The systematic review also confirmed the lack of qualitative studies in this area as well as the need to consider the views of health and social care professionals who ultimately prescribe, dispense and administer these medications. Patient and public involvement in the research process was key and I was able to take advantage of my role as a community pharmacist to talk to patients about the key issues that need to be explored.

Fig.7.2. Researcher's personal experience of the need for patient centric medicines

When recruiting participants for this study, I was aware of the potential for participants to get in touch who may have been ineligible to take part. Although the inclusion criteria were kept as broad as possible, there was a criterion to include older people age 65 or over. There were, however, participants who contacted myself wanting to share their experiences and the importance of this research. I asked participants for permission to share their stories during the write up of this thesis, and an example of this can be found in Fig. 7.3 below. This story is shared to illustrate the importance of this research, and the difficulties that can arise when defining an older person by age alone. The story, for me personally, highlighted the importance of this research within the wider population and the importance of taking a personalised approach for each individual patient.

Fig. 7.3a. Patient A response to People in Research advertisement

I was looking through the NHIR website for something else when I came across your research into designing medicines.

At 63 I am outside your age range for the research but I have RA and am on lots of medications. I have written to my GP recently with the photograph below of my fortnightly medicine regime, pointing out that most of my meds are white, and some are very similar in shape and size.

The three oval tablets in the middle are difficult to tell apart - Nambumatone (NSAID), Aciclovir and Carvedilol (blood pressure)

I am reasonably with it, but as my hands are damaged by RA I drop tablets regularly and when I do it is extremely difficult to tell which tablet is which. I worry about other people older than me who may struggle with this, and potentially how I will manage as I get older.

It would be very helpful if medications could be coloured more frequently as they used to be. e.g. my steroids used to be red and are now white, very similar in shape and size to a blood pressure tablet.

Fig. 7.3b. Illustration of Patient A's medication

When recruiting participants for this study, I undertook interviews in various settings and there were a number of differences in the way I was able to approach participants. For participants who contacted me directly (as a result of advertising on recruitment websites), I undertook the interviews within the patient's home where they were able to show me the tablets they were taking and talk in detail about their experiences of taking them. It was easier to build a rapport with patients within these settings where patients had voluntarily asked to be involved in the research project.

Within care homes and secondary care, health and social care professionals recruited eligible patients and interviews took place on site. Although participants provided consent, I had a greater awareness of inconveniencing the patient but these worries often eased as the interview progressed. After conducting the interviews, care professionals would often ask me how I felt the interviews went. A discussion with one professional in particular led me to consider the context of my findings in greater detail. The care professional remarked that the patients who often have the greatest need to discuss their medication are those who can't provide informed consent. Often this can lead to covert administration of tablets. While this was outside the scope of my study, it provided an important reflection point on the heterogeneity of the older population and the need to consider individual cases. This was recorded in my reflective diary and was reflected on during the discussion of my findings.

During the interviews, it was clear that some older people were dissatisfied with some of the medications they received from the pharmacy, especially when different brands of medication were dispensed. Participants were sometimes aware of my role as a pharmacist and often used the interview as an opportunity to question why they received certain medications. In these instances, I tried to reinforce my role as a researcher and that this was independent of my experience as a pharmacist. I also proposed that any medical issues of concern could be addressed at the end of the interview. On reflection, my previous experience in pharmacy practice and talking to patients facilitated an open discussion with participants and helped me to develop a rapport from the outset.

Measures were taken throughout the data collection and analysis process to minimise the impact of my previous background and experience in this area. Field notes were made and a reflective diary was recorded during data analysis to record any thoughts on how my views developed as the research progressed. Thoughts while analysing the transcripts were recorded and discussed with supervisors at regular intervals.

7.8. Conclusion

This study has explored the key characteristics of oral solid dosage forms that contribute to age appropriate, patient centric medicines that help to improve medication adherence and acceptance in older people. The development of patient centric medicines for the older population requires a holistic, patient-centric approach. Manufacturers should take into account practical problems older people may encounter when considering the dimensions, palatability, and appearance of the final drug product. These areas have an impact on the medication taking process, including medication identification and memorability, medication handling, and swallowability. Small round tablets (≤7 mm) are least accepted amongst older people and their carers and had a negative impact on all stages. The use of bright, two-coloured preparations and interesting shapes improves identification and further aids memorability of indications and the timing of tablets. Palatability, while useful to enhance swallowability, also has an impact on the visual appeal and memorability of medication. 3D printing provides an ideal tool for the pharmaceutical industry to move away from a ‘one size fits-all’ approach, allowing for the manufacture of personalised medication that can achieve the best therapeutic outcomes. In all cases, patient centric medicines must then be prescribed, dispensed and administered appropriately so that patients receive the most suitable formulation.

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Appendices

Appendix 1: Results from scoping search using a search in Google Scholar

Author/ Year	Country	Length of time	Sample	Design	Purpose	Key findings	Gaps and further research
Drumond et al[326] 2017	Austria	No limits set on time frame or date of publication	No age limit	Literature Review	To identify clinical evidence for patient appropriateness, acceptability, and preference for drug products among all the target age populations. A secondary objective of this work was to recognize validated methodology used to determine such endpoints and to identify suitable methodology for testing the appropriateness and usability of drug products by patients	45 studies identified: All of the 45 published studies evaluated different aspects related to drug product design and how patients interact with them. The publications fell into one of two main categories depending on their research focus: packaging design and dosage form design. The majority of studies are problem descriptive in nature, and studies performed to improve or compare drug product design are still very limited	Only ten studies used validated methodology to investigate patient appropriateness. Little attention is being given to the development of suitable methodologies for the evaluation of drug products appropriateness among different patient populations, as well as studies investigating the patient-drug product interface for appropriateness
Gellad et al[327] 2011	USA	Review of articles published between Jan 1998	Review of articles looking at older patients (over 65 years) in the US	Systematic Review	To conduct a systematic review of the published literature describing potential nonfinancial barriers to medication	Four studies used pharmacy records or claims data to assess adherence, 2 studies used pill count or electronic monitoring, and 3 studies	Medication nonadherence in older people is not well described in the literature, despite being a major cause of morbidity, and thus it is difficult to draw a systematic conclusion on potential barriers based on the current literature. Future research should focus on standardizing medication adherence measurements among older people to

		and Jan 2010			adherence among older people	used other methods to assess adherence	gain a better understanding of this important issue.
George et al[104] 2008	Australia	Studies ranging from 1966-2006	Studies which looked at community dwelling older patients prescribed at least three or a mean/median of four or more, long term medications	Systematic Review	To determine the effectiveness of interventions to improve medication adherence in older community dwelling patients prescribed multiple long-term medications.	Eight studies identified, only four demonstrated significant improvement as a result of interventions (incl. verbal/written information). Change in adherence variable, ranging from 13% to 55.5%.	Due to inconsistent methodology and findings across studies, they were unable to draw firm conclusions in favour of any particular intervention. Innovative strategies for enhancing medication adherence in older people, and reliable measures of adherence are needed
Hughes et al[105] 2016	Northern Ireland			Review	To review the issue of polypharmacy in older people and potential pharmaceutical strategies to optimize the use of multiple medicines	Screening tools being adopted-provide prescribers with explicit prescribing rules, e.g. meds that should be avoided in older people- However few if any screening tools provide any guidance on the selection of appropriate formulations when prescribing for older people	Older people are routinely and systematically excluded from clinical trials- one study found only 7% of trials were designed for older people, with an average of 70 years- creates the "geriatric pharmacoparadox". The EMA has established a Geriatrics Expert Group to provide advice on a range of issues pertaining to medicines' use in older people. In 2011, the EMA issued a 'Geriatrics Medicines Strategy' which states that appropriate numbers of older patients should be included in trials
Kairuz et al[328] 2008	New Zealand	2008	31 older people (> or = 65 years of age) living in the community	Semi-structured interviews and observation	To identify the types of medicine compliance issues that occur among older people.	Identified intentional and non-intentional compliance issues that could hinder the optimal use of medicines by older people who are at greater risk of medicine-related adverse effects	Took place in New Zealand, further studies required in the UK
Liu et al[106] 2016	UK	Oct 2014-Nov 2014	156 patients from 10 community pharmacies aged	Questionnaires administered	Validate the Medicines Acceptability Questionnaire (MAQ).	11% suffered from symptomatic dysphagia.	Formulation characteristics play an important role in medicine acceptability in older patients.

			over 65 (average age 74)	via face to face interviews	Assess acceptability of OSM in older ambulatory patients with and without dysphagia using the Sydney Swallow Questionnaire (SSQ)	No significant correlation between age and SSQ dysphagia score. Significant correlation between number of OSMs taken and SSQ. Patients with dysphagia had difficulties swallowing larger tablets- 11mm and 13mm tablets.	Chewable tablets considered least acceptable alternative dosage form- decline in chewing ability due to tooth loss. Dispersible/effervescent highest acceptability score as alternative dosage form. Polypharmacy linked to dysphagia.
Marquis et al[83] 2013	Switzerland	March 2010- May 2010	410 patients aged 18 years or over on more than 3 OSDFs	Semi-structured questionnaire	To determine the prevalence, characteristics and duration of swallowing difficulties among primary care patients, to explore impairment of daily life & coping strategies used by patients, and to explore whether these difficulties were explored by HPS	Large size and sticky coating of drugs perceived as main causes of swallowing difficulties. Most frequently used techniques to overcome difficulties were to drink more water, split/crush tablet/mix with food. Self-reported omission in 22.8% of patients	Two patients only mentioned that their physician inquired about their swallowing difficulties, but none mentioned the pharmacist- highlights need for better communication with healthcare professionals. 63% of patients did not mention it to their GP. This study looked mainly at impact of polypharmacy- but did not take into account age
Messina et al[4] 2015	Italy, Germany, The Netherlands, Austria	Articles dated from January 1, 1987 to January 31, 2014	Studies which had at least 10 patients, age greater than or equal to 65	Preliminary Review	To identify scientific evidence and studies dedicated to investigating the appropriateness of a medicinal product through respective formulation, dosage form, drug delivery technology, route of administration or	Only 34 studies identified. Categorised into three main categories: 1) routes of administration more or less easy for the patient, 2) Acceptance and preference of the patient using a specific medicinal product 3) possible medication errors or administration problems in the use of a medicinal	Major finding: small number of studies published on the appropriateness of medicinal products for older patients. The majority of studies (32) did not investigate the product or delivery system for patient appropriateness directly in the targeted older population. No study could be identified that evaluated a pharmaceutical preparation, formulation, delivery system or other product design aspect for its appropriateness in an older adult patient population based on a scientific and clinical methodology. Excluded publications on

					frequency of dosing for use by older adult patients.	product by older adult patients. The terms "adherence" and "compliance" were present in all the studies identified	product modification, e.g. tablet splitting- could have provided useful info
Notenboom et al[117] 2014	Netherlands	2014	59 community dwelling, aged 70 and older, and using at least three different oral prescription medicines daily.	Qualitative study using semi structured interviews, conducted in patients' homes	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 thereof	211 problems reported. Problems identified with: 1) Reading and understanding instructions for use 2) Handling outer packaging 3) Handling immediate packaging 4) Preparation before use 5) Drug taking	Study took place in the Netherlands, this kind of research is scarce in the UK. Furthermore, the views of caregivers or other professionals involved in the management of older people's meds were not included
Perrie et al[329] 2012	UK	2012		Review	Evaluate age-related changes in pharmacokinetics and pharmacodynamics when using different methods of drug delivery	Increased use of medication in older population, with polypharmacy becoming more common. There is a need for improved formulation and development of medicines suitable for older patients. Yet, recognition of this need is still limited.	Currently there is inadequate representation of older people within clinical trials which cannot be fully related to the practical issues of involving older people in clinical trials
Quinn et al[330] 2016	UK	Sept 2015		Review	To consider alternative methods of drug administration for the treatment and care of older patients, incl ODTs	ODTs developed for the treatment of conditions that are common in the older population such as pain, depression, Parkinson's disease and Alzheimer's disease.	Aspects of ODTs still need to be improved on: Balance between appropriate mechanical strength and fast disintegration time, incorporation of high doses of drug or poorly soluble drugs, taste-masking of unpleasant or unpalatable drugs and the ability to sustain release.

						However, dry mouth may cause an issue- caused by anticholinergics- 1 in 5 older people suffer from xerostomia	Other oral solid dosage forms not covered by this review
Schiele et al[84] 2013	Germany	Nov 2010-Feb 2011	16 GPs in 11 GP practices Consecutive adult patients taking at least one oral solid dosage form for at least 4 weeks (1,051)	Questionnaire survey	To assess the prevalence of difficulties in swallowing OSDFs- views of patients and the awareness of GPs of these difficulties	37.4% had difficulties swallowing tablets and capsules 70.4% of these were not identified by their GP 9.4% of these non-adherent Reasons given for difficulties related to the dosage form were size (74.6 %), surface (70.5 %), shape (43.5 %), and flavour (22.1 %)	Study looked at all patients but found that special attention should be paid to specific patient groups- women and patients with dysphagia, dysphagia indicators, or mental illness Older people in particular suffer from dysphagia due to age related diseases, e.g. Alzheimer's, stroke Older patients with severe dysphagia are often visited at home by their GP, seen in hospitals/nursing homes and therefore weren't included in this study
Stegemann et al[103] 2012	Belgium, Austria, Germany	Feb 2012-March 2012		Review	To review evidence that swallowing issues and dysphagia are an increasing problem of the aging population and how this Is affecting oral medication administration	Swallowing impacted by saliva production & xerostomia- seen in conjunction with e.g. anticholinergics & polypharmacy CNS pathologies e.g. Parkinson's, Alzheimer's have highest prevalence of dysphagia Decisive criteria for swallowability- size, shape & surface texture Omitting drug intake, tablet crushing and capsule opening	Prevalence of dysphagia still underestimated- medical doctors and other caregivers do not consider it a health issue and do not systemically investigate swallowing issues of their patients. Older people living alone are presumed to manage meds and aren't questioned by GPs Quarter of old people believe dysphagia is part of aging. Nurses don't feel comfortable making decisions about med administration

						major interventions for outpatients	
Stegemann et al[102] 2017	Austria	2017	22 participants who had Type 2 Diabetes, lived independently, were aged 55 years or older and received polypharmacy (5 different medications).	Observational task performance and semi structured interviews	To investigate the impact of shape, size and colour on the identification of solid oral dosage forms in T2D patients receiving polypharmacy under simulated home conditions.	The mean time to identify the Study Medication was longer for the small sizes except with the bi-chromatic design. For the large sizes, round shape and bi-chromatic design were identified fastest, followed by oblong shape (white or yellow) and diamond shape. Only one error was made for round shapes and most errors occurred with white colour and oblong shapes	When asked what problems they experience with their own medication at home, all answered spontaneously that they have no problems since they have already been using the medication for a long time- it would be interesting to observe them at home and check whether this is the case. Patients were aged 55 or above- would the same results be obtained for patients over 65?
Tordoff et al[331] 2010	New Zealand	2010	20 community-dwelling people 65 years and older (10 male and 10 female), taking at least one prescription medicine	In-depth interviews, conducted in patients' homes	To explore how New Zealanders aged 65 years and older manage their medicines in their own homes, and determine the problems and concerns they might have with taking them	Several themes emerged and were explored, under the topics: accessing medicines, remembering to take medicines, following instructions, practical problems, adverse effects, concerns about medicines, and beliefs about medicines	Took place in New Zealand, further studies required in the UK- interesting that "most people had no difficulty swallowing tablets" Is this due to different brands being available in New Zealand compared to the UK?

Appendix 2: Complete search strategy for mixed methods systematic review

Medline Search Strategy (May 2019)	
1	1) ((MH=(Chemistry, Pharmaceutical)) OR TS= Pharmaceutical design OR TS= dosage form design OR TS= medic* design OR TS= drug product design OR TS= pharmaceutical formulation OR TS= drug formulation OR TS= medic* formulation OR TS= formulation factors OR TS= patient centric OR TS= patient-centric OR TS= physical characteristics OR TS= physical attributes OR TS= appearance OR TS= tablet dress OR MH=(Patient-Centered))
2	2) ((MH=(Administration, Oral) OR TS= “Oral solid” OR TS= “oral dosage” OR TS= “solid oral” OR TS= “solid dosage” OR TS= *tablet* OR TS= *capsule* OR TS= chewable OR TS= orodispersible OR TS= effervescent OR TS= “small tablet$” OR TS= “mini tablet$” OR TS= “hard capsule$” OR TS= “soft capsule$” OR TS= “fixed dose combination$”))
3	3) (((MH=(Patient Compliance OR Medication Adherence OR Treatment Refusal OR Patient Preference))))
4	4) TS= elderly OR TS= aged OR TS= older OR TS= geriatric OR TS= "over 60"
5	1 AND 2 AND 3 AND 4

Cochrane Library Search Strategy (May 2019)	
1	("pharmaceutical design" or "dosage form design" or "medic* design" or "drug product design" or "pharmaceutical formulation" or "drug formulation" or "medic* formulation" or "formulation factors" or "patient centric" or "patient-centric" or "physical characteristics" or "physical attributes" or appearance or "tablet dress") in Title Abstract Keyword
2	("Oral solid" or "oral dosage" or "solid oral" or "solid dosage" or *tablet* or *capsule* or chewable or orodispersible or effervescent or "small tablet" or "mini tablet" or "hard capsule" or "soft capsule" or "fixed dose combination") in Title Abstract Keyword
3	(appropriate* OR acceptab* OR usab* OR swallow* OR dysphagia OR prefer* OR persist* OR adhere* OR complian* OR nonadhere* OR non-adhere* OR noncomplian* OR non-complian* OR concordan*) in Title Abstract Keyword
4	(elderly OR aged OR older OR geriatric OR "over 60")
5	1 AND 2 AND 3 AND 4

Scopus (May 2019)	
1	TITLE-ABS-KEY ("Pharmaceutical design" OR "dosage form design" OR "medic* design" OR "drug product design" OR "pharmaceutical formulation" OR "drug formulation" OR "medic* formulation" OR "formulation factors" OR "patient centric" OR "physical characteristics" OR "physical attributes" OR appearance OR "tablet dress")

2	TITLE-ABS-KEY ("Oral solid" OR "oral dosage" OR "solid oral" OR "solid dosage" OR *tablet* OR *capsule* OR chewable OR orodispersible OR effervescent OR "small tablet" OR "mini tablet" OR "hard capsule" OR "soft capsule" OR "fixed dose combination")
3	TITLE-ABS-KEY (appropriate* OR acceptab* OR usab* OR swallow* OR dysphagia OR prefer* OR persist* OR adhere* OR complian* OR nonadhere* OR non-adhere* OR noncomplian* OR non-complian* OR concordan*)
4	TITLE-ABS-KEY (elderly OR aged OR older OR geriatric OR "over 60")
5	1 AND 2 AND 3 AND 4

Web of Science (May 2019)	
1	TS= “Pharmaceutical design” OR TS= “dosage form design” OR TS= “medic* design” OR TS= “drug product design” OR TS= “pharmaceutical formulation” OR TS= “drug formulation” OR TS= “medic* formulation” OR TS= “formulation factors” OR TS= “patient centric” OR TS= “patient-centric” OR TS= “physical characteristics” OR TS= “physical attributes” OR TS= appearance OR TS= “tablet dress”
2	TS= “Oral solid” OR TS= “oral dosage” OR TS= “solid oral” OR TS= “solid dosage” OR TS= *tablet* OR TS= *capsule* OR TS= chewable OR TS= orodispersible OR TS= effervescent OR TS= “small tablet$” OR TS= “mini tablet$” OR TS= “hard capsule$” OR TS= “soft capsule$” OR TS= “fixed dose combination$”
3	TS= Appropriate* OR TS= acceptab* OR TS= usab* OR TS= swallow* OR TS= dysphagia OR TS= prefer* OR TS= persist* OR TS= adhere* OR TS= complian* OR TS= nonadhere* OR TS= non-adhere* OR TS= noncomplian* OR TS= non-complian* OR TS= concordan*
4	TS= elderly OR TS= aged OR TS= older OR TS= geriatric OR TS= "over 60"
5	1 AND 2 AND 3 AND 4

Google Scholar Search Strategy (June 2018)	
1	“Oral Solid”
2	Adherence
3	“Older”
4	1 AND 2 AND 3

Other Sources:

1) BASE (May 2019)

“oral solid” “adherence” “older”

2) EThOS (May 2019)

“oral” AND “adherence” AND “older people”

3) OpenGrey (May 2019)

("oral") AND (adherence) AND (older OR elderly OR geriatric OR "over 60")

4) WoS Conference Proceedings: Conference Proceedings Citation Index- Science (CPCI-S) --1990-present (May 2019)

TOPIC: (oral AND (older OR elderly OR geriatric) AND adherence)

Appendix 3: Completed PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	30
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.	Reference provided on 29
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	15-28
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	31-33
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.	36-37
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.	31-33
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.	35-36, Appendix 2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	37

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.	37
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	37
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.	37-38
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.	38-39
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).	41
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.	40
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.	43-53
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).	Appendix 5
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.	N/A
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 (see Item 15).	Appendix 5
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
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).	57-61
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).	59-60
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	58-61
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Reference provided on 29

Appendix 4: Reasons for exclusion at full text

#	Study Name	Reason for Exclusion
1	ALEKSOVSKI, A., DREU, R., GAŠPERLIN, M. & PLANINŠEK, O. 2015. Mini-tablets: A contemporary system for oral drug delivery in targeted patient groups. Expert Opinion on Drug Delivery, 12, 65-84.	Review from which no additional references were found
2	ANDERSEN, O., ZWEIDORFF, O. K., HJELDE, T. & RODLAND, E. A. 1995. Problems when swallowing tablets. A questionnaire study from general practice. Tidsskrift for den Norske lageforening : tidsskrift for praktisk medicin, ny rakke, 115, 947-9.	Only available in German
3	ARGOFF, C. E. & KOPECKY, E. A. 2014. Patients with chronic pain and dysphagia (CPD): unmet medical needs and pharmacologic treatment options. Curr Med Res Opin, 30, 2543-59.	Review from which no additional references were found
4	BAYER, A. J., DAY, J. J., FINUCANE, P. & PATHY, M. S. J. 1988. BIOAVAILABILITY AND ACCEPTABILITY OF A DISPERSIBLE FORMULATION OF LEVODOPA-BENSERAZIDE IN PARKINSONIAN PATIENTS WITH AND WITHOUT DYSPHAGIA. Journal of Clinical Pharmacy and Therapeutics, 13, 191-194.	Does not explore the formulation characteristics that affected preference for each formulation
5	BHOSLE, M., BENNER, J. S., DEKOVEN, M. & SHELTON, J. 2009. Difficult to swallow: Patient preferences for alternative valproate pharmaceutical formulations. Patient Preference and Adherence, 3, 161-171.	1.2% (5 participants) aged over 65 and no data provided that would added to results
6	BITTER, I., TREUER, T., DILBAZ, N., OYFFE, I., CIORABAI, E. M., GONZALEZ, S. L., RUSCHEL, S., SALBURG, J. & DYACHKOVA, Y. 2010. Patients' preference for olanzapine orodispersible tablet compared with conventional oral tablet in a multinational, randomized, crossover study. The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry, 11, 894-903.	Participants aged 18-65 however unable to extract data for older people
7	**B**LANCO, M. A., PRIETO, M., MEARIN, F., PLAZAS, M. J., ARMENGOL, S., HERAS, J., MAS, M., PIQUE, J. M. & EL GRUPO DEL ESTUDIO, L. A. N. 2009. Evaluation of preferences in patients with gastroesophageal reflux disease and dysphagia concerning treatment with lansoprazole orally disintegrating tablets. Gastroenterologia y hepatologia, 32, 542-8.	Only available in Spanish

8	BOATENG, J. 2017. Drug Delivery Innovations to Address Global Health Challenges for Pediatric and Geriatric Populations (Through Improvements in Patient Compliance). Journal of Pharmaceutical Sciences, 106, 3188-3198.	Commentary from which no additional references were found
9	BREITKREUTZ, J. & BOOS, J. 2007. Paediatric and geriatric drug delivery. Expert Opinion on Drug Delivery, 4, 37-45.	Review from which no additional references were found
10	BUCKALEW, L. W. & ROSS, S. 1991. Medication property effects on expectations of action. Drug Development Research, 23, 101-108.	Unable to extract data for older people on preferences for formulation characteristics. Focus is more on perceived indications based on colour.
11	CASIAN, T., BOGDAN, C., TARTA, D., MOLDOVAN, M., TOMUTA, I. & IURIAN, S. 2018. Assessment of oral formulation-dependent characteristics of orodispersible tablets using texture profiles and multivariate data analysis. Journal of Pharmaceutical and Biomedical Analysis, 152, 47-56.	Participants aged 22-57
12	CHANNER, K. S. & VIRJEE, J. P. 1985. The effect of formulation on oesophageal transit. Journal of Pharmacy and Pharmacology, 37, 126-129.	Unable to extract data for older people due to differences in mean age between the groups given differing formulations. Focus on esophageal transit rather than patient acceptability.
13	CHU, X. Y., GAO, C. H., GE, C. & GAO, C. S. 2018. Progress in researches of patient-centric individualized formulation approaches. Chinese Journal of New Drugs, 27, 409-416.	Only available in Chinese
14	DANILEVICIUTE, V., ADOMAITIENE, V., SVEIKATA, A., MACIULAITIS, R., KADUSEVICIUS, E. & VOLBEKAS, V. 2006. Compliance in psychiatry: results of a survey of depressed patients using orally disintegrating tablet. Medicina (Kaunas, Lithuania), 42, 1006-12.	Only available in Lithuanian
15	DE ARGILA, C. M., PONCE, J., MARQUEZ, E., PLAZAS, M. J., GALVAN, J., HERAS, J. & PORCEL, J. 2007. Acceptability of lansoprazole orally disintegrating tablets in patients with gastro-oesophageal reflux disease : ACEPTO study. Clinical drug investigation, 27, 765-70.	Unable to extract data for older people

16	DENNEBOOM, W., DAUTZENBERG, M. G. H., GROL, R. & DE SMET, P. A. G. M. 2005. User-related pharmaceutical care problems and factors affecting them: the importance of clinical relevance. Journal of clinical pharmacy and therapeutics, 30, 215-23.	Does not explore formulation as defined for the review
17	DEROSA, G., ROMANO, D., BIANCHI, L., D'ANGELO, A. & MAFFIOLI, P. 2015. Metformin Powder Formulation Compared to Metformin Tablets on Glycemic Control and on Treatment Satisfaction in Subjects With Type 2 Diabetes Mellitus. Journal of Clinical Pharmacology, 55, 409-414.	Does not explore the formulation characteristics that affected preference for each formulation
18	DESAI, R. J., SARPATWARI, A., DEJENE, S., KHAN, N. F., LII, J., ROGERS, J. R., DUTCHER, S. K., RAOFI, S., BOHN, J., CONNOLLY, J., FISCHER, M. A., KESSELHEIM, A. S. & GAGNE, J. J. 2018. Differences in rates of switchbacks after switching from branded to authorized generic and branded to generic drug products: cohort study. BMJ (Clinical research ed.), 361, k1180.	Does not explore the formulation characteristics that impacted the rates of switchbacks in sufficient detail for the review
19	DRUMOND, N., VAN RIET-NALES, D. A., KARAPINAR-CARKIT, F. & STEGEMANN, S. 2017. Patients' appropriateness, acceptability, usability and preferences for pharmaceutical preparations: Results from a literature review on clinical evidence. Int J Pharm, 521, 294-305.	Review from which no additional references were found
20	FAISAL, W., FARAG, F., ABDELLATIF, A. A. H. & ABBAS, A. 2018. Taste masking approaches for medicines. Current Drug Delivery, 15, 167-185.	Review from which no additional references were found
21	FOROUGH, A. S., LAU, E. T., STEADMAN, K. J., CICHERO, J. A., KYLE, G. J., SANTOS, J. M. S. & NISSEN, L. M. 2018. A spoonful of sugar helps the medicine go down? A review of strategies for making pills easier to swallow. Patient preference and adherence, 12, 1337.	Review- additional reference (Schiele et al., 2013) retrieved
22	GOYANES, A., SCARPA, M., KAMLOW, M., GAISFORD, S., BASIT, A. W. & ORLU, M. 2017. Patient acceptability of 3D printed medicines. Int J Pharm, 530, 71-78.	Participants aged 18-45
23	GRADY, H., KUKULKA, M. J., ONO, T. & NUDURUPATI, S. V. 2018. Evaluation of physical characteristics of dexlansoprazole orally disintegrating tablets. Pharmaceutical Technology, 42, 30-37.	Unable to extract data for older people
24	HANNING, S. M., LOPEZ, F. L., WONG, I. C. K., ERNEST, T. B., TULEU, C. & GUL, M. O. 2016. Patient centric formulations for paediatrics and geriatrics: Similarities and	Review from which no additional references were found

	differences. International Journal of Pharmaceutics, 512, 355-359.	
25	HEY, H., JØRGENSEN, F., SØRENSEN, K., HASSELBALCH, H. & WAMBERG, T. 1982. Oesophageal transit of six commonly used tablets and capsules. British Medical Journal, 285, 1717-1719.	Focus on oesophageal transit of medication, rather than patient adherence or acceptance
26	HOWELL, E. H., SENAPATI, A., HSICH, E. & GORODESKI, E. Z. 2017. Medication self-management skills and cognitive impairment in older adults hospitalized for heart failure: A cross-sectional study. SAGE open medicine, 5, 2050312117700301.	Does not explore formulation as defined for the review- focus more on the impact of cognitive impairment on health literacy
27	IBRAHIM, I. R., IZHAM, M. M. & AL-HADDAD, M. 2010. Consumer preferences and perceptions towards the use colored oral solid dosage forms in Baghdad. Archives of Pharmacy Practice, 1, 15.	Unable to extract data for older people
28	IMAI, K. 2013. Alendronate sodium hydrate (oral jelly) for the treatment of osteoporosis: Review of a novel, easy to swallow formulation. Clinical Interventions in Aging, 8, 681-688.	Review from which no additional references were found
29	JAMISON, J., SUTTON, S., MANT, J. & DE SIMONI, A. 2017. Barriers and facilitators to adherence to secondary stroke prevention medications after stroke: analysis of survivors and caregivers views from an online stroke forum. BMJ open, 7, e016814.	Does not explore formulation in older people as defined for the review.
30	KAKUDA, T. N., BERCKMANS, C., DE SMEDT, G., LEEMANS, R., LEOPOLD, L., PEETERS, M., NIJS, S., VYNCKE, V., VAN SOLINGEN-RISTEA, R. & HOETELMANS, R. M. W. 2013. Single-dose pharmacokinetics of pediatric and adult formulations of etravirine and swallowability of the 200-mg tablet: results from three Phase 1 studies. International Journal of Clinical Pharmacology and Therapeutics, 51, 725-737.	Unable to extract data for older people. Mean age 49 for swallowability study
31	KELLY, J., D'CRUZ, G. & WRIGHT, D. 2009. A qualitative study of the problems surrounding medicine administration to patients with dysphagia. Dysphagia, 24, 49-56.	Does not explore formulation as defined for the review- focus more on healthcare professionals' administration of medication
32	KRAEMER, S., CHARTIER, F., AUGENDRE-FERRANTE, B., PSARRA, V., D'YACHKOVA, Y., BESELIN, A. & ROUILLON, F. 2012. Effectiveness of two formulations of oral olanzapine in patients with schizophrenia or bipolar disorder in a	Unable to extract data for older people

	natural setting: results from a 1-year European observational study. Human psychopharmacology, 27, 284-94.	
33	LAM, P. W., LUM, C. M. & LEUNG, M. F. 2007. Drug non-adherence and associated risk factors among Chinese geriatric patients in Hong Kong. Hong Kong medical journal =Xianggang yi xue za zhi, 13, 284-92.	Does not explore formulation factors which may lead to non-adherence as defined for the review
34	LENAHAN, J. L., MCCARTHY, D. M., DAVIS, T. C., CURTIS, L. M., SERPER, M. & WOLF, M. S. 2013. A drug by any other name: patients' ability to identify medication regimens and its association with adherence and health outcomes. Journal of health communication, 18, 31-39.	Does not explore formulation factors which may impact adherence or acceptance as defined for the review
35	LIU, F., RANMAL, S., BATCHELOR, H. K., ORLU-GUL, M., ERNEST, T. B., THOMAS, I. W., FLANAGAN, T. & TULEU, C. 2014. Patient-Centred Pharmaceutical Design to Improve Acceptability of Medicines: Similarities and Differences in Paediatric and Geriatric Populations. Drugs, 74, 1871-1889.	Review from which no additional references were found
36	LIU, Y., LI, P., QIAN, R., SUN, T., FANG, F., WANG, Z., KE, X. & XU, B. 2018. A novel and discriminative method of in vitro disintegration time for preparation and optimization of taste-masked orally disintegrating tablets of carbinoxamine maleate. Drug development and industrial pharmacy, 44, 1317-1327.	In vivo testing carried out in 6 healthy volunteers- unable to extract data for older people
37	LOPEZ, F. L., BOWLES, A., GUL, M. O., CLAPHAM, D., ERNEST, T. B. & TULEU, C. 2016. Effect of formulation variables on oral grittiness and preferences of multiparticulate formulations in adult volunteers. *Eur J Pharm Sci,* 92**,** 156-62.	Participants aged 20-25
38	LUMBRERAS, B. & LOPEZ-PINTOR, E. 2017. Impact of changes in pill appearance in the adherence to angiotensin receptor blockers and in the blood pressure levels: a retrospective cohort study. Bmj Open, 7.	Does not explore the formulation characteristics in detail which may lead to a change in adherence
39	MACKENZIE-SMITH, L., MARCHI, P., THORNE, H., TIMEUS, S., YOUNG, R. & LE CALVÉ, P. 2018. Patient Preference and Physician Perceptions of Patient Preference for Oral Pharmaceutical Formulations: Results from a Real-Life Survey. Inflammatory Intestinal Diseases, 3, 43-51.	Unable to extract data for older people
40	MARQUEZ-CONTRERAS, E., GIL, V., LOPEZ, J., PLAZAS, M. J., HERAS, J., GALVAN, J. & PORCEL, J. 2008. Pharmacological compliance and acceptability of	Unable to extract preferences for formulation characteristics for older people

	lansoprazole orally disintegrating tablets in primary care. Current medical research and opinion, 24, 569-76.	
41	MATUSZEWSKI, K., KAPUSNIK-UNER, J., MAN, M., PARDINI, R. & SUKO, J. 2018. Variation in Generic Drug Manufacturers' Product Characteristics. Pharmacy and Therapeutics, 43, 485-504.	Does not measure impact of formulation on adherence or acceptance as defined for the review
42	MC GILLICUDDY, A., KELLY, M., SWEENEY, C., CARMICHAEL, A., CREAN, A. M. & SAHM, L. J. 2016. Modification of oral dosage forms for the older adult: An Irish prevalence study. Int J Pharm, 510, 386-93.	Does not explore the formulation characteristics which led to swallowing difficulties and the resulting modifications
43	MC GILLICUDDY, A., KELLY, M., CREAN, A. M. & SAHM, L. J. 2019. 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.	Conference Abstract (Published paper not yet available)
44	MEHUYS, E., DUPOND, L., PETROVIC, M., CHRISTIAENS, T., VAN BORTEL, L., ADRIAENS, E., DE BOLLE, L., VAN TONGELEN, I., REMON, J. P. & BOUSSERY, K. 2012. Medication management among home-dwelling older patients with chronic diseases: possible roles for community pharmacists. The journal of nutrition, health & aging, 16, 721-6.	Does not explore the formulation characteristics which cause the practical problems when taking medicines
45	MIEHLKE, S., HRUZ, P., VIETH, M., BUSSMANN, C., VON ARNIM, U., BAJBOUJ, M., SCHLAG, C., MADISCH, A., FIBBE, C., WITTENBURG, H., ALLESCHER, H. D., REINSHAGEN, M., SCHUBERT, S., TACK, J., MUELLER, M., KRUMMENERL, P., ARTS, J., MUELLER, R., DILGER, K., GREINWALD, R. & STRAUMANN, A. 2016. A randomised, double-blind trial comparing budesonide formulations and dosages for short-term treatment of eosinophilic oesophagitis. Gut, 65, 390-+.	Does not explore the characteristics of each formulation which led to the patient's preferred preference
46	MILLER, C. A. 2003. Safe medication practices: Administering medications to elders who have difficulty swallowing. Geriatric Nursing, 24, 378-379.	Review from which no additional references were found
47	OGATA, I., YAMASAKI, K., TSURUDA, A., TSUZAKI, S., ISHIMATSU, T., HIRAYAMA, H. & SEO, H. 2008. Some problems for dosage form based on questionnaire surveying compliance in patients taking tamsulosin hydrochloride. Yakugaku zasshi : Journal of the Pharmaceutical Society of Japan, 128, 291-7.	Only available in Japanese

48	PAPANASTASIOU, A. & KALANTZI, L. 2018. Innovation in Formulation Development for Older People. J Aging Sci, 6, 2.	Review from which no additional references were found
49	PARK, C., MEGHANI, N. M., AMIN, H. H., NGUYEN, V. H. & LEE, B.-J. 2017. Patient-centered drug delivery and its potential applications for unmet medical needs. Therapeutic delivery, 8, 775-790.	Review from which no additional references were found
50	PATEL, M. X., DE ZOYSA, N., BERNADT, M. & DAVID, A. 2009. Depot and oral antipsychotics: patient preferences and attitudes are not the same thing. Journal of Psychopharmacology, 23, 789-796.	Does not explore formulation characteristics of the oral antipsychotics as defined for the review
51	PATSALOS, P. N., RUSSELLJONES, D., FINNERTY, G., SANDER, J. & SHORVON, S. D. 1990. THE EFFICACY AND TOLERABILITY OF CHEWABLE CARBAMAZEPINE COMPARED TO CONVENTIONAL CARBAMAZEPINE IN PATIENTS WITH EPILEPSY. Epilepsy Research, 5, 235-239.	Does not explore the formulation characteristics that led to a preference for either formulation
52	PEPIĆ, I. & LOVRIĆ, J. 2018. Challenges in patient-centric oral dosage form design – The example of sumamed®. Medicus, 27, 171-175.	Only available in Croatian
53	PEREIRA, B. C., ISREB, A., FORBES, R. T., DORES, F., HABASHY, R., PETIT, J. B., ALHNAN, M. A. & OGA, E. F. 2019. 'Temporary Plasticiser': A novel solution to fabricate 3D printed patient-centred cardiovascular 'Polypill' architectures. European Journal of Pharmaceutics and Biopharmaceutics, 135, 94-103.	Unable to extract data for older people (Only in vitro testing conducted)
54	PERKINS, A. C., WILSON, C. G., FRIER, M., VINCENT, R. M., BLACKSHAW, P. E., DANSEREAU, R. J., JUHLIN, K. D., BEKKER, P. J. & SPILLER, R. C. 1999. Esophageal transit of risedronate cellulose-coated tablet and gelatin capsule formulations. International journal of pharmaceutics, 186, 169-175.	Does not measure patient adherence or acceptance, rather looks at esophageal transit
55	QUINN, H. L., HUGHES, C. M. & DONNELLY, R. F. 2016. Novel methods of drug administration for the treatment and care of older patients. International Journal of Pharmaceutics, 512, 366-373.	Review from which no additional references were found
56	REILLY, T. M. 2009. Medication management in the elderly: Major opportunity for advances in drug delivery & formulation technologies. Drug Delivery Technology, 9, 52-57.	Review from which no additional references were found
57	ROGER, A., FORTEA, J., MORA, S. & ARTÉS, M. 2008. Ebastine fast-dissolving tablets versus regular tablets: Acceptability and preference in patients with allergic	Sample excludes older people

	rhinitis. Expert Review of Clinical Pharmacology, 1, 381-389.	
58	ROGER REIG, A., PLAZAS FERNANDEZ, M. J., GALVAN CERVERA, J., HERAS NAVARRO, J., ARTES FERRAGUD, M. & GABARRON HORTAL, E. 2006. Acceptance survey of a fast dissolving tablet pharmaceutical formulation in allergic patients. Satisfaction and expectancies. Allergologia et immunopathologia, 34, 107-12.	Unable to extract data for older people
59	ROMAN, B. 2009. Patients' Attitudes towards Generic Substitution of Oral Atypical Antipsychotics A Questionnaire-Based Survey in a Hypothetical Pharmacy Setting. Cns Drugs, 23, 693-701.	Unable to extract data for older people
60	ROOSE, S. P. 2003. Compliance: the impact of adverse events and tolerability on the physician's treatment decisions. European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology, 13 Suppl 3, S85-92.	Review from which no additional references were found
61	SAJATOVIC, M., THOMPSON, T. R., NANRY, K., EDWARDS, S. & MANJUNATH, R. 2013. Prospective, open-label trial measuring satisfaction and convenience of two formulations of lamotrigine in subjects with mood disorders. Patient Preference and Adherence, 7, 411-417.	Unable to extract data for older people
62	SATYANARAYANA, D. A., KULKARNI, P. K. & SHIVAKUMAR, H. G. 2011. Gels and jellies as a dosage form for dysphagia patients: A review. Current Drug Therapy, 6, 79-86.	Review from which no additional references were found
63	SCHWARTZ, J. I., YEH, K. C., BERGER, M. L., TOMASKO, L., HOOVER, M. E., EBEL, D. L., STAUFFER, L. A., HAN, R. & BJORNSSON, T. D. 1995. Novel oral medication delivery system for famotidine. Journal of clinical pharmacology, 35, 362-7.	Unable to extract data for older people on the formulation characteristics of the wafer and tablet that led to patient preference
64	SERRANO-CASTRO, P. J., MAURI-LLERDA, J. A., GARCIA, A., ROCAMORA, R., PARDO-MERINO, A. & GARCIA-GARCIA, P. 2016. Treatment adherence with levetiracetam: a non-interventionist retrospective observation-based study. Revista De Neurologia, 62, 481-486.	Only available in Spanish
65	SLAVKOVA, M. & BREITKREUTZ, J. 2015. Orodispersible drug formulations for children and elderly. European Journal of Pharmaceutical Sciences, 75, 2-9.	Review from which no additional references were found
66	STEGEMANN, S., GOSCH, M. & BREITKREUTZ, J. 2012. Swallowing dysfunction and dysphagia is an unrecognized challenge for oral drug therapy. International journal of pharmaceutics, 430, 197-206.	Review from which no additional references were found

67	STEGEMANN, S., TERNIK, R. L., ONDER, G., KHAN, M. A. & VAN RIET-NALES, D. A. 2016. Defining Patient Centric Pharmaceutical Drug Product Design. Aaps Journal, 18, 1047-1055.	White Paper- No additional references found
68	TAHAINEH, L. & WAZAIFY, M. 2017. Difficulties in swallowing oral medications in Jordan. International journal of clinical pharmacy, 39, 373-379.	Unable to extract data for older people
69	TAO, D., WANG, T., WANG, T. & QU, X. 2018. Influence of drug colour on perceived drug effects and efficacy. Ergonomics, 61, 284-294.	Unable to extract data for older people
70	THIRION, O., NEGGAZI, N., ALMAQDISSI, A., BORDES-PICARD, F. & STEGEMANN, S. 2014. "Patient centric design'": Contribution to medicine safety. S.T.P. Pharma Pratiques, 24, 347-351.	Review article from which no additional references were found
71	TRENFIELD, S. J., AWAD, A., GOYANES, A., GAISFORD, S. & BASIT, A. W. 2018. 3D printing pharmaceuticals: drug development to frontline care. Trends in pharmacological sciences, 39, 440-451.	Review from which no additional references were found
72	TRIVEDI, M. R., PATEL, H. H. & DAVE, R. H. 2017. A Review on Tablet Scoring: Background, History and Current Regulatory Considerations. British Journal of Pharmaceutical Research, 20.	Review from which no additional references were found
73	VAN RIET-NALES, D. A., HUSSAIN, N., SUNDBERG, K. A. E., EGGENSCHWYLER, D., FERRIS, C., ROBERT, J. L. & CERRETA, F. 2016. Regulatory incentives to ensure better medicines for older people: From ICH E7 to the EMA reflection paper on quality aspects. International Journal of Pharmaceutics, 512, 343-351.	Review from which no additional references were found
74	WALSH, J., RANMAL, S. R., ERNEST, T. B. & LIU, F. 2017. Patient acceptability, safety and access: A balancing act for selecting age-appropriate oral dosage forms for paediatric and geriatric populations. International journal of pharmaceutics.	Review from which no additional references were found
75	WIGHT, L. J., VANDENBURG, M. J., POTTER, C. E. & FREETH, C. J. 1992. A large scale comparative study in general practice with nitroglycerin spray and tablet formulations in elderly patients with angina pectoris. European Journal of Clinical Pharmacology, 42, 341-342.	Does not explore the characteristics of each formulation which led to the patient's preferred preference

76	WILLIAMS, B., SHAW, A., DURRANT, R., CRINSON, I., PAGLIARI, C. & DE LUSIGNAN, S. 2005. Patient perspectives on multiple medications versus combined pills: a qualitative study. QJM : monthly journal of the Association of Physicians, 98, 885-93.	Does not explore the formulation characteristics in detail that impact acceptability as defined for the review
77	YANZE, M. F., DURU, C., JACOB, M., BASTIDE, J. M. & LANKEUH, M. 2001. Rapid therapeutic response onset of a new pharmaceutical form of chloroquine phosphate 300 mg: Effervescent tablets. Tropical Medicine and International Health, 6, 196-201.	Participants aged between 19-51
78	ZANARDI, R., COLOMBO, L., MARCHEGGIANI, E., ROSSINI, D., DELMONTE, D., FULGOSI, M. C., GAVINELLI, C. & COLOMBO, C. 2013. Paroxetine drops versus paroxetine tablets: Evaluation of compliance in a six-month study. Rivista di Psichiatria, 48, 261-267.	Unable to extract data for older people
79	ZGRAGGEN, L., FARE, P. B., LAVA, S. A. G., SIMONETTI, G. D., FOSSALI, E. F., AMORUSO, C. & BIANCHETTI, M. G. 2012. Palatability of crushed SS-blockers, converting enzyme inhibitors and thiazides. Journal of clinical pharmacy and therapeutics, 37, 544-6.	Participants aged between 24-50

Appendix 5: Results from quality appraisal using the MMAT

		1. QUALITATIVE STUDIES					Pharma Sponsored/Funding
First Author	**Year**	**1.1. Is the qualitative approach appropriate to answer the research question?**	**1.2. Are the qualitative data collection methods adequate to address the research question?**	**1.3. Are the findings adequately derived from the data?**	**1.4. Is the interpretation of results sufficiently substantiated by data?**	**1.5. Is there coherence between qualitative data sources, collection, analysis and interpretation?**	
Kelly	2010	Yes	Yes	Yes	Yes	Yes	No
Notenboom	2014	Yes	Yes	Yes	Yes	Yes	No
Notenboom	2017	Yes	Yes	Yes	Yes	Yes	No
		2. RANDOMISED CONTROLLED TRIALS					
		2.1. Is randomization appropriately performed?	**2.2. Are the groups comparable at baseline?**	**2.3. Are there complete outcome data?**	**2.4. Are outcome assessors blinded to the intervention provided?**	**2.5 Did the participants adhere to the assigned intervention?**	
den Uyl	2010	Yes	Can't tell	Yes	No	Yes	Yes
Hofmanová	2019	Yes	Can't tell	Yes	Yes	Yes	Yes
Philips	1992	Can't tell	Can't tell	No	Can't tell	Yes	No
Rees	2001	Can't tell	Yes	Yes	Yes	Yes	No
Reginster	2005	Yes	Can't tell	No	No	No	Yes

		3. QUANTITATIVE NON-RANDOMISED STUDIES					
		3.1. Are the participants representative of the target population?	**Are measurements appropriate regarding both the outcome and intervention (or exposure)?**	**3.3. Are there complete outcome data?**	**3.4. Are the confounders accounted for in the design and analysis?**	**3.5. During the study period, is the intervention administered (or exposure occurred) as intended?**	
Scott	2018	Yes	Yes	No	Yes	Yes	Yes
Vallet	2018	Yes	Yes	Yes	Yes	Can't tell	No
		4. QUANTITATIVE DESCRIPTIVE STUDIES					
		4.1. Is the sampling strategy relevant to address the research question?	**4.2. Is the sample representative of the target population?**	**4.3. Are the measurements appropriate?**	**4.4. Is the risk of nonresponse bias low?**	**4.5. Is the statistical analysis appropriate to answer the research question?**	
Heikkilä	2011	Yes	Yes	Yes	Yes	Yes	No
Jones	2000	No	No	Can't tell	Can't tell	No	Yes
Liu	2016	Yes	Yes	Yes	Can't tell	Yes	No
Marquis	2013	Yes	Yes	Can't tell	No	Yes	No
Rodenhuis	2003	Can't tell	Can't tell	Can't tell	Can't tell	No	No
Schiele	2013	Yes	Yes	Can't tell	Can't tell	Yes	No

Appendix 6: Interview schedules for semi-structured interviews

Interview Schedule: Patients

This semi-structured interview will consist of open-ended questions, which are split into four sections. However, these questions will depend upon how much detail the participant wants to give and some questions may be expanded upon. Minor amendments may be made as the interview progresses as issues may arise that the researcher had not considered.

Introductory statements

Thank you for taking part in this interview, I appreciate the time you have given. Before we begin, I want to make it clear that if you wish to skip any question(s) during the interview, or if you want to stop the interview, all you have to do is say; you do not need to give any explanation for doing so.

Are you happy for me to begin?

Section one: Background information

1) Can you tell me a little bit of background information about yourself- including your age, current diagnoses and which medications you are currently taking?

Section two: Details regarding current medication

This next section will cover more details about the medication you take

2) Can you tell me a little bit more about the current medication that you take?
    a. Prompt: How easy do you find it to take the medication as directed by your doctor?
    b. Prompt: Do you need any help, e.g. carer, compliance packs

We're going to look now in more detail at the characteristics of tablets, so things like the shape, colour and size. We have some sugar-covered tablets which you can refer to if you'd like to help better explain your answers.

3) How do things like the shape, size, colour and coating (we call these the physical characteristics) affect your ability to take the medication as directed by the doctor?
    a. Prompt: Are there any types of medications that are more difficult or easy to take than others?
    b. Prompt: If you did find a tablet that was difficult to take, how would you deal with this?
    c. Prompt: Are you able to tell your different pills apart?

This final section is going to look at what changes you feel will make your tablets easier for you to take. Again, please feel free to refer to the sugar tablets.

4) With reference to the physical characteristics that we've just talked about (so that's the shape, size, colour and coating), what changes would help make your medications easier for you to take?
    a. Prompt: Are there any characteristics which are more/less important to you than others?

Thank you. Is there anything that you would like to add or any questions you would like to go back to?
End of Interview

Interview schedule: Carers

This semi-structured interview will consist of open-ended questions, which are split into four sections. However, these questions will depend upon how much detail the participant wants to give and some questions may be expanded upon. Minor amendments may be made as the interview progresses as issues may arise that the researcher had not considered.

Introductory statements

Thank you for taking part in this interview, I appreciate the time you have given. Before we begin, I want to make it clear that if you wish to skip any question(s) during the interview, or if you want to stop the interview, all you have to do is say; you do not need to give any explanation for doing so.

Are you happy for me to begin?

Section one: Background information

1) Can you tell me a little bit of background information about yourself- including your age and how long you've been a carer? Can you also tell me a little about the person you care for, including their age and diagnoses?

This next section will cover more details about the medication you administer

2) Could you tell me a little about your caring role focussing on giving medication?
    a. Prompt: Which medicines do you administer?
    b. Prompt: How easy do you find it to administer medication as directed by the doctor?

We're going to look now in more detail at the characteristics of tablets, so things like the shape, colour and size. We have some placebo tablets which you can make reference to if you'd like to help better explain your answers.

3) How do things like the shape, size, colour and coating (we call these the physical characteristics) affect your ability to administer the medication as directed by the doctor?
    a. Prompt: Are there any types of medications that are more difficult or easy to administer than others?
    b. Prompt: If you did find a tablet that was difficult to administer, how would you deal with this?
    c. Prompt: Are you able to tell the different pills apart?

This final section is going to look at what changes you feel will make the tablets easier for you to administer. Again, please feel free to refer to the sugar tablets.

1) With reference to the physical characteristics that we've just talked about (so that's the shape, size, colour and coating), what changes would help make the medications easier for you to administer?
    a. Prompt: Are there any characteristics which are more/less important to you than others?

Thank you. Is there anything that you would like to add or any questions you would like to go back to?

End of Interview

Interview schedule: Health and Social Care Professionals

This semi-structured interview will consist of open-ended questions, which are split into four sections. However, these questions will depend upon how much detail the participant wants to give and some questions may be expanded upon. Minor amendments may be made as the interview progresses as issues may arise that the researcher had not considered.

Introductory statements

Thank you for taking part in this interview, I appreciate the time you have given. Before we begin, I want to make it clear that if you wish to skip any question(s) during the interview, or if you want to stop the interview, all you have to do is say; you do not need to give any explanation for doing so.

Are you happy for me to begin?

Section one: Background information

1) Can you tell me a little bit of background information about yourself- including your role, the setting in which you work and the length of time in your current role?

This next section will cover more details about your experience with older people/their carers, their medication and the impact of the medicine's physical characteristics. We have some placebo tablets which you can make reference to if you'd like to help better explain your answers.

2) Overall, based on your experience, are older people or their carers normally able to take or administer medication as directed by the doctor?
    a. Prompt: How important are the physical characteristics (e.g. the shape, size, colour and coating) in determining whether an older person or their carer will adhere to their medication or administer medication as directed?
    b. Are there instances where you've had to change the formulation or brand due to difficulties arising as a result of the physical characteristics?

This section is going to look at what changes you feel will make tablets easier for older people or their carers to take/administer. Again, please feel free to make reference to the placebo tablets.

3) Overall, based on your experience, what particular physical characteristics would help to improve adherence?
    a. Prompt: How could the pharmaceutical industry change the physical characteristics of tablets to help improve adherence in older people?

This final section will look at the role of health and social care professionals in relation to optimising the physical characteristics of medication.

4) How can health and social care professionals ensure that the physical characteristics of tablets are appropriate for individual patients?
    a. Prompt: Who should identify any problems and what should they do once these problems have been identified?

Thank you. Is there anything that you would like to add or any questions you would like to go back to?

End of Interview

Appendix 7: Template email to recruit professionals

Document to be localised

Dear Sir/Madam

I am currently looking for health/social care professionals to participate in my study titled "Patient Centric Medicine Design to Improve Medicine Adherence and Acceptance in Older People." Your time would be invaluable to creating a successful project and advancing our knowledge of the topic. Furthermore, taking part in this study could help to increase your understanding and bring you up to date with the latest ideas in the area.

This research aims to explore how the physical characteristics of tablets and capsules, such as the shape, colour and size, currently affect the way in which older people are able to take their medication. It will further look at how these characteristics can be optimised in order to improve medication adherence.

The study involves two stages but you can choose to only take part in stage one:

1) An initial interview which will last between 30-45 minutes- this can take place in person or via videoconference/Skype depending on your preference.

2) A second interview or focus group which will take place a few months later.

Prior to the study, you will receive an information sheet which explains the study further and you will then be asked to sign a consent form to confirm you are happy to take part. On the consent form, you will have the option to choose whether you are happy to take part in both stages, or just the first.

The study has received a favourable opinion from the NHS Research Ethics Committee.

If you are interested in getting involved in this research, or would like to find out more, please contact me by any of the following methods:

Researcher: Zakia Shariff

E-mail: ramjeez1@aston.ac.uk

Phone: [redacted]

Thank you for taking the time to read this information. I look forward to hearing from you.

Yours sincerely,

Zakia Shariff
PhD Student, Aston University

Appendix 8: Poster to advertise research

Research Study:
Are you an older person or their carer taking a number of prescribed tablets or capsules?

What is the research?

We are conducting a study funded by Aston University and Colorcon. **We would like to interview older people (aged 65 or over) OR their carers** in order to help improve the design of tablets and capsules.

We want to know how we can change things like the shape, colour or size of medicines to make them easier for older people to take.

Interested in taking part?

For further information, please contact **Zakia Shariff** at: ramjeez1@aston.ac.uk or [phone no. redacted]

Appendix 9: Spring newsletter to advertise research

SPRING EDITION 1

PATIENT CENTRIC DRUG DESIGN TO IMPROVE ADHERENCE AND ACCEPTANCE IN OLDER PEOPLE

Aston University Birmingham

Colorcon

People are living longer following improvements in healthcare and lifestyle. Older people tend to take more medicines. Remembering to take the medication can be difficult, partly because older people are taking lots of medicines. The form of the medicine (e.g. the shape, size and colour) can have a big impact on whether or not the person takes the medication as recommended by the doctor.

What do we need to think about?

- Use of lots of medications
- Conditions related to age
- The need for a carer
- The ability to tell different pills apart
- Difficulties swallowing

"In all cases, the product should be designed to meet the patient's needs..."

What are the aims of this study?

This study aims to improve the way older people are able to take their medication by improving the design of tablets and capsules. We will look at factors such as the shape, size and colour to help make these medicines as easy as possible to take.

How will we do this?

Step 1: Find out what has already been done- We are currently looking at all the research in this area to find out exactly what has been done so far. We will then use this to identify the gaps that future research should address.

Step 2: Talk to patients, carers and health and social care professionals to understand what factors are most important to them- how can we make these medicines as easy as possible to take?

Step 3: Use the information given to us to design a product which is suitable for an older person to take and confirm this again with older people, their carers and health and social care professionals.

Who can help?

Designing a final product which takes into account the characteristics that older people and their carers prefer will need to consider the views of everyone involved in their treatment:

- **Older people** aged 65 or over and taking any number of tablets or capsules
- **Carers** who provide care as a family member or friend of an older person who has to take tablets or capsules
- **Healthcare professionals** such as doctors, nurses or pharmacists who have experience working with older people who may have difficulties taking tablets or capsules
- **Social care professionals** who have experience working with older people who may have difficulties taking tablets or capsules

Introducing the Lead Researcher

Zakia Shariff, Pharmacist and PhD student
Before starting my PhD, I worked as a community pharmacist for four years. During this time, I encountered older patients on a regular basis who were struggling to take their medication due to factors such as the size and shape. From my experience, older patients are a diverse population with individual needs which I hope to explore further through this research.

Why this project is important to me
The number of drugs on the market has increased, however their benefit depends on a suitable final drug formulation. Unless this issue is addressed, many resources are being wasted due to patient non-adherence.

The difference this project can make
By improving adherence and acceptance, we aim to reduce medicine wastage, reduce adverse events due to non-adherence and ultimately improve quality of life.

WATCH THIS SPACE

If you would like to be involved or receive regular updates, please contact:

Zakia Shariff (Lead Researcher):
ramjeez1@aston.ac.uk

DON'T FORGET TO KEEP AN EYE OUT FOR OUR AUTUMN 2018 NEWSLETTER!

Appendix 10: Autumn newsletter to advertise research

AUTUMN EDITION 2

PATIENT CENTRIC DRUG DESIGN TO IMPROVE ADHERENCE AND ACCEPTANCE IN OLDER PEOPLE

Aston University Birmingham

Colorcon

We are now in the process of analysing data to evaluate the main challenges in relation to the characteristics of tablets and capsules, and how we can overcome these.

"Occasionally it gets stuck in the back of my throat and it can get stuck and you can drink more and more water and it's still stuck, it's really annoying and you get a horrible taste then" Research Participant

What did we do?

We have conducted 52 semi-structured interviews about how we can improve the design of medicines to make them easier to take. We used sugar tablets that helped participants show us the shapes and sizes they prefer. These included circular shapes, caplets and oval shaped tablets of different sizes.

Who have we interviewed?

Older People who are at least 65 years of age, living at home, in care homes or in secondary care and who take at least one tablet or capsule

Informal Carers who provide care as a family member or friend of an older person who has to take tablets or capsules

Health and Social Care Professionals including GPs, Nurses, Pharmacy Technicians, Pharmacists, Healthcare Assistants and Care Support Workers

The interviews took place across the UK, including participants from Birmingham, York, Bradford, Stoke, Dudley, County Durham, London and Amlwch

What are we doing now?

All the interviews have been written up (transcribed) and we are in the process of going through them to identify some of the key challenges when taking tablets and capsules. We're particularly interested in how the characteristics such as the shape, colour and size can be improved and the characteristics that participants found most important.

What are some of the topics we are looking at?

Some of the common issues that we are investigating include:

- Use of lots of medications
- Conditions related to age
- The need for a carer
- The ability to tell different pills apart
- Difficulties swallowing

What happens next?

Following analysis of the interviews, the following steps will be taken:

Step 1: 3D Printing

Based on the answers participants gave in the interviews, we will use 3D printing to make some tablet models.

Step 2: Follow up Focus Group

We will carry out a follow up focus group with participants from the initial interviews who agreed to take part in one. This will be a group discussion in which we present our 3D printed tablet models and participants will have the opportunity to provide us with some feedback. This will take place at Aston University, in the new year- all travel expenses will be paid and participants will receive another £10 gift voucher.

Step 3: Share Recommendations

Our results will be shared with the funders Colorcon who are providing support for this study and shared at conferences in which we will be able to make recommendations for improving age appropriate medication.

"By improving adherence and acceptance, we aim to reduce medicine wastage, reduce adverse events due to non-adherence and ultimately improve quality of life. The characteristics of tablets play a hugely important role in this and we need to make sure that medicines are designed to meet the patient's needs."

Zakia Shariff, Lead Researcher

WATCH THIS SPACE

If you would like to be involved or receive regular updates or be involved in the follow up focus group, please contact:

Zakia Shariff (Lead Researcher):
ramjeez1@aston.ac.uk
[redacted]

Appendix 11: Participant Information Sheets

Aston University
Colorcon

NHS Site Logo
(to be added)

Improving the Design of Medicines for Older People

Participant Information Sheet- Older People

Invitation

We would like to invite you to take part in a research study.

Before you decide if you would like to participate, take time to read the following information carefully and, if you wish, discuss it with others such as your family, friends or colleagues.

Please ask a member of the research team, whose contact details can be found at the end of this information sheet, if there is anything that is not clear or if you would like more information before you make your decision.

What is the purpose of the study?

People are living longer following improvements in healthcare and lifestyle and older people tend to take more medicines. The properties of tablets and capsules (e.g. the shape, size and colour) can have a big impact on whether or not the person takes or administers a medicine as directed by a doctor. This study aims to look at how tablets and capsules can be designed so that they are easier for older people to take or their carers to administer.

Why have I been chosen?

You are being invited to take part in this study because:

You are aged 65 or older taking one or more tablets or capsules a day

What will happen to me if I take part?

The study involves two stages but you can choose to only take part in stage one:

1) An initial interview which will last up to an hour
2) A second interview or focus group which will take place a few months later and which will also last up to an hour

1) Initial Interview

During the interview, you will be asked for some background information about you such as your age and the medications you are taking. It will also explore your experiences of taking tablets and capsules, such as any difficulties you may have. We expect the interview to last up to an hour but this will depend on how much you have to say.

PIS- Older People IRAS ID: 250373, Version 0.8, 20.12.18

You will have access to some sugar (placebo) tablets which you can use to describe the type of tablets that you prefer, for example if you like oval shaped tablets you can use the oval tablet to show the shape you like. You will not be asked to take/swallow any of the tablets, rather we ask you base your answers on their appearance and feel.

The interview will take place at a time and location convenient for you at your own home or other convenient location to make you as comfortable as possible.

With your permission, we will audio record the interview and take notes. The recording will be typed into a document (transcribed) by a transcriber approved by Aston University. This process will involve removing any information which could be used to identify individuals e.g. names, locations etc.

Audio recordings will be destroyed as soon as the transcripts have been checked for accuracy. We will ensure that anything you have told us that is included in the reporting of the study will be anonymous.

You of course are free not to answer any questions that are asked without giving a reason.

2) Second interview/ Focus Groups

After the round of first interviews, we will make some tablet models based on the answers that were given. After making the models, we may, if you are in agreement, contact you again to explore how good these models are.

At this stage, a focus group might be more suitable. This is a group interview containing up to 8 - 10 participants where everyone will have a chance to talk about and give feedback on the models that we have developed. If this is suitable, you may be invited to take part at a time and location convenient to you. It will follow the same conditions in relation to recording, writing up (transcribing) and anonymity as detailed for the interviews above.

If you agree to take part in a focus group, full confidentiality cannot be guaranteed on behalf of the other focus group participants, although all participants will be asked to maintain confidentiality at the start of the focus group.

Do I have to take part?

No. It is up to you to decide whether or not you wish to take part.

If you do decide to participate, you will be asked to sign and date a consent form. You would still be free to withdraw from the study at any time without giving a reason.

Will my taking part in this study be kept confidential?

Yes. A code will be attached to all the data you provide to maintain confidentiality.

Your personal data (name and contact details) will only be used if the researchers need to contact you to arrange study visits or collect data by phone. Analysis of your data will be undertaken using coded data.

The data we collect will be stored in a secure document store (paper records) or electronically on a secure encrypted mobile device, password protected computer server or secure cloud storage device.

To ensure the quality of the research, Aston University may need to access your data to check that the data has been recorded accurately. If this is required, your personal data will be treated as confidential by the individuals accessing your data.

What happens if I tell you something that concerns you about my health or welfare?

In the unlikely event of this happening, we will discuss with you how this should be addressed. Should we have concerns in relation to your health or welfare, we may need to breach confidentiality and discuss concerns with the Project Supervisor who will follow appropriate policies to guide the best course of action. To protect you, this may involve reporting your concern to the appropriate person or bodies. Any disclosure of harm to yourself or others will also be discussed with the research team and then reported to the relevant authorities. Your safety will always be the over-riding principle.

What are the possible benefits of taking part?

Whilst there are no direct benefits to you taking part in this study, it is hoped that the project will result in the future availability of tablets and capsules that are easier for people to take.

What are the possible risks and burdens of taking part?

During the course of the interview, you may discuss some sensitive information such as your personal experiences in relation to illness or medication, which may cause some level of distress. However, you will not have to answer any questions that you don't want to and may take a break at any point. You can also stop the study and withdraw from the study without giving a reason.

The time commitment involved will depend on the answers given at interview and may last up to an hour. You are free to opt out from participating in the second stage of the study should you wish to do so. If participating in the second stage of interviews (which may take place as a focus group), this will also last up to an hour, again depending on the answers given by those participating.

What will happen to the results of the study?

The results of this study may be published in scientific journals and/or presented at conferences. If the results of the study are published, your identity will remain confidential. Anonymised data may be used by research teams for future research.

A lay summary of the results of the study will be available for participants when the study has been completed and the researchers will ask if you would like to receive a copy.

The anonymised results may be shared with the company providing funding for this study. The results of the study will also be used in Zakia Shariff's PhD Thesis and Project Reports that will be shared with the company providing funding for this study.

Expenses and payments

Any travel expenses will be reimbursed. We will also offer £10 gift vouchers as a sign of appreciation for participation in each interview.

Who is funding the research?

The study is being funded by Aston University and Colorcon

Who is organising this study and acting as data controller for the study?

Aston University is organising this study and acting as data controller for the study. You can find out more about how we use your information in Appendix A.

Who has reviewed the study?

This study was given a favorable ethical opinion by the NHS Research Ethics Committee- the Social Care REC

Where can I obtain independent advice about participating in clinical research?

If you would like independent advice on participating in clinical research, please contact the PALS (Patient Advice and Liaison Service) at [Name of NHS organisation and contact details to be added].

What if I have a concern about my participation in the study or wish to make a complaint?

If you have any concerns about your participation in this study, please speak to the research team and they will do their best to answer your questions. Contact details can be found at the end of this information sheet.

If the research team are unable to address your concerns or you wish to make a complaint about how the study is being conducted you should contact the Aston University Director of Governance, Mr. John Walter, who is independent of the project and can be reached at:

Address: Aston University, Birmingham, B4 7ET
E-mail: j.g.walter@aston.ac.uk
Telephone: 0121 204 4869.

Research Team

Zakia Shariff (Lead Researcher):

Email at ramjeez1@aston.ac.uk or phone [redacted]

Ian Maidment (Project Supervisor):

Email at i.maidment@aston.ac.uk or phone 0121 204 3002

Thank you for taking time to read this information sheet. If you have any questions regarding the study please don't hesitate to ask one of the research team.

PIS- Older People IRAS ID: 250373, Version 0.8, 20.12.18

Appendix A: Transparency statement

Aston University is the sponsor for this study based in the United Kingdom. We will be using information from you in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. Aston University will keep identifiable information about you for 6 years after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information at www.aston.ac.uk/dataprotection or by contacting our Data Protection Officer at dp_officer@aston.ac.uk.

If you wish to raise a complaint on how we have handled your personal data, you can contact our Data Protection Officer who will investigate the matter. If you are not satisfied with our response or believe we are processing your personal data in a way that is not lawful you can complain to the Information Commissioner's Office (ICO).

[Name of NHS site to be added] will collect information from you and/or your medical records for this research study in accordance with our instructions.

[Name of NHS site to be added] will use your name, and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from Aston University and regulatory organisations may look at your medical and research records to check the accuracy of the research study. [Name of NHS site to be added] will pass these details to Aston University along with the information collected from you. The only people in Aston University who will have access to information that identifies you will be people who need to contact you to arrange and undertake research visits or audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name or contact details.

When you agree to take part in a research study, the information about your health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research.

This information will not identify you and will not be combined with other information in a way that could identify you. The information will only be used for the purpose of health and care research, and cannot be used to contact you or to affect your care. It will not be used to make decisions about future services available to you, such as insurance.

NHS Site Logo

(to be added)

Improving the Design of Medicines for Older People

Participant Information Sheet- Carers

Invitation

We would like to invite you to take part in a research study.

Before you decide if you would like to participate, take time to read the following information carefully and, if you wish, discuss it with others such as your family, friends or colleagues.

Please ask a member of the research team, whose contact details can be found at the end of this information sheet, if there is anything that is not clear or if you would like more information before you make your decision.

What is the purpose of the study?

People are living longer following improvements in healthcare and lifestyle and older people tend to take more medicines. The properties of tablets and capsules (e.g. the shape, size and colour) can have a big impact on whether or not the person takes or administers a medicine as directed by a doctor. This study aims to look at how tablets and capsules can be designed so that they are easier for older people to take or their carers to administer.

Why have I been chosen?

You are being invited to take part in this study because:

You are the family carer of a person aged 65 or older who takes one or more tablets or capsules a day.

What will happen to me if I take part?

The study involves two stages but you can choose to only take part in stage one:

1) An initial interview which will last up to an hour
2) A second interview or focus group which will take place a few months later and which will also last up to an hour

1) Initial Interview

During the interview, you will be asked for some background information about the older person you care for such as their age and the medications they are taking. It will also explore your experiences in relation to administering medication. We expect the interview to last up to an hour but this will depend on how much you have to say.

You will have access to some sugar (placebo) tablets which you can use to describe the characteristics that are important to you as a carer administering medication to an older person. For example, you may use the size of the placebo tablet to describe what sizes would be more convenient for you to administer. You will not be asked to take/swallow any of the tablets, rather we ask you base your answers on their appearance and feel.

The interview will take place at a time and location convenient for you at your own home or other convenient location to make you as comfortable as possible.

With your permission, we will audio record the interview and take notes. The recording will be typed into a document (transcribed) by a transcriber approved by Aston University. This process will involve removing any information which could be used to identify individuals e.g. names, locations etc.

Audio recordings will be destroyed as soon as the transcripts have been checked for accuracy. We will ensure that anything you have told us that is included in the reporting of the study will be anonymous.

You of course are free not to answer any questions that are asked without giving a reason.

2) Re-interview/ Focus Groups

After the round of first interviews, we will make some tablet models based on the answers that were given. After making the models, we may, if you are in agreement, contact you again to explore how good these models are.

At this stage, a focus group might be more suitable. This is a group interview containing up to 8 - 10 participants where everyone will have a chance to talk about and give feedback on the models that we have developed. If this is suitable, you may be invited to take part at a time and location convenient to you. It will follow the same conditions in relation to recording, writing up (transcribing) and anonymity as detailed for the interviews above.

If you agree to take part in a focus group, full confidentiality cannot be guaranteed on behalf of the other focus group participants, although all participants will be asked to maintain confidentiality at the start of the focus group.

Do I have to take part?

No. It is up to you to decide whether or not you wish to take part.

If you do decide to participate, you will be asked to sign and date a consent form. You would still be free to withdraw from the study at any time without giving a reason.

Will my taking part in this study be kept confidential?

Yes. A code will be attached to all the data you provide to maintain confidentiality.

Your personal data (name and contact details) will only be used if the researchers need to contact you to arrange study visits or collect data by phone. Analysis of your data will be undertaken using coded data.

The data we collect will be stored in a secure document store (paper records) or electronically on a secure encrypted mobile device, password protected computer server or

secure cloud storage device.

To ensure the quality of the research, Aston University may need to access your data to check that the data has been recorded accurately. If this is required, your personal data will be treated as confidential by the individuals accessing your data.

What happens if I tell you something that concerns you about my health or welfare or that of the person I care for?

In the unlikely event of this happening, we will discuss with you how this should be addressed. Should we have concerns in relation to your health or welfare or that of the person you care for, we may need to breach confidentiality and discuss concerns with the Project Supervisor who will follow appropriate policies to guide the best course of action. To protect you, this may involve reporting your concern to the appropriate person or bodies. Any disclosure of harm to yourself or others will also be discussed with the research team and then reported to the relevant authorities. Your safety and that of the person you care for will always be the over-riding principle.

What are the possible benefits of taking part?

Whilst there are no direct benefits to you taking part in this study, it is hoped that the project will result in the future availability of tablets and capsules that are easier for people to take.

What are the possible risks and burdens of taking part?

During the course of the interview, you may discuss some sensitive information such as your personal experiences in relation to illness or medication, which may cause some level of distress. However, you will not have to answer any questions that you don't want to and may take a break at any point. You can also stop the study and withdraw from the study without giving a reason.

The time commitment involved will depend on the answers given at interview and may last up to an hour. You are free to opt out from participating in the second stage of the study should you wish to do so. If participating in the second stage of interviews (which may take place as a focus group), this will also last up to an hour, again depending on the answers given by those participating.

What will happen to the results of the study?

The results of this study may be published in scientific journals and/or presented at conferences. If the results of the study are published, your identity will remain confidential. Anonymised data may be used by research teams for future research.

A lay summary of the results of the study will be available for participants when the study has been completed and the researchers will ask if you would like to receive a copy.

The anonymised results may also be shared with the company providing funding for this study. The results of the study will be used in Zakia Shariff's PhD Thesis and Project Reports that will be shared with the company providing funding for this study.

Expenses and payments

Any travel expenses will be reimbursed. We will also offer £10 gift vouchers as a sign of appreciation for participation in each interview.

Who is funding the research?

The study is being funded by Aston University and Colorcon

Who is organising this study and acting as data controller for the study?

Aston University is organising this study and acting as data controller for the study. You can find out more about how we use your information in Appendix A.

Who has reviewed the study?

This study was given a favorable ethical opinion by the NHS Research Ethics Committee- the Social Care REC

Where can I obtain independent advice about participating in clinical research?

If you would like independent advice on participating in clinical research, please contact the PALS (Patient Advice and Liaison Service) at [Name of NHS organisation and contact details to be added].

What if I have a concern about my participation in the study or wish to make a complaint?

If you have any concerns about your participation in this study, please speak to the research team and they will do their best to answer your questions. Contact details can be found at the end of this information sheet.

If the research team are unable to address your concerns or you wish to make a complaint about how the study is being conducted you should contact the Aston University Director of Governance, Mr. John Walter, who is independent of the project and can be reached at:

Address: Aston University, Birmingham, B4 7ET
E-mail: j.g.walter@aston.ac.uk
Telephone: 0121 204 4869.

Research Team

Zakia Shariff (Lead Researcher):
Email at ramjeez1@aston.ac.uk or phone [redacted]
Ian Maidment (Project Supervisor):
Email at i.maidment@aston.ac.uk or phone 0121 204 3002

Thank you for taking time to read this information sheet. If you have any questions regarding the study please don't hesitate to ask one of the research team.

PIS- Carers IRAS ID: 250373, Version 0.8, 20.12.18

Appendix A: Transparency statement

Aston University

Aston University is the sponsor for this study based in the United Kingdom. We will be using information from you in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. Aston University will keep identifiable information about you for 6 years after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information at www.aston.ac.uk/dataprotection or by contacting our Data Protection Officer at dp_officer@aston.ac.uk.

If you wish to raise a complaint on how we have handled your personal data, you can contact our Data Protection Officer who will investigate the matter. If you are not satisfied with our response or believe we are processing your personal data in a way that is not lawful you can complain to the Information Commissioner's Office (ICO).

[Name of NHS site to be added] will collect information from you and/or your medical records for this research study in accordance with our instructions.

[Name of NHS site to be added] will use your name and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from Aston University and regulatory organisations may look at your medical and research records to check the accuracy of the research study. [Name of NHS site to be added] will pass these details to Aston University along with the information collected from you. The only people in Aston University who will have access to information that identifies you will be people who need to contact you to arrange and undertake research visits or audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name or contact details.

When you agree to take part in a research study, the information about your health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research.

This information will not identify you and will not be combined with other information in a way that could identify you. The information will only be used for the purpose of health and care research, and cannot be used to contact you or to affect your care. It will not be used to make decisions about future services available to you, such as insurance.

NHS Site Logo

(to be added)

Improving the Design of Medicines for Older People

Participant Information Sheet- Practitioners

Invitation

We would like to invite you to take part in a research study.

Before you decide if you would like to participate, take time to read the following information carefully.

Please ask a member of the research team, whose contact details can be found at the end of this information sheet, if there is anything that is not clear or if you would like more information before you make your decision.

What is the purpose of the study?

This study aims to look at how tablets and capsules can be designed so that they are easier for older people to take. People are living longer following improvements in healthcare and lifestyle and older people tend to take more medicines. The form of the medicine (e.g. the shape, size and colour) can have a big impact on whether or not the person takes or administers a medicine as directed by the doctor.

This project involves interviews with older people, their carers and health and social care professionals such as GPs, pharmacists and formal carers. This will allow us to design a product that takes into account the views of everyone involved in an older person's therapy. The final aim is to design a product which is much simpler for an older person or their carer to take or administer.

Why have I been chosen?

You are being invited to take part in this study because:

You are a health or social care professional who has experience of working with people over the age of 65 who take oral solid dosage forms such as tablets and capsules.

What will happen to me if I take part?

If you choose to take part, the study will involve two stages:

1) An initial interview which will last up to an hour

2) Re-interview/ Focus group which will take place a few months later and which will also last up to an hour

1) Initial Interview

The interview will ask for some background information about you such as your current role and will also ask for your experience when treating older people who take tablets and capsules. You will have access to some sugar (placebo) tablets which you can use to describe the characteristics you feel are important, for example you may use the size of the placebo tablets to describe what size you think is suitable for an older person. You will not be asked to take/swallow any of the tablets, rather we ask you base your answers on their appearance and feel.

The interview will last up to an hour and will take place at a time and location convenient for you. This can be via Skype/Videoconference if preferred.

With your permission, we will audio record the interview and take notes. The recording will be typed into a document (transcribed) by a transcriber approved by Aston University. This process will involve removing any information which could be used to identify individuals e.g. names, locations etc.

Audio recordings will be destroyed as soon as the transcripts have been checked for accuracy. We will ensure that anything you have told us that is included in the reporting of the study will be anonymous.

You of course are free not to answer any questions that are asked without giving a reason.

2) Re-interview/ Focus Groups

As we develop our findings about how the design of tablets and capsules might be improved, we may, if you are in agreement, contact you again to ask to re-interview you. This would be to understand if the 3D models that have been made as a result of the initial interviews seem appropriate and likely to improve the way older people are able to take their medication.

If a focus group appears to be a more suitable way of continuing your involvement at this stage, as an alternative to being re-interviewed, you may be invited to take part in one, at a time and location convenient to you. It will follow the same conditions in relation to recording, writing up (transcribing) and anonymity as detailed for the interviews above.

If you agree to take part in a focus group, full confidentiality cannot be guaranteed on behalf of the other focus group participants, although all participants will be asked to maintain confidentiality at the start of the focus group.

Do I have to take part?

No. It is up to you to decide whether or not you wish to take part.

If you do decide to participate, you will be asked to sign and date a consent form. You would still be free to withdraw from the study at any time without giving a reason.

Will my taking part in this study be kept confidential?

Yes. A code will be attached to all the data you provide to maintain confidentiality.

Your personal data (name and contact details) will only be used if the researchers need to contact you to arrange study visits or collect data by phone. Analysis of your data will be undertaken using coded data.

The data we collect will be stored in a secure document store (paper records) or electronically on a secure encrypted mobile device, password protected computer server or secure cloud storage device.

To ensure the quality of the research, Aston University may need to access your data to check that the data has been recorded accurately. If this is required, your personal data will be treated as confidential by the individuals accessing your data.

What are the possible benefits of taking part?

Whilst there are no direct benefits to you taking part in this study, the data gained will enable the development of a final product that takes into account the views of all those involved in an older person's therapy. Your views and suggestions will be taken into account during the development of 3D tablet models which you will have the opportunity to evaluate during the second stage of the project. This will enable recommendations to be made to help design products which are easier for older people to take, therefore improving adherence.

What are the possible risks and burdens of taking part?

During the course of the interview, you may discuss some sensitive information such as personal experiences with patients which may cause some level of distress. However, you will not have to answer any questions that you don't want to and may take a break at any point. You can also stop the study and withdraw from the study without giving a reason.

The time commitment involved will depend on the answers given at interview and may last up to an hour at each stage. You are free to opt out from participating in the second stage of the study should you wish to do so.

What will happen to the results of the study?

The results of this study may be published in scientific journals and/or presented at conferences. If the results of the study are published, your identity will remain confidential. Anonymised data may be used by research teams for future research.

A lay summary of the results of the study will be available for participants when the study has been completed and the researchers will ask if you would like to receive a copy.

The anonymised results may be shared with the company providing funding for this study. The results of the study will also be used in Zakia Shariff's PhD Thesis and Project Reports that will be shared with the company providing funding for this study.

Expenses and payments

Any travel expenses will be reimbursed. We will also offer £10 gift vouchers as a sign of appreciation for participation in each interview.

Who is funding the research?

The study is being funded by Aston University and Colorcon

PIS- Practitioners IRAS ID: 250373, Version 0.7, 20.12.18

Who is organising this study and acting as data controller for the study?

Aston University is organising this study and acting as data controller for the study. You can find out more about how we use your information in Appendix A.

Who has reviewed the study?

This study was given a favorable ethical opinion by the NHS Research Ethics Committee [REC name to be added once approval obtained]

What if I have a concern about my participation in the study or wish to make a complaint?

If you have any concerns about your participation in this study, please speak to the research team and they will do their best to answer your questions. Contact details can be found at the end of this information sheet.

If the research team are unable to address your concerns or you wish to make a complaint about how the study is being conducted you should contact the Aston University Director of Governance, Mr. John Walter, who is independent of the project and can be reached at:

Address: Aston University, Birmingham, B4 7ET
E-mail: j.g.walter@aston.ac.uk
Telephone: 0121 204 4869.

Research Team

Zakia Shariff (Lead Researcher):

Email at ramjeez1@aston.ac.uk or phone 

Ian Maidment (Project Supervisor):

Email at i.maidment@aston.ac.uk or phone 0121 204 3002

Thank you for taking time to read this information sheet. If you have any questions regarding the study please don't hesitate to ask one of the research team.

Appendix A: Transparency statement

Aston University

Aston University is the sponsor for this study based in the United Kingdom. We will be using information from you in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. Aston University will keep identifiable information about you for 6 years after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information at www.aston.ac.uk/dataprotection or by contacting our Data Protection Officer at dp_officer@aston.ac.uk.

If you wish to raise a complaint on how we have handled your personal data, you can contact our Data Protection Officer who will investigate the matter. If you are not satisfied with our response or believe we are processing your personal data in a way that is not lawful you can complain to the Information Commissioner's Office (ICO).

[Name of NHS site to be added] will collect information from you for this research study in accordance with our instructions.

[Name of NHS site to be added] will keep your name, and contact details confidential and will not pass this information to Aston University. [Name of NHS site to be added] will use this information as needed, to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Certain individuals from Aston University and regulatory organisations may look at your medical and research records to check the accuracy of the research study. Aston University will only receive information without any identifying information. The people who analyse the information will not be able to identify you and will not be able to find out your name or contact details.

When you agree to take part in a research study, the information about your health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research.

This information will not identify you and will not be combined with other information in a way that could identify you. The information will only be used for the purpose of health and care research, and cannot be used to contact you or to affect your care. It will not be used to make decisions about future services available to you, such as insurance.

Appendix 12: Consent Forms

NHS Site Logo
(to be added)

Improving the Design of Medicines for Older People

Consent Form

Name of Chief Investigator:_Ian Maidment_____

Please initial boxes

1.	I confirm that I have read and understand the Participant Information Sheet (Version Number 0.8, 20.12.18) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2.	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my legal rights being affected.	
3.	I agree to my personal data and data relating to me collected during the study being processed as described in the Participant Information Sheet.	
4.	I understand that if during the study I tell the research team something that causes them to have concerns in relation to my health and/or welfare they may need to breach my confidentiality.	
5.	I agree to interviews and focus groups being audio recorded and to anonymised direct quotes from me being used in publications resulting from the study.	
6.	I agree to Aston University accessing medical/research records for the purposes of monitoring/auditing.	
7.	I agree to my anonymised data being used by research teams for future research as stated in the Participant Information Sheet.	
8.	I agree to being re-interviewed to give my opinion on the research recommendations. I may also be offered the opportunity to take part in a focus group to do this.	Y/N
9.	I agree to take part in this study.	

_____	_____	_____
Name of participant	Date	Signature
_____	_____	_____
Name of Person receiving	Date	Signature

Consent- Older People/Carers IRAS ID: 250373, Version Number 0.8, 20.12.18

consent.

1- Site File

1- Participant Copy

Aston University
Coloreon

NHS Site Logo

(to be added)

Improving the Design of Medicines for Older People

Consent Form

Name of Chief Investigator:_Ian Maidment_____

Please initial boxes

1.	I confirm that I have read and understand the Participant Information Sheet (Version Number 0.7, 20.12.18) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2.	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my legal rights being affected.	
3.	I agree to my personal data and data relating to me collected during the study being processed as described in the Participant Information Sheet.	
4.	I agree to interviews and focus groups being audio recorded and to anonymised direct quotes from me being used in publications resulting from the study.	
5.	I agree to Aston University accessing medical/research records for the purposes of monitoring/auditing.	
6.	I agree to my anonymised data being used by research teams for future research as stated in the Participant Information Sheet.	
7.	I agree to being re-interviewed to give my opinion on the research recommendations. I may also be offered the opportunity to take part in a focus group to do this.	Y/N
8.	I agree to take part in this study.	

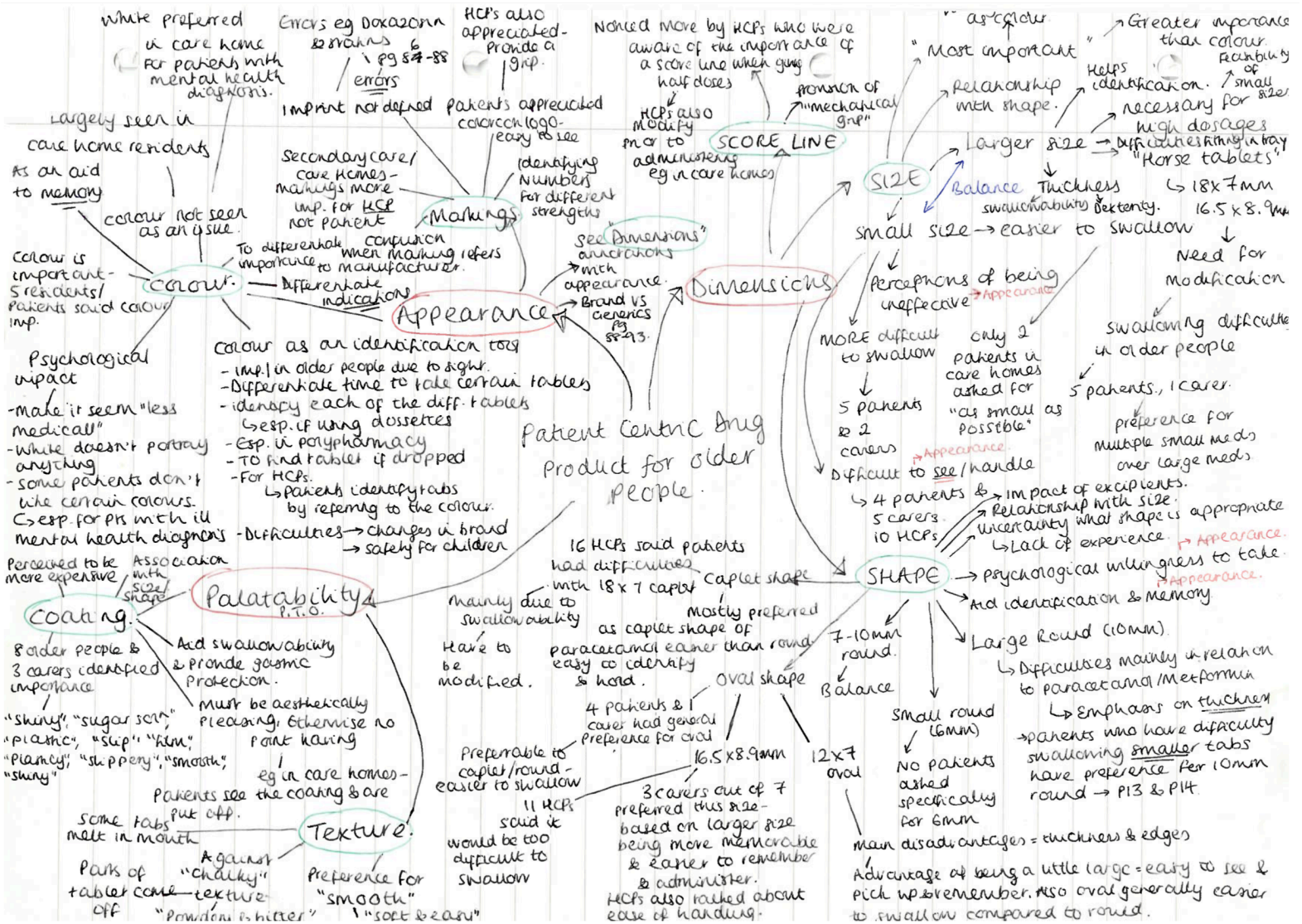
_____	_____	_____
Name of participant	Date	Signature
_____	_____	_____
Name of Person receiving consent.	Date	Signature

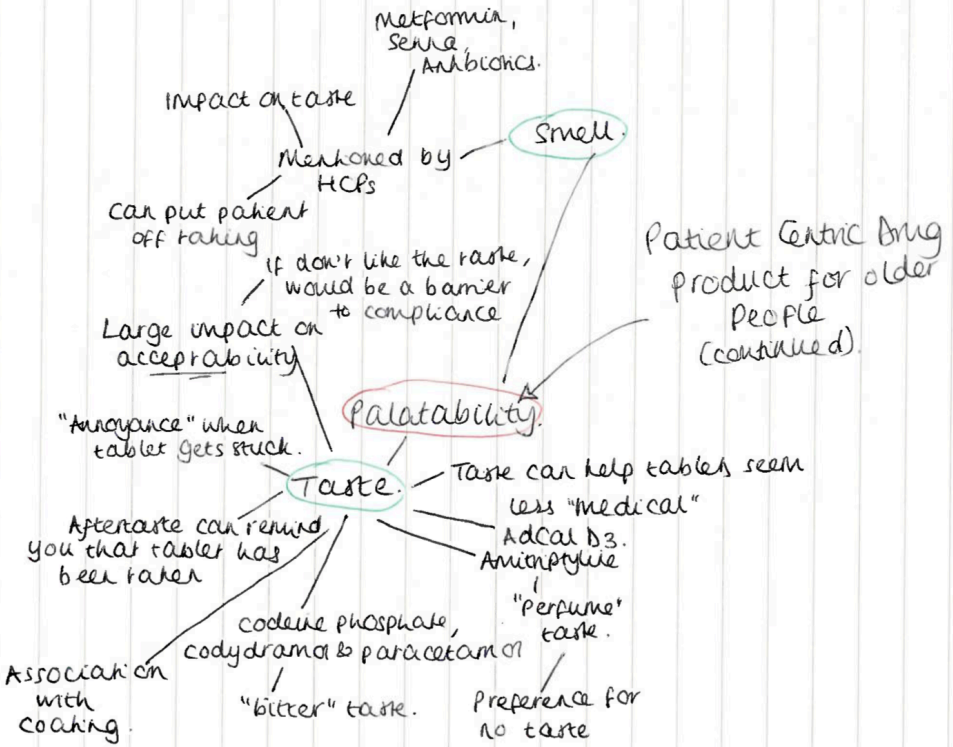
1- Site File

1- Participant Copy

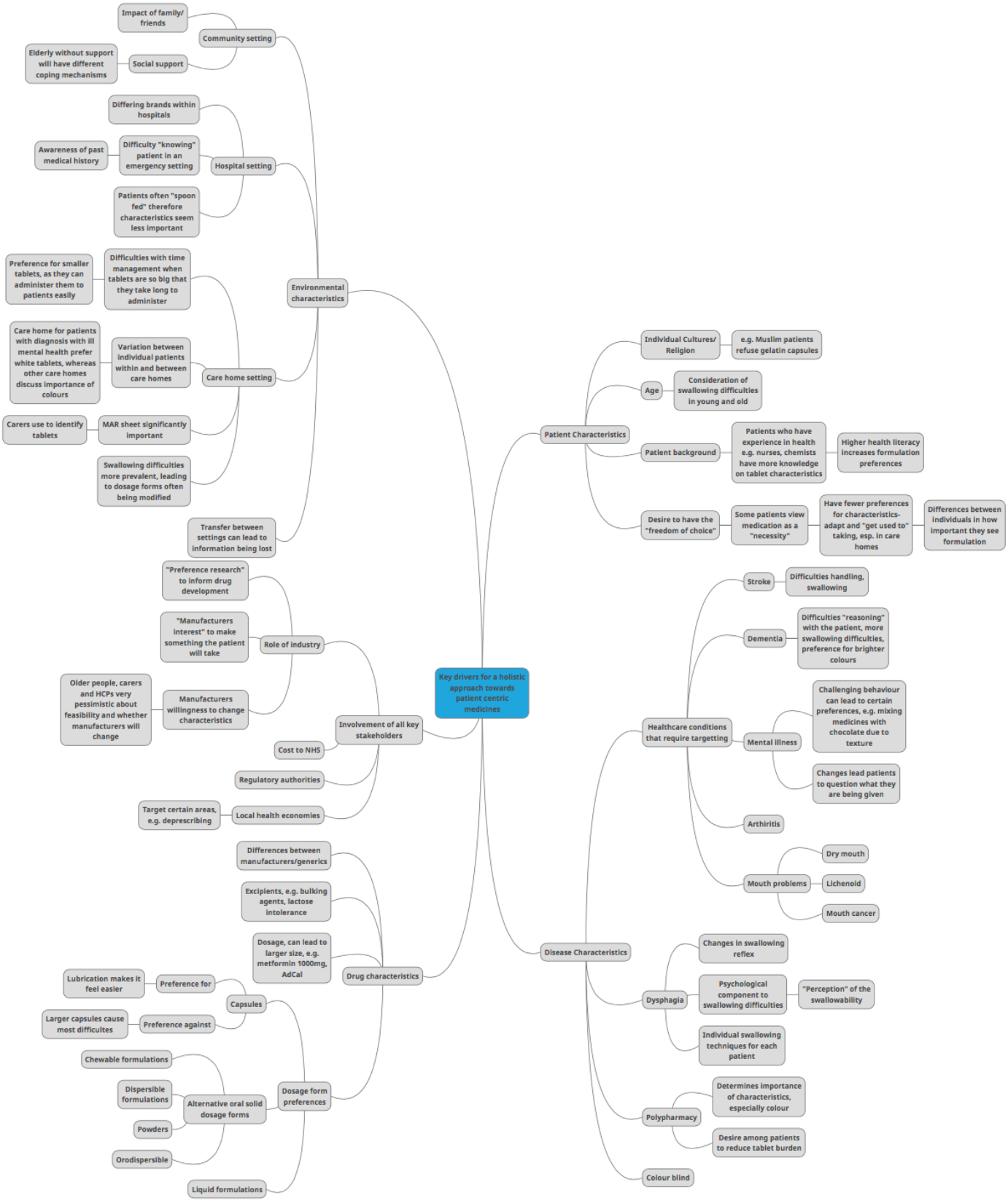
Consent- Practitioners IRAS ID: 250373, Version Number 0.8, 20.12.18

Appendix 13: Initial theme map developed from thematic analysis




Metformin, Senna, Antibiotics.
Impact on taste
Smell.
Mentioned by HCPs
Can put patient off taking
If don't like the taste, would be a barrier to compliance
Large impact on acceptability
Patient Centric Drug product for older people (continued).
Palatability.
"Annoyance" when tablet gets stuck.
Taste.
Taste can help tablets seem less "medical"
Adcal D3.
Amitriptyline
"Perfume" taste.
Aftertaste can remind you that tablet has been taken
Codeine phosphate, codydramol & paracetamol
Association with coaching.
"bitter" taste.
Preference for no taste

Appendix 14: Theme map illustrating the development of more patient focussed themes during thematic analysis



Appendix 15: Initial assessment from the HRA and responses

Dear Dr Maidment

RE: IRAS 250373 Patient Centric Medicine Design to Improve Adherence in Older People.

I have now undertaken an assessment of your application, and am contacting you to request some clarifications. For clarity, I have split the requests into sections so it is easy to determine by when you should respond to each request.

Information to complete initial assessment

Please would you provide the following information to enable me to issue the initial assessment letter?

Thank you for providing the statement of activities ('SOA') and Schedule of Events ('SOE') for both site types involved in the study. On review, I have made some minor changes and request that you also make some further changes:

PIC Site – SOA:

- Name of Participating Organisation: I have removed these details as this should be completed on a per-site basis

This has been noted and each SOA will be updated as required

- HRA version control: I have added 17/12/2018 v1

PIC Site: SOE:

- HRA version control: I have added 17/12/2018 v1.
- Please ensure all activities taking place at NHS sites either by local/external research staff are included

This has been updated to include the Eligibility Check (exclusions) which will be conducted by local members of staff. Identifying potential participants and the eligibility check will be the only activities conducted by the NHS PIC sites.

- Please update who the activities are undertaken by to reflect that 'local members of staff' will undertake them, as not all PIC staff are 'GPs'.

This has been updated to "Local Administrative and Clerical Staff"

All Site Activities – SOA:

- Name of Participating Organisation: Again, I have removed these details as this section should be completed on a per-site basis.

This has been noted and each SOA will be updated as required

- Location within Participating Organisation: I have removed these details as this section should be completed on a per-site basis.

Each location will be completed on a per-site basis

- HRA version control: I have added 17/12/2018 v1.

- Q9 (Person responsible for research activities at site): I have changed this to 'Local Principal Investigator' as local members of staff are undertaking research activities at site over and above facilitating access arrangements

This has been noted and the Local Principle Investigators are the local members of staff named in Section C of the IRAS form

All Site Activities – SOE:

- HRA version control: I have added 17/12/2018 v1.
- Ensure all activities that are taking place at NHS site are listed that are undertaken either by local/external research staff.

I can confirm that all activities that are taking place at NHS sites have been listed on this version.

Additional information for assessment

Please would you also provide the following information regarding the application? This information is not essential for issue of the initial assessment letter, but these requests for information will have to be addressed prior to issue of HRA and HCRW Approval.

- A72 of IRAS lists 4 NHS sites, 1 educational establishment and 11 community pharmacies however Part C of IRAS only lists 3 CCGs and 2 NHS Trusts. Please confirm the names of the NHS sites involved in the study

A72 has been amended to list 5 NHS Sites- the 3 CCGs and 2 NHS Trusts.

The educational establishment hosting the research is Aston University, and the community pharmacies are the Research Ready Community pharmacies who will advertise the research through displaying promotional material (e.g. posters).

- Make the following changes to the consent forms:
    - Add consent for the sponsor/NHS Trust to access medical/research records for the purposes of monitoring/auditing.

The following wording has been included in the consent forms:

"I agree to Aston University accessing medical/research records for the purposes of monitoring/auditing"

    - Add completed consent form filing arrangements (e.g. 1-site file; 1-participant copy; 1-medical records).

Completed consent form filing arrangements have been included at the end of the consent forms as:

1-site file, 1-participant copy

- Make the following changes to the participant information sheets:

- The General Data Protection Regulation (GDPR) applied from 25 May 2018. The HRA has published recommended transparency wording which you can use to ensure that your Participant Information Sheet (PIS) is compliant with the GDPR. Please include this in the Patient Information sheets for all 3 participant groups.
  You should include the text in the first box in all cases, and then select text from the sections marked A and B as appropriate and within these, select the options in italics as relevant. Replace text in square brackets [ ] as appropriate.

The Information Sheets have been amended to include the recommended transparency wording- please see amended Information Sheets.

- Add a statement to make clear to participants that disclosures of harm to themselves/others will be reported to research team and then authorities

The following statement has been included on the Information Sheets under "What happens if I tell you something that concerns you about my health or welfare or that of the person I care for?"

Any disclosure of harm to yourself or others will also be discussed with the research team and then reported to the relevant authorities.

- Confirm whether 'All Site Activities' site will be required to facilitate the booking of a meeting room for the interviews to take place.

The "All Site Activities" will be required to facilitate the booking of a meeting room for the interviews to take place. This has been included on the SoA for All Sites under Q12- "A confidential area will also be required where the interview can take place."

Please note that if any documentation required for REC review is to be updated as a result of these requests, do not submit these revised documents prior the REC meeting. It is acceptable to make changes following the REC meeting, updating documents inresponse to both REC and assessment at the same time. Where changes are to documents specific for assessment, such as theStatement of Activities/Schedule of Events, you are able to submit updated documents to me ahead of the REC meeting.

If you have any questions please do not hesitate to contact me.

Appendix 16: Initial assessment letter from the Social Care REC

NHS
Health Research Authority

Social Care REC
Ground Floor
Skipton House
80 London Road
London
SE1 6LH

Telephone: 0207 972 2568
Fax:

13 December 2018

Dr Ian Maidment
Aston University
Aston Triangle
Birmingham
B4 7ET

Dear Dr Maidment

Study Title:	**Patient Centric Medicine Design: An Investigation into Understanding and Enhancing Older Peoples' Adherence to Oral Solid Dosage Forms**
REC reference:	**18/IEC08/0047**
Protocol number:	**227-2018-ZR**
IRAS project ID:	**250373**

The Research Ethics Committee reviewed the above application at the meeting held on 07 December 2018. Thank you and Mrs Shariff for attending to discuss the application. The Committee would like to congratulate you on a well written and thoughtfully prepared application.

Provisional opinion

The Committee would be content to give a favourable ethical opinion of the research, subject to receiving a complete response to the request for further information set out below.

Authority to consider your response and to confirm the Committee's final opinion has been delegated to the Chair.

Further information or clarification required

1. Explain to the Committee how the interviews with the carers and older people together/at the same address would be managed to ensure sensitive information was not discussed which could lead to conflicts between the two.

2. The Committee requested the following changes to the participant documentation:

a. The Committee noted that the PIS was well written but long and requested that the research team review it to see if it could be shortened, but they were aware that it was important that participants were fully informed of the research.
b. The following statement was in the consent forms 'I agree to my anonymised data being used by research teams for future research' but not the PISs. Add this statement to the PISs.
c. The Committee thought the breaching confidentiality statement (item 4) in the Consent Form for Older People/Carers was clear and should be included in the section of the PISs 'What happens if I tell you something that concerns you about my health or welfare?'
d. Could the research team consider changing the title of the PISs and consent forms to a more plain English one?
e. Change the contact details for advice/complaint in the PISs currently PALS, to the research team for concerns about the project and a person independent of the project for complaints. Full contact details needs to be provided: a named person, postal and email address and a telephone number.

If you would find it helpful to discuss any of the matters raised above or seek further clarification from a member of the Committee, you are welcome to contact Mrs Barbara Cuddon, REC Manager, nrescommittee.social-care@nhs.net

When submitting a response to the Committee, the requested information should be electronically submitted from IRAS. Please refer to the guidance in IRAS for instructions on how to submit a response to provisional opinion electronically.

Please submit revised documentation where appropriate underlining or otherwise highlighting the changes which have been made and giving revised version numbers and dates. You do not have to make any changes to the REC application form unless you have been specifically requested to do so by the REC.

The Committee will confirm the final ethical opinion within a maximum of 60 days from the date of initial receipt of the application, excluding the time taken by you to respond fully to the above points. A response should be submitted by no later than 12 January 2019.

Extract of the meeting minutes

Social or scientific value; scientific design and conduct of the study

The Committee queried why the study was limited to oral solid dosage forms and does not include liquids, for example?

Ms Shariff explained that the design of this study was based on a recent European Medicines Agency reflection paper which outlined the potential for mistakes when older people take oral solid dosage forms of medicines. Oral solid dosage forms of medication are the most commonly used.

The Committee had noted that this PhD was partially funded by the sponsor and queried their involvement in the design of the study.

Ms Shariff confirmed that the design had been driven by her previous research.

The Committee accepted these explanations.

Recruitment arrangements and access to health information, and fair participant selection

The Committee asked if the research findings could be shared with the participants

Ms Shariff confirmed that a lay summary would be available.

The Committee accepted this confirmation.

Favourable risk benefit ratio; anticipated benefit/risks for research participants (present and future)

The Committee were concerned that the older people taking part in the study may become distressed talking about their experience of taking medication and queried Mrs Shariff's experience of working with this age group.

Mrs Shariff confirmed that she had been working as a Community Pharmacist for 4 years and had experience of working with this age group. The interview questions would be open-ended to gather as much information as possible and would not just relate to the formulation of the medication. At the end of the interview there would be an opportunity for participants to ask questions and if the need arose Ms Shariff would refer participants to appropriate sources of support.

The Committee accepted this clarification.

Care and protection of research participants; respect for potential and enrolled participants' welfare and dignity

The Committee questioned whether it would be possible for participants not to be audio-recorded.

Mrs Shariff confirmed that unfortunately it was not possible for the interviews not to be audio-recorded. In her experience participants usually agree to this and the audio-recordings would be anonymised before they were transcribed.

The Committee accepted this clarification.

The Committee queried whether the older people and carers would be linked.

Mrs Shariff explained that they do not have to be linked or interviewed together but they could if this was what they wanted.

The Committee accepted this clarification but agreed to request information of how Mrs Shariff would manage interviewing the carers and older people together/at the same address, especially as sensitive information could be discussed leading to conflicts between the two.

Informed consent process and the adequacy and completeness of participant information

The Committee advised Mrs Shariff that they would be requesting a number of changes to the participant documentation, listed below in the decision section of these minutes.

Please contact the REC Manager if you feel that the above summary is not an accurate reflection of the discussion at the meeting.

Documents reviewed

The documents reviewed at the meeting were:

Document	*Version*	*Date*
Copies of advertisement materials for research participants [E-mail to Advertise Research]	0.4	21 November 2018
Copies of advertisement materials for research participants [Poster to Advertise Research]	0.3	30 July 2018
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Aston Indemnity Insurance]		
Interview schedules or topic guides for participants [Interview Schedule Carers]	V0.3	30 July 2018
Interview schedules or topic guides for participants [Interview Schedule Older People]	V0.3	30 July 2018
Interview schedules or topic guides for participants [Interview Schedule Practitioners]	V0.3	30 July 2018
IRAS Application Form [IRAS_Form_22112018]		22 November 2018
IRAS Application Form XML file [IRAS_Form_22112018]		22 November 2018
Letter from sponsor [Sponsor Agreement]		15 November 2018
Other [Placebo Tablets Used in Phase 1]	0.3	30 July 2018
Other [GCP Face to Face Training Cert]		31 October 2018
Participant consent form [Consent Form Practitioners]	0.6	05 November 2018
Participant consent form [Consent Form Older People/Carers]	0.6	05 November 2018
Participant information sheet (PIS) [PIS Carers]	0.6	05 November 2018
Participant information sheet (PIS) [PIS Older People]	0.6	05 November 2018
Participant information sheet (PIS) [PIS Practitioners]	V0.5	23 October 2018
Research protocol or project proposal [Protocol V0.6 19.11.18]	0.6	19 November 2018
Summary CV for Chief Investigator (CI) [CV- IM]		
Summary CV for student [CV Research Student ZS]		
Summary CV for supervisor (student research) [CV Research Supervisor]		
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Flow Chart Summarising Protocol]	0.3	30 July 2018

Membership of the Committee

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

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

18/IEC08/0047	**Please quote this number on all correspondence**

Yours sincerely

Pp Dr Martin Stevens
Chair

Email: nrescommittee.social-care@nhs.net

Enclosures: *List of names and professions of members who were present at the meeting and those who submitted written comments.*

Copy to: *Mr Matthew Richards*
Ms Jill Stacey, University Hospitals of North Midlands NHS Trust

Appendix 17: Responses to assessment from the REC

Aston University,
Aston Triangle,
Birmingham,
B4 7ET

ramjeez1@aston.ac.uk
i.maidment@aston.ac.uk

8th January 2019

Dear Mrs Cuddon,

Study Title:	**Patient Centric Medicine Design: An Investigation into Understanding and Enhancing Older Peoples' Adherence to Oral Solid Dosage Forms**
REC reference:	**18/IEC08/0047**
Protocol number:	**227-2018-ZR**
IRAS project ID:	**250373**

Thank you for your letter dated the 13th December 2018. As requested, we have addressed the comments in this letter and have also addressed the comments received from Ms Gemma Oakes from the HRA dated 18/12/2018.

Queries from Ethics (any amendments to study documentation have been underlined in blue):

1) Explain to the Committee how the interviews with the carers and older people together/at the same address would be managed to ensure sensitive information was not discussed which could lead to conflicts between the two.

The lead researcher is a community pharmacist with four years' experience of working with older people and their carers. She therefore has experience of discussing sensitive issues appropriately and will guide the interviews to ensure that no sensitive information is discussed which may cause any potential distress. Should any sensitive issues arise in the presence of the older person which may lead to conflicts, the lead researcher will cease the interview. This situation will then be discussed with the supervisor who will provide further guidance in this area.

2) 2. The Committee requested the following changes to the participant documentation:
   a) The Committee noted that the PIS was well written but long and requested that the research team review it to see if it could be shortened, but they were aware that it was important that participants were fully informed of the research.

The PISs have been reviewed to see if they can be shortened and the following text amended:

i) Paragraph 6, pg. 2:

"It will follow the same conditions set out for interviews as detailed below:

The recording will be typed into a document (transcribed) by a transcriber approved by Aston University. During the transcription process, any names that have been used will be replaced with a pseudonym.

Audio recordings will be destroyed as soon as the transcripts have been checked for accuracy. Any extracts from the group discussions that are included in the reporting of the study will be anonymous"

has been shortened to:

" It will follow the same conditions in relation to recording, writing up (transcribing) and anonymity as detailed for the interviews above."

This change has shortened the PIS slightly. Further amendments were difficult to make as it is important participants are fully aware of the research, however the lead researcher will ensure that potential participants have enough time to thoroughly read through the information sheet and will have the opportunity to ask any questions (as detailed in A30-1)

b) The following statement was in the consent forms "I agree to my anonymised data being used by research teams for future research" but not in the PISs. Add this statement to the PISs.

"Anonymised data may be used by research teams for future research" has been added under "What will happen to the results of the study?"

c) The Committee thought the breaching confidentiality statement (item 4) in the Consent Form for Older People/Carers was clear and should be included in the section of the PISs 'What happens if I tell you something that concerns you about my health or welfare?'

The following statement has been added under the relevant section:
"Should we have concerns in relation to your health or welfare or that of the person you care for, we may need to breach confidentiality"

d) Could the research team consider changing the title of the PISs and consent forms to a more plain English one?

The titles of the PISs and Consent Forms have been changed from "Patient Centric Medicine Design to Improve Adherence in Older People to:
"Improving the Design of Medicines for Older People"

e) Change the contact details for advice/complaint in the PISs currently PALS, to the research team for concerns about the project and a person independent of the project for complaints. Full contact details needs to be provided: a named person, postal and email address and a telephone number.

The contact details for PALS has been included in the PIS as the study is taking place at NHS Organisations and so participants can contact the relevant person for advice about taking part in clinical research. The contact details for advice/complaints has been clarified in the next section: "What if I have a concern about my participation in the study or wish to make a complaint?" This

section gives details to contact the research team for concerns about the project and the full contact details for Mr John Walter who is independent of the project and is in charge of complaints:

"If you have any concerns about your participation in this study, please speak to the research team and they will do their best to answer your questions. Contact details can be found at the end of this information sheet.
If the research team are unable to address your concerns or you wish to make a complaint about how the study is being conducted you should contact the Aston University Director of Governance, Mr. John Walter, who is independent of the project and can be reached at:

Address: Aston University, Birmingham, B4 7ET
E-mail: j.g.walter@aston.ac.uk
Telephone: 0121 204 4869

Outstanding HRA queries (any amendments to study documentation have been underlined in red):

1) A72 of IRAS lists 4 NHS sites, 1 educational establishment and 11 community pharmacies however Part C of IRAS only lists 3 CCGs and 2 NHS Trusts. Please confirm the names of the NHS sites involved in the study.

A72 has been amended to list 5 NHS Sites- the 3 CCGs and 2 NHS Trusts.

The educational establishment hosting the research is Aston University, and the community pharmacies are the CRN Research Ready Community pharmacies who have agreed to help with recruitment and will advertise the research through displaying promotional material (e.g. posters).

2) Make the following changes to the consent forms:
    a) Add consent for the sponsor/NHS Trust to access medical/research records for the purposes of monitoring/auditing.

The following wording has been included in the consent forms:

"I agree to Aston University accessing medical/research records for the purposes of monitoring/auditing"

    b) Add completed consent form filing arrangements (e.g. 1-site file; 1-participant copy; 1-medical records).

Completed consent form filing arrangements have been included at the end of the consent forms as:

1-site file, 1-participant copy

3) Make the following changes to the participant information sheets:
    a) The General Data Protection Regulation (GDPR) applied from 25 May 2018. The HRA has published recommended transparency wording which you can use to ensure that your Participant Information Sheet (PIS) is compliant with the GDPR. Please include this in the Patient Information sheets for all 3 participant groups.
    You should include the text in the first box in all cases, and then select text from the sections marked A and B as appropriate and within these, select the options in italics as relevant. Replace text in square brackets [ ] as appropriate.

The Information Sheets have been amended to include the recommended transparency wording- please see amended Information Sheets. Each Information Sheet will be site specific, and so the names of each of the NHS Organisations hosting the research will be added.

b) Add a statement to make clear to participants that disclosures of harm to themselves/others will be reported to research team and then authorities

The following statement has been included on the Information Sheets under "What happens if I tell you something that concerns you about my health or welfare or that of the person I care for?"

Any disclosure of harm to yourself or others will also be discussed with the research team and then reported to the relevant authorities.

4) Confirm whether 'All Site Activities' site will be required to facilitate the booking of a meeting room for the interviews to take place.

The "All Site Activities" will be required to book a meeting room for the interviews to take place, and will be required to facilitate this when a date and time is confirmed for the interview to take place. This has been included on the SoA for All Sites under Q12- "A confidential area will also be required where the interview can take place."

We look forward to hearing from you in due course.

Yours Sincerely,

Zakia Shariff,
Aston University

Appendix 18: HRA approval letter

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Dr Ian Maidment
Aston University
Aston Triangle
Birmingham
B4 7ET
i.maidment@aston.ac.uk

Email: hra.approval@nhs.net

14 January 2019

Dear Dr Maidment

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Patient Centric Medicine Design: An Investigation into Understanding and Enhancing Older Peoples' Adherence to Oral Solid Dosage Forms**
IRAS project ID:	**250373**
Protocol number:	**227-2018-ZR**
REC reference:	**18/IEC08/0047**
Sponsor	**AHRIC (Aston Health Research and Innovation Cluster)**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

How should I continue to work with participating NHS organisations in England and Wales?
You should now provide a copy of this letter to all participating NHS organisations in England and Wales, as well as any documentation that has been updated as a result of the assessment.

Following the arranging of capacity and capability, participating NHS organisations in England and Wales that are **Site Type 1 – All Site Activities** should **formally confirm** their capacity and capability to undertake the study. How this will be confirmed is detailed in the "*summary of assessment*" section towards the end of this letter. You should then work with each organisation that has confirmed capacity and capability and provide clear instructions when research activities can commence.

Participating NHS organisations in England and Wales that are **Site Type 2 – Participant Identification Centre ('PIC Site') will not** be required to formally confirm capacity and capability before you may commence research activity at site. As such, you may commence the research at each organisation **immediately** following sponsor provision to the site of the local information pack, so long as:

- You have contacted participating NHS organisations (see below for details)
- The NHS organisation has not provided a reason as to why they cannot participate
- The NHS organisation has not requested additional time to confirm.

You may start the research prior to the above deadline if the site positively confirms that the research may proceed.

If not already done so, you should now provide the local information pack for your study to your participating NHS organisations. A current list of R&D contacts is accessible at the NHS RD Forum website and these contacts MUST be used for this purpose. After entering your IRAS ID you will be able to access a password protected document (password: **Redhouse1**). The password is updated on a monthly basis so please obtain the relevant contact information as soon as possible; please do not hesitate to contact me should you encounter any issues.

Commencing research activities at any NHS organisation before providing them with the full local information pack and allowing them the agreed duration to opt-out, or to request additional time (unless you have received from their R&D department notification that you may commence), is a breach of the terms of HRA and HCRW Approval. Further information is provided in the "*summary of assessment*" section towards the end of this document.

It is important that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details of the research management function for each organisation can be accessed here.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within the devolved administrations of Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) has been sent to the coordinating centre of each participating nation. You should work with the relevant national coordinating functions to ensure any nation specific checks are complete, and with each site so that they are able to give management permission for the study to begin.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?
The document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

IRAS project ID	250373

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

I am a participating NHS organisation in England or Wales. What should I do once I receive this letter?
You should work with the applicant and sponsor to complete any outstanding arrangements so you are able to confirm capacity and capability in line with the information provided in this letter.

The sponsor contact for this application is as follows:

Name: Mr Matthew Richards
Tel: 0121 204 5069
Email: m.richards3@aston.ac.uk

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **250373**. Please quote this on all correspondence.

Yours sincerely

Gemma Oakes
Assessor

Email: hra.approval@nhs.net

Copy to: *Mr Matthew Richards, Aston University [Sponsor Contact]*
m.richards3@aston.ac.uk
Ms Jill Stacey, University Hospitals of North Midlands NHS Trust [Lead NHS R&D Contact]
Jill.Stacey@uhnm.nhs.uk

IRAS project ID	250373

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
Copies of advertisement materials for research participants [E-mail to Advertise Research]	0.4	21 November 2018
Copies of advertisement materials for research participants [Poster to Advertise Research]	0.3	30 July 2018
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Aston Indemnity Insurance]		
HRA Schedule of Events [Site Type 1 - All Site Activities]	1	17 December 2018
HRA Schedule of Events [Site Type 2 - PIC Site]	1	17 December 2018
HRA Statement of Activities [Site Type 2 - PIC Site]	1	17 December 2018
HRA Statement of Activities [Site Type 1 - All Site Activities]	1	17 December 2018
Interview schedules or topic guides for participants [Interview Schedule Carers]	V0.3	30 July 2018
Interview schedules or topic guides for participants [Interview Schedule Older People]	V0.3	30 July 2018
Interview schedules or topic guides for participants [Interview Schedule Practitioners]	V0.3	30 July 2018
IRAS Application Form [IRAS_Form_22112018]		22 November 2018
IRAS Application Form XML file [IRAS_Form_22112018]		22 November 2018
Letter from funder [Funding Letter from Colorcon]		26 November 2018
Letter from sponsor [Sponsor Agreement]		15 November 2018
Other [Placebo Tablets Used in Phase 1]	0.3	30 July 2018
Other [GCP Face to Face Training Cert]		31 October 2018
Other [250373: REC and HRA Response to Amendments]		08 January 2019
Participant consent form [Consent Form Practitioners V0.8 as Tracked Changes]	V0.8	10 January 2019
Participant consent form [Consent Form Older People/Carers]	0.8	20 December 2018
Participant consent form [Consent Form V0.8 Older People/Carers as Tracked Changes]	0.8	10 January 2019
Participant consent form [Consent Form Practitioners]	0.8	20 December 2018
Participant information sheet (PIS) [PIS Carers as Tracked Changes]	0.8	20 December 2018
Participant information sheet (PIS) [PIS Carers]	0.8	20 December 2018
Participant information sheet (PIS) [PIS Older People]	0.8	20 December 2018
Participant information sheet (PIS) [PIS Older People V0.8 as Tracked Changes]	0.8	10 January 2019
Participant information sheet (PIS) [PIS Practitioners]	0.7	20 December 2018
Participant information sheet (PIS) [PIS Practitioners V0.7 as Tracked Changes]	0.7	10 January 2019
Research protocol or project proposal [Protocol V0.6 19.11.18]	0.6	19 November 2018
Summary CV for Chief Investigator (CI) [CV- IM]		
Summary CV for student [CV Research Student ZS]		
Summary CV for supervisor (student research) [CV Research Supervisor]		
Summary, synopsis or diagram (flowchart) of protocol in non-technical language [Flow Chart Summarising Protocol]	0.3	30 July 2018

IRAS project ID	250373

Summary of assessment

The following information provides assurance to you, the sponsor and the NHS in England and Wales that the study, as assessed for HRA and HCRW Approval, is compliant with relevant standards. It also provides information and clarification, where appropriate, to participating NHS organisations in England and Wales to assist in assessing, arranging and confirming capacity and capability.

Assessment criteria

Section	Assessment Criteria	Compliant with Standards	Comments
1.1	IRAS application completed correctly	Yes	The applicant has confirmed there are 5 NHS sites involved in the study; 3 CRNs and 2 NHS Trusts.
2.1	Participant information/consent documents and consent process	Yes	As part of the applicant's response to REC provisional opinion, modified participant information sheets and consent forms were submitted to comply with HRA Standards.
3.1	Protocol assessment	Yes	No comments
4.1	Allocation of responsibilities and rights are agreed and documented	Yes	There are 2 site types participating in the study: • **Site Type 1 – All Site Activities:** A statement of activities has been submitted, and the sponsor is not requesting and does not expect any other site agreement to be used. • **Site Type 2 – PIC Site:** A statement of activities has been submitted for information, and the sponsor is not requesting and does not expect any other site agreement to be used. Although formal confirmation of capacity and capability is not expected of all or some organisations participating in this study, and such organisations would therefore be assumed to have confirmed their capacity and capability should they not respond to the contrary, we would ask

IRAS project ID	250373

Section	Assessment Criteria	Compliant with Standards	Comments
			that these organisations pro-actively engage with the sponsor in order to confirm at as early a date as possible. Confirmation in such cases should be by email to the CI and Sponsor confirming participation based on the relevant Statement of Activities and information within this letter.
4.2	Insurance/indemnity arrangements assessed	Yes	Where applicable, independent contractors (e.g. General Practitioners) should ensure that the professional indemnity provided by their medical defence organisation covers the activities expected of them for this research study.
4.3	Financial arrangements assessed	Yes	External funding has been secured from Colorcon. No funding will be provided to the participating NHS sites.
5.1	Compliance with the Data Protection Act and data security issues assessed	Yes	As part of the applicant's response to REC provisional opinion, modified participant information sheets and consent forms were submitted to comply with GDPR.
5.2	CTIMPS – Arrangements for compliance with the Clinical Trials Regulations assessed	Not Applicable	No comments
5.3	Compliance with any applicable laws or regulations	Yes	No comments
6.1	NHS Research Ethics Committee favourable opinion received for applicable studies	Yes	REC Favourable Opinion was issued on 14 January 2019.
6.2	CTIMPS – Clinical Trials Authorisation (CTA) letter received	Not Applicable	No comments
6.3	Devices – MHRA notice of no	Not Applicable	No comments

Section	Assessment Criteria	Compliant with Standards	Comments
	objection received		
6.4	Other regulatory approvals and authorisations received	Not Applicable	No comments

Participating NHS Organisations in England and Wales

This provides detail on the types of participating NHS organisations in the study and a statement as to whether the activities at all organisations are the same or different.

There are 2 site types participating in the study. The research activities taking place at the participating NHS sites is as follows:

- **Site Type 1 – All Site Activities**: these organisations will recruit and consent participants, and undertake all study activities.

- **Site Type 2 – PIC Sites**: these organisations will advertise the research through displaying promotional materials (e.g. posters), identify potential participants, send out mail outs and carry out eligibility checks. The remainder of the study activities (including consent) will take place at Site Type 1.

We note potential participants will also be recruited through non-NHS organisations (Join Dementia Research and People in Research); these activities fall outside the remit of HRA Approval.

Please note that the remit of HRA Approval is limited to the NHS involvement in the study. Research activity undertaken at non-NHS sites is therefore not covered and the research team should make appropriate alternative arrangements with relevant management at these organisations to conduct the research there.

The Chief Investigator or sponsor should share relevant study documents with participating NHS organisations in England and Wales in order to put arrangements in place to deliver the study. The documents should be sent to both the local study team, where applicable, and the office providing the research management function at the participating organisation. Where applicable, the local LCRN contact should also be copied into this correspondence.

If chief investigators, sponsors or principal investigators are asked to complete site level forms for participating NHS organisations in England and Wales which are not provided in IRAS or on the HRA or HCRW websites, the chief investigator, sponsor or principal investigator should notify the HRA immediately at hra.approval@nhs.net, or HCRW at Research-permissions@wales.nhs.uk. We will work with these organisations to achieve a consistent approach to information provision.

IRAS project ID	250373

Principal Investigator Suitability

This confirms whether the sponsor position on whether a PI, LC or neither should be in place is correct for each type of participating NHS organisation in England and Wales, and the minimum expectations for education, training and experience that PIs should meet (where applicable).

The sponsor position and training requirements for all [two] types of participating NHS sites in England are appropriate for the study, as follows:

- **Site Type 1 – All Site Activities:** A Local Principal Investigator is required and has been identified. The sponsor will not provide any training for the study, however it does expect the local research team members to undertake or to have already undertaken NIHR CRN Training in Good Clinical Practice and NIHR Training in Informed Consent with Adults Lacking Capacity.

- **Site Type 2 – PIC Site:** No Principal Investigator or Local Collaborator is required at participant identification centres (PICs). The sponsor will not provide any training for the study, however it does expect the local research team members to undertake or to have already undertaken NIHR CRN Training in Good Clinical Practice and NIHR Training in Informed Consent with Adults Lacking Capacity.

GCP training is not a generic training expectation, in line with the HRA/HCRW/MHRA statement on training expectations.

HR Good Practice Resource Pack Expectations

This confirms the HR Good Practice Resource Pack expectations for the study and the pre-engagement checks that should and should not be undertaken

In respect of HR Guidelines, the following arrangements are expected:

- **Site Type 1 – All Site Activities:** Where arrangements are not already in place, network staff (or similar) undertaking any research activities that may impact on the quality of care of the participant, would be expected to obtain an honorary research contract from one NHS organisation (if university employed), followed by Letters of Access for subsequent organisations. This would be on the basis of a Research Passport (if university employed) or an NHS to NHS confirmation of pre-engagement checks letter (if NHS employed). These should confirm enhanced DBS checks, including appropriate barred list checks, and occupational health clearance.

  For research team members undertaking activities that do not impact on the quality of care of the participant (for example, administering questionnaires), a Letter of Access based on standard DBS checks and occupational health clearance would be appropriate.

- **Site Type 2 – PIC Site:** No access arrangements expected.

Where activities are taking place at GP practices, you are advised to contact the primary care management function to follow local processes.

Use of identifiable information held by an NHS organisation to identify potential participants should be undertaken by a member of the direct care team for those participants. No additional

arrangements (honorary research contracts or letters of access) should be necessary for identification and referral of potential participants at the PICs.

Other Information to Aid Study Set-up

This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales to aid study set-up.

- The applicant has indicated that they do not intend to apply for inclusion on the NIHR CRN Portfolio.
- The 'All Site Activities' site type will be required to book a meeting room for the interviews to take place, and will be required to facilitate this when a date and time has been confirmed for the interview to take place.

Appendix 19: REC approval letter

NHS
Health Research Authority

Social Care REC
Ground Floor
Skipton House
80 London Road
London
SE1 6LH

Telephone: 0207 972 2568
Fax:

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

14 January 2019

Dr Ian Maidment
Aston University
Aston Triangle
Birmingham
B4 7ET

Dear Dr Maidment

Study title:	**Patient Centric Medicine Design: An Investigation into Understanding and Enhancing Older Peoples' Adherence to Oral Solid Dosage Forms**
REC reference:	**18/IEC08/0047**
Protocol number:	**227-2018-ZR**
IRAS project ID:	**250373**

Thank you for your letter of 08 January 2019, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact hra.studyregistration@nhs.net outlining the reasons for your request.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA and HCRW Approval (England and Wales)/ NHS permission for research is available in the Integrated Research Application System, at www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Copies of advertisement materials for research participants [E-mail to Advertise Research]	0.4	21 November 2018
Copies of advertisement materials for research participants [Poster to Advertise Research]	0.3	30 July 2018
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Aston Indemnity Insurance]		
HRA Statement of Activities [SoA All Sites]	1.0	18 December 2018
Interview schedules or topic guides for participants [Interview Schedule Carers]	V0.3	30 July 2018
Interview schedules or topic guides for participants [Interview Schedule Older People]	V0.3	30 July 2018
Interview schedules or topic guides for participants [Interview Schedule Practitioners]	V0.3	30 July 2018
IRAS Application Form [IRAS_Form_22112018]		22 November 2018
IRAS Application Form XML file [IRAS_Form_22112018]		22 November 2018
Letter from sponsor [Sponsor Agreement]		15 November 2018
Other [Placebo Tablets Used in Phase 1]	0.3	30 July 2018
Other [GCP Face to Face Training Cert]		31 October 2018
Other [250373: REC and HRA Response to Amendments]		08 January 2019
Participant consent form [Consent Form Practitioners]	0.8	20 December 2018
Participant consent form [Consent Form Practitioners V0.8 as Tracked Changes]	V0.8	10 January 2019
Participant consent form [Consent Form Older People/Carers]	0.8	20 December 2018
Participant consent form [Consent Form V0.8 Older People/Carers as Tracked Changes]	0.8	10 January 2019
Participant information sheet (PIS) [PIS Carers as Tracked Changes]	0.8	20 December 2018
Participant information sheet (PIS) [PIS Carers]	0.8	20 December 2018
Participant information sheet (PIS) [PIS Older People]	0.8	20 December 2018

Participant information sheet (PIS) [PIS Older People V0.8 as Tracked Changes]	0.8	10 January 2019
Participant information sheet (PIS) [PIS Practitioners]	0.7	20 December 2018
Participant information sheet (PIS) [PIS Practitioners V0.7 as Tracked Changes]	0.7	10 January 2019
Research protocol or project proposal [Protocol V0.6 19.11.18]	0.6	19 November 2018
Summary CV for Chief Investigator (CI) [CV- IM]		
Summary CV for student [CV Research Student ZS]		
Summary CV for supervisor (student research) [CV Research Supervisor]		
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Flow Chart Summarising Protocol]	0.3	30 July 2018

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at
http://www.hra.nhs.uk/hra-training/

18/IEC08/0047	Please quote this number on all correspondence

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

Yours sincerely

Pp Dr Martin Stevens
Chair

Email:nrescommittee.social-care@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Mr Matthew Richards*
Ms Jill Stacey, University Hospitals of North Midlands NHS Trust

Appendix 20: Letter of access for primary care

Zakia Shariff
Aston University

20th February 2019

NIHR Clinical Research Network: West Midlands
The University of Birmingham
Murray Learning Centre, Room 145
Edgbaston
Birmingham
B15 2TT
Tel No: 0121 414 7182
Web: www.crn.nihr.ac.uk/wmidlands
Email: studysupportpc.crnwestmidlands@nihr.ac.uk

Dear Zakia

Letter of Access to undertake Research in Primary Care organisations across Arden, Herefordshire and Worcestershire, Birmingham and the Black Country, Shropshire and Staffordshire

This letter is issued on behalf of NHS England by the Clinical Research Network: West Midlands[1].

This letter should be presented to each participating organisation before you commence your research at that site. The participating organisation(s) covered by this *Letter of Access* are primary care organisations across Arden, Herefordshire and Worcestershire, Birmingham and the Black Country, Shropshire and Staffordshire *w*here NHS independent contractors and their premises are involved in NHS research activity.

In accepting this letter, each participating organisation confirms your right of access to conduct research through their organisation for the purpose and on the terms and conditions set out below. Please ensure that you have read and understood the terms and conditions described in this letter before you commence the research activity.

This right of access commences on **20th February 2019** and ends on **30th September 2020** unless terminated earlier in accordance with the clauses below. You have a right of access to conduct such research as confirmed in writing in the HRA approval letter. You should contact each NHS independent contractor directly to finalise your permission to conduct the research activity at their site. **Please note that you cannot start the research until the Principal Investigator has received both HRA approval letter and confirmation of capacity and capability from the primary care organisation to conduct the research activity at their site.**

The information supplied about your role in research at the primary care organisation(s) has been reviewed and you do not require an honorary research contract with them. We are satisfied that such pre-engagement checks as we consider necessary have been carried out. However the final decision rests with each participating primary care organisation, and evidence of checks should be available on request to the organisation(s).

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[1] **Pilot for issuing NHS HR Agreements in Primary Care:**
NHS England Midland and East Region Arden, Herefordshire and Worcestershire, Birmingham and the Black Country and Shropshire and Staffordshire Area Teams are working in partnership with the Clinical Research Network West Midlands to support researchers working in primary care.

All correspondence concerning this HR agreement should be directed to the *CRN: West Midlands* *studysupportpc.crnwestmidlands@nihr.ac.uk*

High quality care for all, now and for future generations

You are considered to be a legal visitor to the primary care organisation(s) premises. You are not entitled to any form of payment or access to other benefits provided by NHS England or any primary care organisations to employees and this letter does not give rise to any other relationship between you and NHS England or any primary care organisations, in particular that of an employee.

While undertaking research through the primary care organisation(s) you will remain accountable to your substantive employer but you are required to follow the reasonable instructions of the organisation(s) or those instructions given on their behalf in relation to the terms of this right of access.

Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by NHS England or the primary care organisation(s) in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.

Whilst carrying out research the Researcher must act at all times in accordance with the policies and procedures of NHS England and the primary care organisation(s) including the Research Governance Framework, copies of which will be made available upon request.

You are required to co-operate with the NHS England and the primary care organisation(s) in discharging its/their duties under the Health and Safety at Work etc Act 1974 and other health and safety legislation and to take reasonable care for the health and safety of yourself and others while on the organisations premises.

You must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of any other contract holder and you must act appropriately, responsibly and professionally at all times.

If you have a physical or mental health condition or disability which may affect your research role and which might require special adjustments to your role, if you have not already done so, you must notify your employer and each primary care organisation prior to commencing your research role at that organisation.

You are required to ensure that all information regarding patients or staff remains secure and *strictly confidential* at all times. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice and the Data Protection Act 1998. Furthermore you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution. Researchers are not permitted any access to personal identifiable information without the prior informed consent of patients/research participants.

You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. Please also ensure that while on the primary care organisations premises you wear your ID badge at all times, or are able to prove your identity if challenged. Please note that neither NHS England nor the primary care organisation(s) accept responsibility for damage to or loss of personal property.

NHS England may revoke this letter and any primary care organisation(s) may terminate your right to attend at any time either by giving seven days' written notice to you or

immediately without any notice if you are in breach of any of the terms or conditions described in this letter or if you commit any act that we reasonably consider to amount to serious misconduct or to be disruptive and/or prejudicial to the interests and/or business of the organisation(s) or if you are convicted of any criminal offence.

You must not undertake regulated activity if you are barred from such work. If you are barred from working with adults or children this letter of access is immediately terminated. Your employer will immediately withdraw you from undertaking this or any other regulated activity and you MUST stop undertaking any regulated activity immediately.

Your substantive employer is responsible for your conduct during this research project and may in the circumstances described above instigate disciplinary action against you.

No organisation will indemnify you against any liability incurred as a result of any breach of confidentiality or breach of the Data Protection Act 1998. Any breach of the Data Protection Act 1998 may result in legal action against you and/or your substantive employer.

Your Research Passport Form may be subject to random checks carried out by NHS England[2] within the lifetime of the project(s) listed in the Appendix. The information it contains must therefore remain up to date and accurate.

If your current role or involvement in research changes, or any of the information provided in your Research Passport changes, you must inform your employer through their normal procedures. You must also inform your nominated manager in each participating primary care organisation and NHS England through the CRN: West Midlands[3]. You should also contact NHS England through the CRN: West Midlands if you are approaching the end date of your employment contract and this is due to expire before the end date of your Research Passport.

Yours sincerely,

Pam Devall
CRN: West Midlands Research Delivery Manager (Primary Care)

Working in Partnership:
NHS England Midland and East Region Arden, Herefordshire and Worcestershire, Birmingham and the Black Country and Shropshire and Staffordshire Area Teams and the Clinical Research Network West Midlands

cc:
HR department of the substantive employer

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[2] Issue of this Letter of Access has been delegated to *the* CRN: West Midlands by NHS England on behalf of primary care organisations where NHS independent contractors and their facilities are involved in research activity.
[3] All correspondence concerning this HR agreement should be directed to the *CRN: West Midlands* *studysupportpc.crnwestmidlands@nihr.ac.uk*

Appendix 21: Letter of access for secondary care

University Hospitals of North Midlands NHS

NHS Trust

RESEARCH AND DEVELOPMENT DEPARTMENT
Academic Research Unit
Courtyard Annexe – C Block
Newcastle Road
Stoke-on-Trent
ST4 6QG
Tel: 01782 675398
Fax: 01782 675399

20th March 2019

Mrs Zakia Shariff
Apartment 12
56 Bath Row
Birmingham
B15 2DG

Dear Mrs Shariff,

Letter of access for research – Patient Centric Medicine Design to Improve Adherence in Older People

This letter should be presented to each participating organisation before you commence your research at that site. The participating organisation(s) is/are: **University Hospitals of North Midlands NHS Trust.**

In accepting this letter, each participating organisation confirms your right of access to conduct research through their organisation for the purpose and on the terms and conditions set out below. This right of access commences on **20th March 2019** and ends on **1st January 2022** unless terminated earlier in accordance with the clauses below.

You have a right of access to conduct such research as confirmed in writing in the letter of permission for research from **University Hospitals of North Midlands NHS Trust.** Please note that you cannot start the research until the Principal Investigator for the research project has received a letter from us giving confirmation from the individual organisation(s) of their agreement to conduct the research.

The information supplied about your role in research at the organisation(s) has been reviewed and you do not require an honorary research contract with the organisation(s). We are satisfied that such pre-engagement checks as we consider necessary have been carried out.

You are considered to be a legal visitor to the organisations premises. You are not entitled to any form of payment or access to other benefits provided by the organisation(s) or this organisation to employees and this letter does not give rise to any other relationship between you and the organisation(s), in particular that of an employee.

While undertaking research through the organisation(s) you will remain accountable to your substantive employer but you are required to follow the reasonable

instructions of the organisation(s) or those instructions given on their behalf in relation to the terms of this right of access.

Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by the organisation(s) in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.
You must act in accordance with the organisations policies and procedures, which are available to you upon request, and the UK policy framework for health and social care research.

You are required to co-operate with the organisation(s) in discharging its/their duties under the Health and Safety at Work etc Act 1974 and other health and safety legislation and to take reasonable care for the health and safety of yourself and others while on the organisations premises. You must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of any other contract holder and you must act appropriately, responsibly and professionally at all times.

If you have a physical or mental health condition or disability which may affect your research role and which might require special adjustments to your role, if you have not already done so, you must notify your employer and each organisation prior to commencing your research role at that organisation.

You are required to ensure that all information regarding patients or staff remains secure and *strictly confidential* at all times. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice and the General Data Protection Regulation and Data Protection Act 2018 for health and care research. Furthermore you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution.

You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. Please also ensure that while on the organisations premises you wear your ID badge at all times, or are able to prove your identity if challenged. Please note that the organisation(s) do not accept responsibility for damage to or loss of personal property.

This organisation may revoke this letter and any organisation(s) may terminate your right to attend at any time either by giving seven days' written notice to you or immediately without any notice if you are in breach of any of the terms or conditions described in this letter or if you commit any act that we reasonably consider to amount to serious misconduct or to be disruptive and/or prejudicial to the interests and/or business of the organisation(s) or if you are convicted of any criminal offence. You must not undertake regulated activity if you are barred from such work. If you are barred from working with adults or children this letter of access is immediately terminated. Your employer will immediately withdraw you from undertaking this or any other regulated activity and you MUST stop undertaking any regulated activity immediately.

Your substantive employer is responsible for your conduct during this research project and may in the circumstances described above instigate disciplinary action against you.

No organisation will indemnify you against any liability incurred as a result of any breach of confidentiality or breach of the General Data Protection Regulation and Data Protection Act 2018 for health and care research. Any breach of the General Data Protection Regulation and Data Protection Act 2018 for health and care research may result in legal action against you and/or your substantive employer.

If your current role or involvement in research changes, or any of the information provided in your Research Passport changes, you must inform your employer through their normal procedures. You must also inform your nominated manager in each participating organisation and the R&D office in this organisation.

Yours sincerely

[redacted]

Mrs Heather Reidy,
Senior Research Governance Facilitator, UHNM

cc: Ian Maidment – Senior Lecturer in Clinical Pharmacy – Aston University

Appendix 22: Non-substantial amendment 1

Partner Organisations:
Health Research Authority, England
NHS Research Scotland
HSC Research & Development, Public Health Agency, Northern Ireland
NIHR Clinical Research Network, England
NISCHR Permissions Co-ordinating Unit, Wales

Notification of Non-Substantial/Minor Amendments(s) for NHS Studies

This template **must only** be used to notify NHS/HSC R&D office(s) of amendments, which are **NOT** categorised as Substantial Amendments.
If you need to notify a Substantial Amendment to your study then you MUST use the appropriate Substantial Amendment form in IRAS.

Instructions for using this template

- For guidance on amendments refer to http://www.hra.nhs.uk/research-community/during-your-research-project/amendments/
- This template should be completed by the CI and optionally authorised by Sponsor, if required by sponsor guidelines.
- This form should be submitted according to the instructions provided for NHS/HSC R&D at http://www.hra.nhs.uk/research-community/during-your-research-project/amendments/which-review-bodies-need-to-approve-or-be-notified-of-which-types-of-amendments/ . If you do not submit your notification in accordance with these instructions then processing of your submission may be significantly delayed.

1. Study Information

Full title of study:	**Patient Centric Medicine Design to Improve Adherence in Older People**
IRAS Project ID:	**250373**
Sponsor Amendment Notification number:	NSA1
Sponsor Amendment Notification date:	07/05/2019
Details of Chief Investigator:	
Name [first name and surname]	Ian Maidment
Address:	Aston University Aston Triangle Birmingham
Postcode:	B4 7ET
Contact telephone number:	0121 204 3002
Email address:	i.maidment@aston.ac.uk
Details of Lead Sponsor:	
Name:	Matthew Richards
Contact email address:	m.richards3@aston.ac.uk
Details of Lead Nation:	
Name of lead nation *delete as appropriate*	England
If England led is the study going through CSP? *delete as appropriate*	No
Name of lead R&D office:	University Hospitals of North Midlands NHS Trust

Partner Organisations:
Health Research Authority, England NIHR Clinical Research Network, England
NHS Research Scotland NISCHR Permissions Co-ordinating Unit, Wales
HSC Research & Development, Public Health Agency, Northern Ireland

2. Summary of amendment(s)

This template **must only** be used to notify NHS/HSC R&D office(s) of amendments, which are **NOT** categorised as Substantial Amendments.
If you need to notify a Substantial Amendment to your study then you MUST use the appropriate Substantial Amendment form in IRAS.

No.	Brief description of amendment *(please enter each separate amendment in a new row)*	Amendment applies to *(delete/ list as appropriate)*		List relevant supporting document(s), including version numbers *(please ensure all referenced supporting documents are submitted with this form)*		R&D category of amendment *(category A, B, C) For office use only*
		Nation	Sites	Document	Version	
1	Amendment of the local PI at Dudley CCG from "Rachael Thornton" to "Clair Huckerby". Email address: clair.huckerby@nhs.net	England	Dudley CCG	N/A	N/A	
2	ARCHA (Aston Research Centre for Healthy Ageing) participant database to be added to recruit participants. This panel has approximately 170 members who take part in research.	England		N/A	N/A	
3						
4						
5						

[Add further rows as required]

Partner Organisations:
Health Research Authority, England | NIHR Clinical Research Network, England
NHS Research Scotland | NISCHR Permissions Co-ordinating Unit, Wales
HSC Research & Development, Public Health Agency, Northern Ireland

3. Declaration(s)

Declaration by Chief Investigator

- I confirm that the information in this form is accurate to the best of my knowledge and I take full responsibility for it.
- I consider that it would be reasonable for the proposed amendment(s) to be implemented.

Signature of Chief Investigator: [redacted]

Print name: IAN MAIDMENT

Date: 17/5/19

Optional Declaration by the Sponsor's Representative (as per Sponsor Guidelines)

The sponsor of an approved study is responsible for all amendments made during its conduct.

The person authorising the declaration should be authorised to do so. There is no requirement for a particular level of seniority; the sponsor's rules on delegated authority should be adhered to.

- I confirm the sponsor's support for the amendment(s) in this notification.

Signature of sponsor's representative: [redacted]

Print name: MATTHEW RICHARDS

Post: RESEARCH INTEGRITY OFFICER

Organisation: ASTON UNIVERSITY

Date: 28/5/2019

Appendix 23: Non-substantial amendment 2

Partner Organisations:
Health Research Authority, England — NIHR Clinical Research Network, England
NHS Research Scotland — NISCHR Permissions Co-ordinating Unit, Wales
HSC Research & Development, Public Health Agency, Northern Ireland

Notification of Non-Substantial/Minor Amendments(s) for NHS Studies

This template **must only** be used to notify NHS/HSC R&D office(s) of amendments, which are **NOT** categorised as Substantial Amendments.
If you need to notify a Substantial Amendment to your study then you MUST use the appropriate Substantial Amendment form in IRAS.

Instructions for using this template

- For guidance on amendments refer to http://www.hra.nhs.uk/research-community/during-your-research-project/amendments/
- This template should be completed by the CI and optionally authorised by Sponsor, if required by sponsor guidelines.
- This form should be submitted according to the instructions provided for NHS/HSC R&D at http://www.hra.nhs.uk/research-community/during-your-research-project/amendments/which-review-bodies-need-to-approve-or-be-notified-of-which-types-of-amendments/ . If you do not submit your notification in accordance with these instructions then processing of your submission may be significantly delayed.

1. Study Information

Full title of study:	**Patient Centric Medicine Design to Improve Adherence in Older People**
IRAS Project ID:	**250373**
Sponsor Amendment Notification number:	NSA2
Sponsor Amendment Notification date:	11/03/2020
Details of Chief Investigator:	
Name [first name and surname]	Ian Maidment
Address:	Aston University Aston Triangle Birmingham
Postcode:	B4 7ET
Contact telephone number:	0121 204 3002
Email address:	i.maidment@aston.ac.uk
Details of Lead Sponsor:	
Name:	Matthew Richards
Contact email address:	m.richards3@aston.ac.uk
Details of Lead Nation:	
Name of lead nation *delete as appropriate*	England
If England led is the study going through CSP? *delete as appropriate*	No
Name of lead R&D office:	University Hospitals of North Midlands NHS Trust

Partner Organisations:
Health Research Authority, England
NIHR Clinical Research Network, England
NHS Research Scotland
NISCHR Permissions Co-ordinating Unit, Wales
HSC Research & Development, Public Health Agency, Northern Ireland

Partner Organisations:
Health Research Authority, England NIHR Clinical Research Network, England
NHS Research Scotland NISCHR Permissions Co-ordinating Unit, Wales
HSC Research & Development, Public Health Agency, Northern Ireland

2. Summary of amendment(s)

This template **must only** be used to notify NHS/HSC R&D office(s) of amendments, which are **NOT** categorised as Substantial Amendments.
If you need to notify a Substantial Amendment to your study then you MUST use the appropriate Substantial Amendment form in IRAS.

No.	Brief description of amendment *(please enter each separate amendment in a new row)*	Amendment applies to *(delete/ list as appropriate)*		List relevant supporting document(s), including version numbers *(please ensure all referenced supporting documents are submitted with this form)*		R&D category of amendment *(category A, B, C) For office use only*
		Nation	Sites	Document	Version	
1	In the follow up focus group, as well as 3D models of tablets, participants will be presented with placebo tablets. These placebo tablets will be similar to those already presented to participants in the first round of interviews. They will be developed in partnership with Colorcon and in accordance with the protocol, they will **not** be taken.	England		N/A	N/A	
2						
3						
4						
5						

[Add further rows as required]

Partner Organisations:
Health Research Authority, England NIHR Clinical Research Network, England
NHS Research Scotland NISCHR Permissions Co-ordinating Unit, Wales
HSC Research & Development, Public Health Agency, Northern Ireland

3. Declaration(s)

Declaration by Chief Investigator

- I confirm that the information in this form is accurate to the best of my knowledge and I take full responsibility for it.
- I consider that it would be reasonable for the proposed amendment(s) to be implemented.

Signature of Chief Investigator: [redacted]

Print name: .....Dr Ian Maidment.....

Date: .....11/3/2020.....

Optional Declaration by the Sponsor's Representative (as per Sponsor Guidelines)

The sponsor of an approved study is responsible for all amendments made during its conduct.

The person authorising the declaration should be authorised to do so. There is no requirement for a particular level of seniority; the sponsor's rules on delegated authority should be adhered to.

- I confirm the sponsor's support for the amendment(s) in this notification.

Signature of sponsor's representative: [redacted]

Print name: MATT RICHARDS

Post: RESEARCH INTEGRITY OFFICER

Organisation: ASTON UNIVERSITY

Date: 12/03/2020

Appendix 24: Table detailing medications being taken by older people and the setting in which they were based

Code	M/F	Age	Ethnicity	Location	Medication List
P1	M	69	A	Birmingham	Metformin Sitagliptin Amlodipine Telmisartan Ezetimibe
P2	M	66	A	Tamworth	Aspirin Ramipril Atorvastatin Sertraline Atorvastatin Lansoprazole Memantine
P3	F	71	A	York	Solpadol Citalopram Levothyroxine Alfacalcidol Cetirizine Cinnarizine Ibuprofen Lansoprazole Paracetamol
P4	F	80	A	Willington	Atorvastatin Lansoprazole Paracetamol Codeine Phosphate Citalopram (Intentional non-compliance)

P5	F	81	A	Willington	Candesartan (two strengths) Clopidogrel Spironolacton Amlodipine Atorvastatin Paracetamol Codeine Phosphate
P6	F	66	A	Dudley	Statin Bisoprolol Lansoprazole Pizotifen Paracetamol
P7	M	74	A	Amlwch	Tamsulosin Glucophage SR Bisoprolol Ramipril Warfarin Simvastatin Colchicine Zapain
P8	F	69	J	Birmingham	Atorvastatin Amlodipine Bisoprolol Calcium & Vitamin D Naproxen Co-dydramol Paracetamol Furosemide
P9	F	81	A	Dudley	AdCal D3 Caplets Amitriptyline

					Lercanidipine Cosmocol Tramadol/Paracetamol
P10	F	74	A	Stoke	Dihydrocodeine Indoemtacin Olmesartan Paracetamol Folic acid Amitriptyline
P11	M	77	A	Birmingham	Ferrous fumarate Ranitidine Tramadol Cyclizine Paracetamol Loperamide
P12	F	97	A	Birmingham	Atenolol Ferrous fumarate Furosemide Monomil XL Lofepramine Simvastatin Paracetamol
P13	F	94	A	Birmingham	Amiodarone Amlodipine Apixaban Docusate Doxazosin Laxido Paracetamol
P14	M	72	A	Birmingham	Clopidogrel

					Mariosea XL Perindopril Simvastatin
P15	M	92	A	Brighton	Alendronic Acid Calceos Carbocisteine Citalopram Folic acid Omeprazole
P16	M	93	A	Brighton	Amlodipine Finasteride Fludorcortisone Paracetamol PRN Laxido
P17	M	94	A	Brighton	Allopurinol Bisoprolol Evacal D3 Furosmeide Levothyroxine Ranitidine Rivaroxaban Tamsulosin
P18	F	67	A	London	Calcium & Vitamin D Chewable Tablets Losartan Doxazosin Amitriptyline

Key:

Black: Older people living independently in the community
Red: Older people within secondary care
Green: Older people in care homes