Children's perceptions, beliefs and experiences of the acceptability of medicine and their perspectives on assessment measures.

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Edge Hill University

Declaration

This thesis is entirely my work and has not been submitted in full, or part, for the award of a higher degree at any other educational institution. Sections of this thesis have already been published, presented at a conference, or are under consideration for publication, with details listed below:

Conference Presentations

Gibson, B. 2018. Best Poster Presentation (Peer Reviewed): Graduate Research Student Symposium at Edge Hill University,

Gibson, B. 2018. Poster Presentation. Public Health PhD Symposium at the Public Health Institute at Liverpool John Moores University.

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Dedication

This thesis is dedicated to the memory of my Nan, Lena, who was my biggest encouragement and supporter, and who sadly passed away in the second year of my PhD. I hope I have made you proud.

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Abstract

Background

Children and young people are often administered medicines which are not tested or approved for use in this population. It is acknowledged that this use of off-label and unlicensed medicines to treat children can lead to over- or under-dosing, adverse drug reactions, and low treatment success (EMA, 2012). A key challenge to developing age-appropriate and acceptable medicines is that limited information is available for the development of paediatric medicines. Patient acceptability of medicines is thought to have a significant impact on treatment adherence and ultimately safety and efficacy. However, a lack of knowledge about what is considered acceptable to children and best practice methods to assess acceptability is limited and fragmented.

Aim and objectives

The aim of this study was to explore the experiences of children in relation to medicines, to incorporate their views to develop a better understanding of the acceptability of medicine, and to relate this to the tools that are used to assess the acceptability of medicines.

Three objectives were proposed to ensure that the overall aim of the study was achieved. These were to:

1. Explore children's experiences of medicines to gain a better understanding about what is acceptable to children in formulations.
2. Evaluate with children methods used to assess the acceptability of medicine.
3. Use this new information to propose ways that existing tools used to assess acceptability of formulations in a paediatric population can be re-designed to better reflect children's perspectives on the acceptability of medicine.

Methods

This study used a generic qualitative methodology and employed child-centred qualitative methods including activity booklets, drawing and ranking activities, interviews and participant observation to generate data with children aged 5-12 years in group workshops and one-to-one. Children were recruited through convenience sampling via schools, clubs, a museum and a hospital.

Findings

One hundred and eleven children participated in the study. The findings are organised into six superordinate themes presented in two separate chapters clearly reflecting the children's perspectives. The first findings chapter, Exploring Children's Perspectives to Improve the Understanding of the Acceptability of Medicines, encompasses three major themes: 1) What children can tell us about the acceptability of medicines, 2) What helps improve the acceptability of medicines to children, and 3) What reduces the acceptability of medicines to children. The second findings chapter, Improving the Methods Used to Assess the Acceptability of Medicines, also has three key themes: 4) Children's experience and understanding of scales, 5) Children's perceptions on and preferences for scales, and lastly, 6) Improving acceptability assessment.

Conclusion

The findings from the study present original contributions to knowledge of the acceptability of medicine in a child population, demonstrating that involving children in acceptability research provides a much-needed perspective on the acceptability of medicine and the factors thought to impact acceptability. A new definition of the acceptability of medicine is presented, grounded in data provided by the children. The "Framework of Children's Medicine Acceptability", provides a novel theoretical framework for the acceptability of medicine. Key recommendations address the factors that should be measured when assessing acceptability, improvements for acceptability assessment measures, and future directions for research.

Abbreviations

AAP	American Associated Pharmacies
ADME	Absorption, Distribution, Metabolism, and Excretion
ADR	Adverse drug reaction
AH	Alder Hey
BPCA	Best Pharmaceuticals for Children Act
CHMP	Committee for Medicinal Products for Human Use
DBS	Disclosure and Barring Service
EHU	Edge Hill University
EMA	European Medicines Agency
EMEA	European Medicines Evaluation Agency
EuPFI	European Paediatric Formulations Initiative
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernisation Act
FDASIA	Food and Drug Administration Safety and Innovation Act
FREC	Faculty Research Ethics Committee
GCP	Good Clinical Practise
GOSH	Great Ormand Street Hospital
HCP	Healthcare Professional
HRA	Health Research Authority
iCAN	International Children Advisory Network
ICH	International Council for Harmonisation
IOM	Institute of medicine
JBI	Joanna Briggs Institute
NHA	National HealthCare Association
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PDCO	Paediatric Committee
PIP	Paediatric investigation plans
PPI	Patient and public involvement
PREA	Paediatric Research Equity Act
PSP	Paediatric study plan

UK	United Kingdom
UREC	University Research Ethics Committee
US	United States
VAS	Visual Analogue Scale
WHO	World Health Organisation
YPAG	Young Person's Advisory Group

Definitions

Acceptability	*"Patient acceptability can be defined as the ability and willingness of a patient to self-administer, and also of any of their lay or professional caregivers, to administer a medicinal product as intended." (EMA, 2017, p3).*
Age-appropriate Formulations	*"a formulation whose pharmaceutical design makes it suitable for use in the target age group(s)" (EMA, 2013).*
Adverse Drug Event	*"an injury resulting from medical intervention related to a drug regardless of whether an error has occurred" (Assiri, 2016., p1).*
Compounding	*"Drug compounding is often regarded as the process of combining, mixing or altering ingredients to create a medication tailored to the needs of an individual patient" (FDA, 2018. P1).*
Excipients	*"An excipient is a constituent of a medicine other than the active substance, added in the formulation for a specific purpose. This may include colouring matter, preservatives, adjuvants, stabilisers, thickeners, emulsifiers, flavouring and aromatic substances" (EMA, 2018., p1).*
Manipulating	*"A manipulation is defined as the physical alteration of a pharmaceutical drug dosage form for the purposes of extracting and administering the required proportion of the drug dose. Examples of the types of manipulation include: 6 Tablets: split/broken/cut and a segment given, crushed and a proportion of the powder given, dispersed in liquid and a portion of the liquid given. Transdermal Patches: patch cut, and a portion of patch uncovered and applied." (Alder Hey, 2013., p5).*

Medication Adherence	*"Adherence to medicines is defined as the extent to which the patient's action matches the agreed recommendations" (NICE, 2009., p1).*
Medication compliance	"*the extent to which the patient's action matches the recommendation of the prescriber" (NCCSDO, 2005., p12)*
Medication Error	*"Medication errors are broadly defined as any error in the prescribing, dispensing, or administration of a drug, irrespective of whether such errors lead to adverse consequences or not." (Williams, 2007., p343).*
Medication Non-adherence	*"Intentional non-adherence refers to non-adherence that is deliberate and largely associated with patient motivation whereas unintentional non-adherence is non-adherence that is largely driven by a lack of capacity or resources to take medications" (Clifford, 2008., p41-46).*
Off-label prescribing	*"Means that the medicine is being used in a way that is different to that described in the licence. E.g. using a medicine for a different illness to that stated in the licence, using a medicine in an age group outside the licensed range, or using a medicine at a higher dose than stated" (NHS, 2019., p4).*
Patient Safety	*"treating and caring for people in a safe environment and protecting them from avoidable harm" (NHS, 2012/2013., Domain 5).*
Unlicensed prescribing	*"Means a medicine has a licence in other countries, but not in the UK; a medicine has a licence but needs to be made up to be taken as an unlicensed formulation" (i.e. a*

specially prepared liquid for someone who has difficulty swallowing tablets); or a medicine that has no licence at all (typically used for treating rare illnesses) (NHS, 2019., p4).

Chapter 1
Introduction

1 Introduction

The aim of this chapter is to introduce the study and provide context and justification for the requirement of this research. In an attempt to contextualise this issue within the broader landscape, this chapter begins by exploring medicine usage within healthcare and the related patient safety concerns, it then focusses on paediatric formulation development and its associated challenges. The chapter emphasises the significance of the acceptability of formulations in paediatric medicine development and highlights what knowledge is currently available and where improvement is necessary. Finally, the chapter concludes by presenting the following structure of the thesis.

1.1 Improving Acceptability and Adherence

Improving the acceptability of medicinal products in the child population is crucial to ensuring adherence to medication regimes, reducing the risk of medication errors, and improving treatment success (Ranmal et al, 2018). For years, paediatric formulation development has been behind that of medicines development for adults. It is reported that 50-90% of drugs used in children have never been studied in the paediatric population as part of drug development, instead relying on adult participants for safety and efficacy studies (Bouzom and Walther, 2008), and in the United Kingdom, fewer than 60% of licensed medicines are approved for the paediatric population (Balakrishnan et al, 2006). This however varies depending on the setting that medicines are prescribed, it is reported that 10-20% of medicines prescribed for children by general practitioners have not been licensed for use in children, however this number rises up to 45% of medicines used in general paediatric wards and for children within neonatal intensive care this number can be over 90% (ABPI, 2004).

Global regulatory initiatives have acknowledged the importance for the development of age-appropriate formulations to treat the child population (Gerrard et al, 2019), and it is understood that there are specific considerations required when developing formulations for children. As well as the diversity of childhood in physiological, biological and cognitive development, there are also patient compliance challenges such as the ability to take doses and taste preferences, as well as specific safety and efficacy concerns relating to the formulations (Sam et al, 2012; Klassen et al, 2008; Kearns, 2003). Additionally, issues related to ethical requirements, developmental

costs and a small, fragmented market also add to the challenge of developing appropriate dosage forms (Schirm et al, 2003; Balakrishnan et al, 2006). By developing age-appropriate formulations to treat children it is hoped that patient adherence will improve, resulting in positive treatment outcomes and ultimately effective treatment regimes.

1.1.1 Improving patient adherence

Prescribing, dispensing or reviewing medicines is made increasingly difficult for healthcare professionals (HCP's) when accounting for complex medical needs and the use of multiple medications in different population groups. A large-scale report published by the National Collaborating Centre for Primary Care (NCPPC) in 2009 outlined that in the UK between 2006-2007 around 10% of NHS expenditure was spent on medical care and drug costs, equating to £10.6 billion (O'Flynn, 2009). It is reported that patients do not take their medicines as prescribed or recommended and adherence figures can be anywhere between 33% to 67% (Elliot et al, 2015), and even with a disease as serious as breast cancer, adherence is on average only 70% (Philbin, 2019). This results in an estimated drug cost for unwanted or unused medications for the NHS in the UK of around £300 million annually (NHS, 2015). A systematic review focusing on interventions for enhancing medication adherence (Haynes et al, 2008) concluded that improving medicines-taking may have a bigger impact on positive clinical outcomes than adapting or improving the treatment itself.

The fact that the cost of unwanted and unused medication is so high is indicative of both a lack of adequate communication between healthcare professionals and patients about their health problems and how they might be treated, and patients' assessment and experiences of ongoing treatments (Nunes et al, 2009). Over the last decade, researchers are becoming more aware that addressing nonadherence might not be about getting patients to take more medicines, rather it should begin with an understanding of patients' perspectives of medicines and the reasons why they might not want or are unable to use them (Suan et al, 2018; Pages-Puigdemont et al, 2016).

Adherence to medication is multifaceted and involves the formulation, the patient and caregiver (where appropriate), and health care team. Within the literature the terms

‘medicine compliance’ and ‘medicine adherence’ are frequently used interchangeably (Jimmy & Jose, 2011). However, medicine compliance has previously been defined as “the extent to which the patient’s action matches the recommendation of the prescriber” (NCCSDO, 2005, p12), whereas medicine adherence is defined as “the extent to which the patient’s action matches the agreed recommendations of the prescriber” (NCCSDO, 2005, p12). Adherence therefore differs from compliance with the requirement for an agreement between the patient and the prescriber. The agreement of the patient to use the medicine, as intended, is an essential factor of treatment success (Brown and Bussell, 2011). Reasons for non-adherence include inappropriate formulations, cognitive and social factors. Within the child population additional factors impact on adherence including parental/caregiver involvement and the age of the child (Rachidi et al, 2017; Chappell, 2015; Gardiner, 2006).

Nonadherence with medication can be due to a number of reasons, which typically fall into two categories: intentional and unintentional (O’Flynn, 2009). Unintentional nonadherence happens when the patient wants to follow the treatment regimen but cannot because of factors outside of their control, such as poor recall or instructions which make it difficult for those with intellectual difficulties to follow. Intentional nonadherence occurs when the person makes a conscious decision to not follow the treatment regimens that they have been prescribed, usually because the medication formulation or dosing regimen is perceived by the patient as being inappropriate in some way. It is well documented that nonadherence or poor adherence to medication regimes result in negative treatment outcomes (Kalogianni, 2011), and adherence is ultimately dependent on the patient’s willingness and ability to take the product as intended (Adeyemi et al, 2012; Drumond et al, 2017). Therefore, when developing medicines for children, it is crucial that formulations are age appropriate and acceptable if they are to be used and adhered to.

1.2 The Development of Paediatric Medicines

In their report *Priority Medicines for Children* the WHO (2013) states that despite the availability of effective molecules, formulations adapted for children are still lacking, and development falls behind that of formulations for adults. They note that: “children

are often either not treated or, based on anecdotal paediatric evidence, treated off label or off licence with formulations for adults" (WHO, 2013, p85).

Compared to adults, there are a number of additional challenges to account for when developing and prescribing dosage formulations for children. During childhood there is a rapid rate of growth and development, and specific changes occur in the body that affect the how medicines are accepted and processed. The bodily organs, systems and enzymes change, affecting response to active drugs and adverse reactions and this happens at different rates depending on the individual child. Therefore, dosage requirements vary across the childhood and are dependent on body surface area and weight (Yewale & Dharmapalan, 2012) as well as other factors. Differences are also observed in children's cognitive and motor skills, including co-ordination (EMA, 2006), which affects the administration of medicines and the ability to take formulations.

Due to the differences and variability in the paediatric population, the magnitude of doses required through childhood can vary 100-fold and the ability to cope with different dosage forms can also vary considerably (EMA, 2006). Developers must consider a number of practicalities when creating or adapting formulations for children such as ensuring the safety of certain excipients (WHO, 2007), being conscious of adverse drug reactions (Ufer et al, 2007), and being aware of adherence issues related to unpalatable formulations (Ernest et al, 2007).

1.2.1 Paediatric population

Understanding that the paediatric population is not homogenous, and that maturation and development are continual processes in childhood are particularly important considerations in the application of physiological, pharmacological and pharmacokinetic characteristics to formulation development (RCPCH, 1999; Moore, 1998; Fernandez et al, 2011; Ernest, 2007). Pharmacokinetics refers to the route of the drug through the body's system and includes the absorption, distribution, metabolism and elimination (ADME) of the formulation. Pharmacodynamics comprises the physiological and biological response to the drug. The pharmacokinetics of drugs vary with age (Kearns, 1998), and one of the most difficult tasks for formulators and

developers is to account for the changes that occur during childhood in order to develop and provide safe and effective medication (NICE, 2015).

Physiological changes in development impact on important pharmacokinetic differences such as intestinal transit, gastric pH and surface area:volume ratio, which all impact on the absorption of the drug. Differences have also been reported in drug distribution and elimination due to variance in body composition such as fat and water levels, and enzyme levels and activity. During infancy and childhood continuous change is observed in body water, fat, and protein levels, indicating that the distribution of drugs in newborns is significantly different to that in older children and adolescents (Ernest, 2006). Between the ages of 2-11 years most drug clearance related processes have matured but these are still usually different to adults (Ernest, 2006). Furthermore, additional notable differences in growth and development in sub-groups within this 2-11year age range further highlight the requirement for dose variability in the infant and child population (Bartelink, 2006). Due to the variability in size, body composition, age and organ function that occurs across childhood, paediatricians and toxicologists cannot predict children's reactions to drug therapy based on adult data (Kearns et al, 2003), and therefore are presented with challenges of prescribing safe and effective treatment for children (Milsap & Jusko, 1994).

Consequently, a range of dosage forms should be available to prescribe a medicinal product allowing different strengths and concentrations to ensure every child can be treated. The International Council for Harmonisation (ICH) E11, classifies the paediatric population into several age groups, this aims to provide the pharmaceutical industry with approximate age bands based on relevant physiological and pharmacokinetic principals to rationalise and licence medicinal products, rather than age groups being 'arbitrarily chosen' (Conroy, 2003; pp49). These groups are preterm neonates (<36 weeks' gestation, 1- 27 days), full term neonates (0-27 days), infants and toddlers (28 days- 23 months), children (2- 11 years old) and adolescents (12-18 years old) (EMA CHMP, 2006). The 'children' category is further broken down into pre-school children (2-5 years) and school age children (6- 11 years). These are the age categorisations commonly used across pharmaceutical development literature (Gauthier & Cardot, 2011; Walsh et al, 2011; Aiache & Gauthier, 2007; Batchelor & Marriot, 2013). Of these age bands, it is reported that more than 80% of the child

population is represented by children over the age of 2 years, and 50% of all children is comprised of preschool (2-5 years) and school age groups (6-11 years) (Gauthier & Cardot, 2011).

Whilst classifying the paediatric population into age groups provides some guidance for research and development, these age groups do not necessarily adequately represent every child within those age brackets. Additionally, different end points may be established within the same age group, and there may be overlap between the age categories (EMA, 2006). A flexible approach, accounting for developmental biology and pharmacology is necessary to ensure that each individual is provided with the best possible treatment (EMA, 2006).

1.3 Current Medicines Use

Even when medicines are licensed for use in children, there are issues such as the suitability of formulations available for use in the paediatric population that limit the extent to which they can be effectively administered. Of the previously mentioned 60% approved medicines for children, 29% did not have a suitable formulation for children (Balakrishnan, 2006). Although a new medicine may not initially be expected to have paediatric licensing, if it is relevant for use in children, it should have the necessary licenses and formulations within a reasonable time frame (Balakrishnan, 2006). The lack of paediatric formulations is particularly telling in the availability of appropriate liquid dosage forms (Ainscough et al (2017). This is an issue for young children and neonates, who are often faced with inappropriate dosing and dosage forms (tablets, capsules, injections), harmful excipients and the stability of the formulation available to them (EMA, 2012; Nahata, 1999).

1.3.1 Off-label and unlicensed medicines use

As a consequence of the lack of paediatric formulations, it is commonplace for healthcare workers to prescribe off-label and unlicensed medicines for paediatric patients (Conroy, 2000; Turner, 1998). ‘Off-label’ use refers to medicine that is used in a way that is different to that described in the licence, for example, using a medicine to treat an illness it was not developed for or using a medicine in an age group outside of the licensed range. ‘Unlicensed’ medication is often a medicine that has a license

in another country that must be imported, a medicine that is adapted from one form to another (e.g. solid to liquid form), or a medicine that does not have a license at all (NHS, 2016).

Whilst it is not illegal to prescribe unlicensed or off-label medicine, there are clinical and ethical issues associated with this practice. A medicine is approved through the licensing process to ensure its efficacy, safety and usability in the target population (Stegemann et al, 2016). When a medicine is prescribed outside of this licence, the clinical support of the treatment is missing, and the treatment of the illness is often based more on assumptions and extrapolations (Stegemann et al, 2016). This has obvious drawbacks in terms of validity and reliability because of the variance between children and adults, and the variability between child sub-populations that were discussed earlier, such as pharmacokinetic and pharmacodynamic differences (EMA, 1997). There is also an increased risk when manipulating the medication from a solid or liquid formulation, or the splitting, crushing or cutting of medicines, as little is known about the quality standards or effects of manipulated drugs on therapeutic outcomes. Inappropriate use of medication can cause unnecessary risk rather than expected treatment benefits (Collier, 1999). Associations between the use of unlicensed drugs and dispensing and administration errors have been reported. In the child population an increase in medication errors and adverse reactions have been significantly more linked to unlicensed drug prescribing than licensed drugs (Conroy, 2011; Bellis et al, 2014). Furthermore, ethical issues related to the off-label and unlicensed use of medications include the extent to which the patient is involved in decision-making about treatment, and the extent of information that can be provided to the patient to inform them of the medication (Stegemann et al, 2016).

Despite the concerns related to the use of off-label or unlicensed products being prescribed for the paediatric population, there is often no other alternative medicine to treat children. The American Academy of Paediatrics (AAP) recently released a statement regarding this issue stating that “Paediatricians must prescribe drugs off-label, simply because an overwhelming number of critical drugs still have no information on the label for use in children” (from Healthychildren.org, para 3). It is commonly agreed that this prescribing is best practice when no suitable alternative is available (GMC, 2013).

1.3.2 Compounding and manipulation of medicine

Often, in order to prescribe medication in a suitable way for use in the paediatric population, the compounding and manipulation of drugs needs to take place. Compounding is regarded as the "process of combining, mixing, or altering ingredients to create a medication tailored to the needs of an individual patient" (FDA, 2018, p1). It is the creation of a particular medication which suits the unique needs of a patient, and the world compounding pharmacies market size was estimated over $9.5 billion in 2019 (Global Market Insights, 2019). There are differing understandings and definitions of drug manipulations (Ghaleb et al, 2006), but drug manipulation has been defined as the "physical alteration of a dosage form for the purpose of extracting a proportion of the drug dose (manipulation with the aim of achieving the required prescribed dose)" (Richey, 2013 p7). The practice of manipulating medicines occurs in the UK and internationally (Bourlon et al, 2006; Kayitare et al, 2009), and there are many different reasons for doing this.

Due to the majority of drugs being developed and tested for use in adults, the drug dose is often only available in dose units suitable for adults (Richey, 2013). In order to adapt these medications into age-appropriate dosage forms for children, manipulation of the existing medicine form may be required. This usually occurs at the point of administration, in the form of splitting, crushing or dispersing the dosage form to produce a smaller dose that matches the requirement of the child. However, this is further complicated considering the variance in dose requirement across childhood and the differences in a child's ability to cope with different dosage forms (Rocchi & Tomasi, 2011). Extensive research and guidance have been developed by researchers at Alder Hey Children's Hospital regarding the Manipulation of Drugs Required in Children (MODRIC). Whilst manipulations such as tablet cutting, crushing and opening capsules may be necessary to administer oral doses given to patients (Standing & Tuleu, 2005), there is a paucity of evidence on drug manipulations, and a review of the literature has found that there is a need for guidance to ensure dose accuracy (Richey et al, 2011). It is not uncommon for parents and caregivers who often have to crush or split oral dosage forms and mix them with food or drinks in order to mask the taste of the formulation to administer it to the child (Meirer et al, 2007). This

is also not limited to young children, with drug manipulations observed across a range of childhood ages (Skwierczynski & Conroy, 2008).

Whilst drug manipulations are commonly required for clinical reasons (such as providing an age-appropriate form for children), there are also some instances where drug manipulation is driven by economic factors. There may be a considerable price difference between medication strengths and so it may be cheaper to split doses than buy the formulation with the optimal dose (Quinzler et al, 2006) Similarly, cheaper unlicensed formulations may be used to treat children to save on costs, even when a licensed, more expensive medication is available.

There are numerous issues with the manipulation of medication, including time restraints, inaccuracies, lack of information on the stability and bioavailability of the drug (Nunn, 2003; Skwierczynski & Conroy, 2008). These manipulations may compromise drug efficacy and safety and increase the risk of dose calculation errors such as under or over-dosing (Richey, 2013). Under and overdosing are labelled as the most common medication error in neonatal and paediatric practice (Krzyzaniak & Bajorek, 2016). Although the requirement for drug manipulation is clear, there is little research on the subject, and the risks are not fully investigated in the paediatric population (Miller et al, 2007).

1.3.3 Age-appropriate formulations

Using adult studies to calculate safety and efficacy for the paediatric population based on age, body weight and/or body surface area is neither an accurate nor appropriate method to produce appropriate medicines for children. This method relies on the assumption that children are “small adults”, which is not the case (Yewale and Dharmapalan, 2012; p1). A clinical guideline published in 2009 from the National Institute for Health Care and Excellence (NICE) provides recommendations to formulators and developers for the development and prescription of appropriate medicines for children, conscious that inappropriate medicines have significant detrimental effects on children, the healthcare system and society. Similarly, there has been a global regulatory movement to improve medicines for children, fostering the development of patient-centric pharmaceutical products that account for the needs of children (Ranmal et al, 2018).

Past medication errors in paediatric patients have prompted the implementation of legal regulations and requirements in the development, approval, and use of paediatric formulations (Ward et al, 2017). Despite this, off-label, unlicensed, and manipulated medicines are still administered to the paediatric population.

The misuse of formulations in the paediatric population has led to tragedies of infant illness and death, such as the misuse of morphine (Borchers et al, 2007), the tragedy of the polio clinical trials in 1954, in which more than 250 children were infected with the polio virus from a vaccine (FDA, 2006), the fatal use of diethylene glycol in sulphanilamide formulations (FDA, 1981), and the devastating effects on newborns of the use of thalidomide in pregnant women (McBride, 1961). Whilst the implementation of legal regulations to prevent tragedies such as these has made testing in children safer, children still do not have access to appropriate dosage forms and strengths across disease state and across the age range. Most dosage forms are limited in some way in regard to clinical use.

Whilst oral dosage formulations are the most commonly used in the paediatric population (PDCO, 2013; Tuleu & Breikreutz, 2013), solid oral dosage forms have some risk of choking or inadvertent inhalation (Thompson et al, 2009). Liquid oral dosage forms, whilst posing less of a risk of choking, present issues such as measurement difficulties (Chappelle, 2015), palatability, as taste-masking becomes more difficult (Matsui, 2007), shorter shelf life, and increased prices (Reider, 2017). Non oral routes of administration include nasal, ocular, rectal, dermal, parenteral, and optic (Batchelor & Marriot, 2015). These provide difficulties in ease of use, adverse side effects, difficulties in administering, appropriateness of administration, and issues in paediatric distribution and absorption (Batchelor & Marriot, 2015).

An additional issue in formulations administered to children are the excipients. Excipients are anything other than the active pharmaceutical ingredient in a medicine (Haywood & Glass, 2011), and are often used in oral formulations in order to improve palatability and shelf-life. Excipient choice in developing paediatric formulations, and formulation choice in administering formulations to children off-label is compounded because of the unavailability of information regarding what is “safe” or “approved” for

paediatric patients (WHO, 2012; EMEA, 2000). It is known that certain excipients including ethanol, propylene glycol, benzyl alcohol and parabens (Tuleu, 2013) should not to be used in children, due to adverse reactions in organ development. Both the EU and US recognised the concerns of paediatric drug use and collaborated to develop the Safety and Toxicity of Excipients for Paediatrics (STEP) database (EUPFI. Salunke et al, 2012/2013), as well as for neonates with the European Study of Neonatal Exposure to Excipients: An Update (Turner et al, 2013). As well as this, the requirement for new paediatric regulatory guidance and legislation on the development and availability of age-appropriate formulations for children was recognised.

The initiative to develop age appropriate medicine is now at the forefront of paediatric pharmaceutical development, an age appropriate medicine is defined as one that is "suitable for use in the target age group(s)" (EMA, 2013, p23). The WHO states that "the ideal children's medicine is one that suits the age, physiological condition and body weight of the child taking them and is available in a flexible solid oral dosage form that can be taken whole, dissolved in a variety of liquids, or sprinkled on foods, making it easier for children to take" (WHO, 2010, online).

1.3.4 Regulations and policy for developing paediatric drug formulations

For decades, paediatric drug discovery, development, and regulation have been years behind adult therapies (Maron, 2017). This has resulted in products that do not go through the same rigorous safety and efficacy testing as adult formulations, leading to inappropriate and unacceptable drug products for the paediatric population. This means that doctors and pharmacists are presented with two options: to not treat the child or to prescribe off-label or unlicensed medication, which often carries unknown risks and side effects (AAP, 1995; Maron, 2017). As well as the risk of complications, morbidities and mortality outlined above, this has also resulted in significant delays in drug discovery in this population.

Over the last decade, policy and regulations for paediatric drug development have provided incentives and obligations for pharmaceutical companies to invest in the development of paediatric medicinal products (Penkov et al, 2017; Zisowsky et al, 2010). Collectively with child advocacy groups, international consortia and paediatric

drug development networks, there has been a shift from research ‘in’ children to drug development research ‘for’ children (Bucci-Rechtweg, 2017).

Specific legislation and policy in the EU and the US have driven the pharmaceutical industry to take a more active stance in the investment of time and resources to develop child appropriate formulations.

1.3.4.1 US Food and Drug Administration (FDA) regulations

The US was first to produce regulatory initiatives addressing paediatric pharmaceutical development (Penkov, 2017; Turner et al, 2014). In 1997, the Paediatric Labelling Rule was issued (FDA, 2010), outlining that manufacturers were to submit a new drug application (NDA) in order to have the labelling of an existing medication (developed for adults) amended to also include children in the drug labelling. Whilst this rule was designed to improve paediatric drug labelling, it was entirely voluntary, and so only a minority of studies resulted from it (NICH, 2010). This was amended and reauthorised as the Paediatric Rule (FDA, 2010), which required the manufacturer to submit safety and effectiveness information in the relevant paediatric groups before approval (CDER, 2010). Alongside this, the FDA produced the Food and Drug Administration Modernisation Act (FDAMA), which provided incentives for companies to develop specific products that were deemed beneficial for the paediatric population (FDA, 1997). This was largely successful, and many drugs in the US have been labelled through this act (Zisowsky et al, 2010).

Drawbacks with these early initiatives and regulations were identified in the early 2000s and addressed within two following acts: Best Pharmaceuticals for Children Act (BPCA) in 2002, and Paediatric Research Equity Act (PREA), 2003. The BPCA provides the incentives for drug development; however, this act only refers to drugs and is voluntary. In contrast, the PREA includes the requirements for drug development, referring to both drugs and biologics and is mandatory (Zisowsky, 2010). Both acts provide encouragement for additional paediatric research and development in drug formulation. Both acts were amended and reauthorised in 2007 within the Food and Drug Administration Amendments Act (FDAAA), this ensured the acts were in use until 2012, when, with modifications, they were made permanent. These acts are the

current legislation in the US and are found in within the Food and Administration Safety and Innovation Act (FDASIA) (Penkov et al, 2017) (Table 1.1).

Table 1.1: Regulatory milestones of paediatric legislation in the US and EU

1994	1997	1998	2000-2001	2002	2003	2006	2007
FDA: Food and Drug Administration- United States (US)							
Paediatric Labelling Rule	Paediatric Rule FDAMA (FDA Modernisation Act)			BPCA (Best Pharmaceutical for Children Act)	PREA (Paediatric Research Enquiry Act)		FDAAA (FDA Amendments Act)
EMA: European Medicines Agency- European Union (EU)							
	EMEA Round Table/ Guidance Note	ICH Discussion	Guideline ICH E11	Consultation Paper		Paediatric Regulation Agreed	Paediatric Regulation enforced

1.3.4.2 European Medicines Agency (EMA) regulation

Similarly, in the late 1990s the EU also recognised the necessity for pharmaceutical companies to be accountable to legal obligations in paediatric pharmaceutical development. In 1997, the first 'round table' talks were established to discuss paediatric medicines at the EMA (Zisowsky et al, 2017). In 2002, following a call from the European Health Council for action to be taken on the usage of unauthorised medicinal products in children, the consultation paper *Better Medicines for Children* was produced. This proposes specific regulatory actions on paediatric medicinal products. This was followed by a guidance note on the clinical investigations of medicinal products in children, and the need to strengthen legislation (EMEA, 2009). The International Conference on Harmonisation (ICH) discussions followed this, supporting the need for international discussion on the conduct of clinical trials in children (EMEA, 2009; CMPM, 2009), this preceded the official European ICH E11 guidelines (EMEA, 2009; CMPM, 2009).

Similarly, the European Council produced recommendations that the European Commission make appropriate proposals to develop governance and regulatory measures in respect of clinical trials on children, and to ensure that the specific needs of children are met in the newly developed medicinal products (The Council of the European Union, 2008(1); 2008(2)). The proposals for the new legislation were

assessed and accepted in June 2006 (EU Regulation, 2006), and the law was entered into force in all EU countries in January 2007 (Hawcutt & Smyth, 2008). The aim of the Paediatric Regulation is to improve the health of children by increasing the development of medicines for children and improving the available information on the information we have available about paediatric medicines (Hawcutt & Smyth, 2008).

1.3.5 Additional considerations: acceptability to improve adherence

The current regulations in the US and Europe help to provide developers with guidance in paediatric formulations. However, gaps still remain. Poor adherence is an issue for developers. It is reported that paediatric adherence rates in the paediatric population range from 11%-93%, with a median rate of 58% (Matsui, 2007). In regard to the factors that influence adherence, figures recently published as part of a systematic review (Brown & Bussell, 2011) state that in paediatric patients with asthma, less than 50% of medications are taken as prescribed, with the key reason for not taking their medicine being the taste.

Of particular consideration is the draft *European Regulation on Medicinal Products for Paediatric Use (2004).* This requires that companies submitting Paediatric Investigation Plans (PIPs) should ensure they describe the measures taken to adapt the formulations to make their use in paediatric populations acceptable, easy, safe and effective. Similarly, pharmaceutical companies are also asked to submit a Paediatric Study Plan (PSP) when marketing a new formulation for children. PSP's are documents that outline the safety and effectiveness of a medicine, and require pharmaceutical companies to consider the active ingredients, dosage form, dosing regimen or route of administration of the medicine in line with the study objective, age groups and appropriateness (Randovan & Beeby, 2018). Building on this, the regulatory guideline published by the EMA (2012) places emphasis on ensuring that the pharmaceutical design of the formulation is age-appropriate, highlighting the importance of acceptability and preference of dosage forms. It states that "the child's age, individual health status, behaviour, disabilities, background and culture are currently considered as the most likely parameters determining the child's acceptability and preference" of dosage forms (EMA/CHMP, 2012, p3). It also outlines that whilst ensuring the acceptability of formulations, attention should be paid to developing the

“minimum number of acceptable dosage forms which are capable of meeting the needs of the majority of the children in the target age groups” (EMA/CHMP, 2012, p3).

Acceptability is key in the development of age-appropriate formulations, and this is well understood within regulations. In the same guideline paper, the EMA calls for pharmaceutical companies to account for acceptability when they are developing new dosage forms and to consider route(s) of administration, dosage form, dosing needs/flexibility and excipients (EMA/CHMP, 2012). If a medicine is not acceptable to a child, even when the formulation meets the requirements of safety, stability, absorption and cost, the child is unlikely to be willing to take the product, and therefore the treatment will not be effective. As knowledge on the factors that influence age-appropriateness of paediatric formulations increases, the effectiveness and/or usefulness of the products should be re-evaluated in the interest of the children and their caregivers. This approach is in accordance with *Article 23 of the Directive 2001/83/EC* which requires companies to monitor the progress of their formulations during the life cycle of a medicinal product, adapting and improving their products for the benefit of the patient.

All medicines should be appropriately designed to meet the requirements of the patient and to consistently deliver the necessary treatment. However, there is currently only limited knowledge available to pharmaceutical developers and scientists about the acceptability of different dosage forms, administration volumes, dosage form sizes, tastes and excipients in relation to the age and development of children. Due to this lack of available information, practices mentioned earlier such as the manipulation, off label and unlicensed prescribing of drugs still takes place. Considerations of the acceptability of the formulation itself are essential due to its impact on adherence, and ultimately treatment effectiveness, success and safety (Jimmy & Jose, 2011).

1.4 Improving Acceptability in the Paediatric Population

As a result of the aforementioned legalities and policies, a new paediatric regulatory environment has been formed, implemented in the US and Europe and is under development in other parts of the world. This change in perception regarding the development and availability of age appropriate and acceptable medicines for children

has been a springboard for companies and researchers to create better medicines for children (BPCA, 2002; FDA, 2007).

The purpose of the BPCA, PREA, and the EU Paediatric Regulation to promote clinical trials in children and produce safety and efficacy data has been relatively successful (BPCA, 2013; van Riet-Nales et al, 2011; Ivanovska, 2017). Between 1997 and 2016, over 620 products were studied in the paediatric population and now have new paediatric information in the label; of these, over 560 involved new paediatric studies (Califf, 2017). The importance of paediatric labelling relates to ensuring that pharmacists and doctors are provided with the necessary paediatric-specific information including relevant age range and dosing information (Mazer-Amirshahi, 2014).

Nevertheless, there are still substantial areas to improve upon in paediatric formulation development, such as concerns that the EU regulation and PIP's have generated drugs for children which are driven by adult needs (because companies have to rely on adult participants in studies) rather than unmet paediatric needs. Similarly, reporting of efficacy data is often missing; negative results are often omitted or published at a substantially later date (IMNA, 2013; Benjamin et al, 2013). Additionally, despite the requirement for age-appropriate and child-acceptable medication, the heterogeneity of the child population is becoming increasingly recognised, and the selection of an appropriate paediatric formulation requires a case-by-case basis (CHMP; PDCO, 2013).

Both the FDA and EMA (2013; 2018) have developed recommendations for designing age-appropriate formulations (Zisowsky et al, 2010). In a commentary on the EMA (EMA, 2013) guidelines, it is stated that "acceptability aspects should be evaluated, (preferably) during the clinical study (preferably) with patients from all target age groups" (Kosarevitz, 2014). However, the lack of guidance from regulators about how exactly to undertake acceptability assessment provides issues for industry when developing medicines. Despite requiring that companies describe and justify their choice of formulation and acceptability assessment measures (Kosarevitz, 2014) for all target populations, this choice is left to the discretion of the companies. Therefore, the understanding and definition of acceptability is dependent on the questions asked

and the perspective adopted by each individual company. As the WHO (2007, p90) state, “the essential question is to determine whether a formulation proposed for registration is acceptable for the relevant target populations of children: can the claim for age appropriate medicines for children be effectively substantiated?”.

Similarly, the way in which that acceptability assessment is carried out varies depending on the researcher and the methods used to assess it. There is a lack of standardisation in measures used, and a lack of coherence in which aspects of acceptability are assessed. The Literature Review in Chapter 2 addresses these issues and explores the variation in how acceptability of all dosage forms in the paediatric population are defined and assessed.

1.5 Conclusion

In summary, to provide medicines that are both acceptable and age appropriate to the paediatric population, it is crucial that formulators and regulators work together with children and their caregivers. Moreover, undertaking patient-centric practices in the development of paediatric formulations and collaboration will ensure that children’s voices are heard. Through an enhanced understanding of children’s acceptability of medicine, pharmacists and formulation scientists may be better informed on how to create medicines that are more appropriate and acceptable for children. Therefore, the following chapter addresses the literature evidence of the acceptability of medicines for children, and the methodology used to assess acceptability.

Chapter 1: Introduction. This chapter has provided the background information on the core topic of this thesis. The following seven chapters provide details of literature, methodology, methods, findings, discussion and conclusions. In brief they are composed of:

Chapter 2: Literature Review. This chapter presents an integrative literature review, synthesising and summarising the key literature related to the specific topic of the acceptability of medicine and the methods used to assess acceptability in a paediatric population. This chapter concludes with the identification of research gaps and outlines the research aim and objectives of the study.

Chapter 3: Methodology. This chapter outlines the methodology adopted by the research and provides a justification for the methodological approach.

Chapter 4: Methods. This chapter describes the selected methods of data collection and analysis and explains the sampling and recruitment of the participants.

Chapter 5: Improving Acceptability Understanding. This findings chapter begins by outlining the characteristics of the participants and presents the findings for the first objective of the study. The findings include super-ordinate that encompass *1) What children can tell us about the acceptability of medicines, 2) What helps improve the acceptability of medicines to children,* and 3) *What reduces the acceptability of medicines to children.*

Chapter 6: Improving Acceptability Assessment. This second findings chapter discusses the findings related to objectives two and three. These are presented in themes encompassing *1) Children's experience and understanding of scales, 2) Children's perceptions on, and preferences for scales,* and lastly, 3) *Improving acceptability assessment.*

Chapter 7: Discussion. This chapter presents the discussion and provides an in-depth synthesis and interpretation of the two findings chapters. The findings are critically discussed and applied in the context of existing literature.

Chapter 8: Conclusion: This chapter concludes this study, including the strengths and weaknesses of the study, reflections of the researcher and recommendations for future research.

Chapter 2
Literature Review

2 Integrative Literature Review

2.1 Introduction

The previous chapter presented a comprehensive background to this study, outlining the development of, and specific considerations regarding paediatric formulation development. It also introduced the acceptability of paediatric medicine, the associated challenges and identified gaps where these challenges can be improved. One of the key barriers to developing acceptable medicines for children relates to the paucity of knowledge regarding what is considered acceptable to children in medicines and how the acceptability of paediatric formulations is assessed. Therefore, the overarching aim of this chapter is to review, update and summarise the literature that reports on the methods of measurement or assessment of paediatric formulations. This chapter begins with a description of the methodological approach to the literature review and then follows with a synthesised account of the literature focusing on the acceptability of paediatric formulations.

2.1.1 Integrative literature review

The purpose of a literature review is primarily to summarise the pre-existing knowledge that is already available of a research topic or question (Noble and Smith, 2018). The review can be used to provide an overview of existing information, make recommendations to support decisions in healthcare, and highlight gaps in knowledge to guide future research (Noble and Smith, 2018; Hart, 2018). The most common approach in healthcare is to conduct a systematic review to answer a specific clinical question, however, literature reviews are undertaken for a number of different purposes (Whittemore and Knafl, 2005). The integrative review is one of many approaches to conducting a literature review, its purpose is to summarise past literature to provide a more complete understanding of a topic or healthcare problem (Broome, 1993). Integrative reviews are argued to be the most comprehensive methodological approach of reviews, allowing for the inclusion of diverse methodologies including experimental and non-experimental research, as well as theoretical and empirical studies (Whittemore and Knafl, 2005; Tavares de Souza et al, 2010). In contrast to integrative reviews, systematic reviews focus more specifically on one primary research question and typically include only experimental studies. Additionally, systematic reviews are designed to overcome bias at every stage of the

review process, adhering to strict methods to search and select papers, assess relevance and validity, collect, synthesise and interpret data (Tavares de Souza, 2010). A critique of integrative reviews is that they do not focus on the same rigorous procedures as systematic reviews and can therefore be at risk of increased errors during the review process (Dunkin, 1996).

Overall, it was decided that an integrative review would be the most appropriate in the current study. A strength of this type of review relates to its inclusion of a broad range of research, and its wide range of purposes (Broome, 1993). Both of these factors have “the potential to result in a comprehensive portrayal of complex concepts, theories or health care problems of importance” (Whittemore and Knafl, 2005., p548). This seemed a suitable method for assessing the literature base regarding the acceptability of medicines. Whilst integrative reviews can be conducted in a number of ways, the author is still expected to follow structured processes to ensure the reduction of errors (Torraco, 2016). This relates to the processes of the methodology outlined, how the literature was identified, analysed, synthesised and reported. Therefore, the following section of this chapter will outline these processes and provide justification of the robustness of the literature review (Mallett et al., 2012).

However, before outlining the processes of the current review, it is recommended that an integrative review broadly outlines the topic it is intending to address (Torraco, 2016). There are, in general, two kinds of topics - mature topics and new emerging topics - and most are placed somewhere along this continuum. As a topic grows, the corresponding knowledge base also develops, this is where an integrative review of a mature topic would review, critique and reconceptualise the knowledge base as it develops. In contrast, an integrative review that addresses new or emerging topics benefits from a holistic synthesis of the overall literature to date (Torraco, 2016). The current topic relating to the methods used to assess the acceptability of medicines is somewhere along the continuum from new to mature, at the time of writing, no review has attempted to evaluate and synthesise the methods used to assess acceptability of all types of medicine formulation in a child population. However, it is acknowledged that two notable reviews, one systematic (Ranmal et al, 2018) and one systematically searched and narratively presented (Mistry & Batchelor, 2017) have been published

in the last two years that do partly address this topic, both specifically focussing solely on oral formulations.

In line with Torraco's (2016) recommendation of outlining the topic, the following section will provide a brief overview of what is already known about this topic and argue that the current review which addresses all formulations builds on these broader literature and the findings from the two recent reviews (Mistry & Batchelor, 2017; Ranmal et al, 2018) to provide an update and expanded review.

2.1.2 Current knowledge of the topic

Children's acceptability of medicines has been defined as "the overall ability and willingness of the patient to use a medicinal product as intended and its care giver to administer the medicine as intended" (EMA, 2013, p20). Patient acceptability is thought to have a significant impact on treatment adherence and consequently the safety and efficacy of the medicine (EMA, 2013). Whilst the EMA states that patient acceptability is an integral part of pharmaceutical development that should be evaluated in children themselves (EMA, 2013), knowledge regarding best practice methods to do this is limited and fragmented (Bekele et al, 2014). Additionally, there is little knowledge about what is currently considered acceptable to the children (Drumond et al, 2017; Mistry & Batchelor, 2017; Walsh et al, 2017). A recent review has presented evidence of acceptability of pharmaceutical formulations in children and older adult patients (Squires, 2013), and two notable reviews have provided a synthesis of literature focussed on the methodological approaches used to assess children's, and children's and older adults' acceptance of oral formulations (Mistry & Batchelor, 2017; Ranmal, 2018).

The systematic search and narrative review conducted by Mistry & Batchelor (2017) aimed to synthesise the currently available information regarding the acceptability of oral medicines for children. This review led to the identification of key gaps within the literature, specifically that methods to define what is classified as acceptable to children is still required. It was also reported that gaps specific to the acceptability of oral formulations, such as knowledge relating to the shape of tablets, minitablets and capsules, and the size and volume of multiparticulates is also necessary. This review

also identified that a standardised methodology or criteria was necessary to formally evaluate the acceptability of formulations within studies that could be used to standardise research reporting on acceptability.

Building on this, a systematic review published by Ranmal et al (2018) identified papers reporting on formulation factors of oral medications that affect acceptability, with a particular emphasis on evaluating the methodologies employed within the studies. This paper focussed on both children and older adults and concluded that methodologies used within studies reporting acceptability vary considerably. A key finding of this review was that acceptability definitions and criteria used to assess acceptability varied significantly across the literature. This review mirrored the conclusions of the Mistry & Batchelor (2017) review, that the standardisation for reporting acceptability testing and study methodology would be beneficial.

Building on the recommendations of these reviews, and acknowledging the limitations related to the focus of only one formulation type, the current review aims to review, update and summarise the available literature related to the methods used to assess acceptability of medicines in the paediatric population. Furthermore, this work differs from these previous works which focused on the application of adult tools to a paediatric population thus limiting their potential child-centeredness and value. This work specifically took this limitation into account with its ultimate aim and focus being on the development of age-appropriate tools; this focus makes this work unique.

2.2 Methods

2.2.1 Review aim and purpose

As previously mentioned, an integrative literature review, whilst not typically systematic, is written in a structured manner. It is reported that specifying the topic or purpose of an integrative review leads to a coherent structure for presenting the findings (Torraco, 2016).

Therefore, the overarching aim of this integrative literature review was to review what methods are used to assess the acceptability of medicines within the paediatric

population (0<18yrs). The purpose being to critically examine this in relation to the three main concepts which comprise the topic and which are outlined in section 2.4.

2.2.2 Search Strategy

A well-defined search strategy is reportedly critical for increasing rigor in any literature review (Cooper, 1998). Whittemore & Knafl (2005) report that ideally, all of the relevant literature should be included in the review. However, limitations associated with inconsistent search terminology and indexing problems can mean that only around 50% of eligible studies are identified in computerised databases (Jadad, 1998; Whittemore & Knafl, 2005). Despite this, within an integrative review, at least two or three search databases should be used, and this should be accompanied by hand searching, networking or searching research registries (Conn et al, 2003).

Therefore, in the current study the electronic literature search was initially performed in May 2018, updated in January 2019 and further updated in August 2020 using the PubMed, Scopus, and Embase databases. The search protocol adhered to the Population, Concept, Context (PCC) model (The Joanna Briggs Institute, 2015), which has roots in the PICO (population, intervention, comparator and outcome) framework commonly used to focus clinical questions and develop systematic literature search strategies.

The electronic literature search followed the three-step search strategy outlined in the Joanna Briggs Methodology for Joanna Briggs Institute (JBI) Scoping Reviews (2015). The initial preliminary search was undertaken on the PubMed database, in line with the second step of this three-step process, the key words were then reviewed and amended to aim for the inclusion of all potentially relevant key text words in titles and abstracts of papers. The key terms used in this search strategy were further refined in collaboration with a health sciences librarian, and a table of all index terms used to search for papers in this study is presented below in Table 2.1. Thirdly, two additional searches were carried out on the Embase and Scopus databases, and the reference lists of all identified relevant papers were searched for additional studies. This is presented in Table 2.1.

Table 2.1: Search Terms

Population	
0-18 years	1. Paediatric OR pediatric OR child* OR infant OR newborn OR adolesc* OR teen* OR “young adult” OR “young person”
Concept	
Acceptability of medicine	2. Satisfaction OR acceptance OR preference OR approval OR acceptability OR palatability OR taste OR smell OR size OR shape OR appearance OR swallowability OR good OR bad OR ok 3. Formulation OR “dosage form” OR medicine OR drug OR form OR dose
Context	
Methods of assessment	4. Methods OR assessment OR methodologies OR development OR evaluation 5. “Taste-test” OR “hedonic scale” OR “facial affective scale” OR observation

2.2.3 Inclusion and exclusion criteria

Criteria used to ascertain whether papers are included and excluded should be stated and consistent with the goals of the review (Torraco, 2016). The selection criteria in the current study was dependent on the language and accessibility of the papers, whether the paper stated the methodology/assessment measures used to evaluate acceptability, and the population. Papers were excluded if they were not a primary source, if they did not report the methodology or assessment of acceptability and if the population was outside of the relevant age range (Table 2.2).

Table 2.2: Inclusion and exclusion criteria

Inclusion criteria
• Publications in English • Primary sources (excluding guidelines) • Primary articles relating to paediatric formulation development, specifically papers that reported the method/methodology used in acceptability assessment testing • Studies reporting on child population (<18 years old) • No limits were set for date of publication.
Exclusion criteria
• Articles that did not report the methodology or assessment of acceptability

2.3 Search Results

In integrative reviews, although not essential, authors are encouraged to present a matrix or table of the papers identified and either included or rejected from the study (Torraco, 2016). The criteria that is used to retain or discard papers should be explained, and selection criteria may include populations of interest, time restraints or the research methods used (Torraco, 2016). In the current study, only primary papers that reported the methodology used to evaluate the acceptability of medicine in a child population were included. (Note: although the two reviews by Ranmal et al (2018) and Mistry & Batchelor (2017) were not included in the review itself, their reference lists were examined to provide a further means of checking that all eligible primary papers were included).

Therefore, in the current study a total of 3712 papers were identified through the electronic searches, after all document titles and abstracts were manually screened for relevance, and duplicates were removed, the full text articles were accessed and evaluated for inclusion. Thirty-eight papers were eligible for inclusion, and an additional 26 papers were included following the manual screening of references resulting in 64 papers that were included in the review (Figure 2.1).

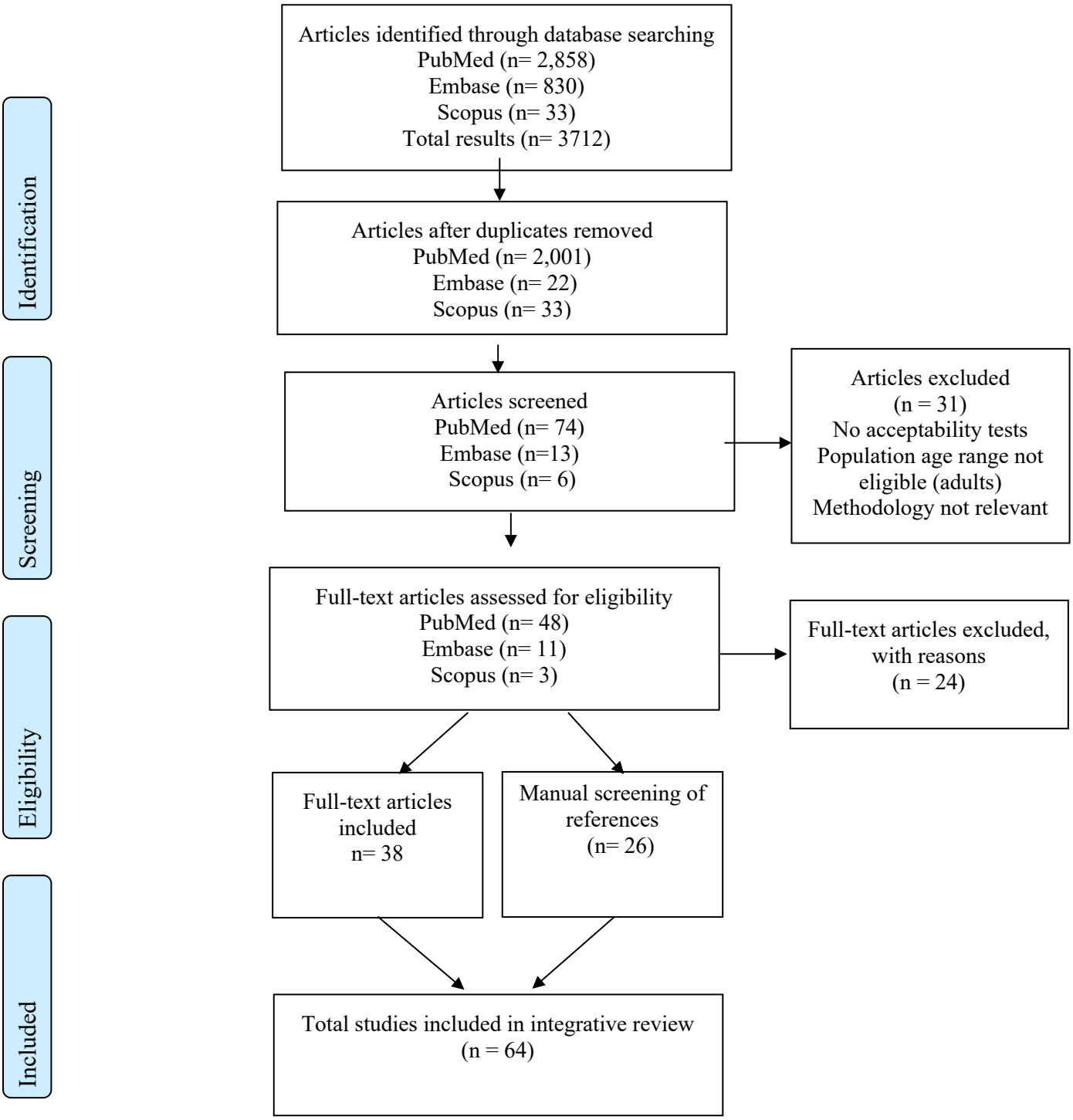


Figure 2.1: PRISMA flowchart showing results of search

2.4 Findings from the Review

2.4.1 Structuring the findings

As previously mentioned, specifying the topic and purpose of the literature review provides some guidance for the structure of presenting the review's findings. Whilst there is no one way of organising a literature review, it is suggested they can be organised by grouping articles dependent on similarities in concepts or theories, methodological similarities among studies or historical development (American Psychological Association, 2010). The current review has employed the conceptual or thematic structure. Conceptual structuring provides coherence and clarity about how the main themes of the topic come together as one combined piece and is key to how the literature review is organised (Torraco, 2016). Most healthcare topics are comprised of several key concepts (Torraco, 2016) or themes, and the current review is focussed around the key themes relating to the acceptability of medicines.

This review focuses on how the acceptability of medicines is defined, the factors identified in the literature that impact on acceptability, and the methodology or assessments used to evaluate acceptability. A conceptual map (Figure 2.2) that represents the structure of the review has been created; this map presents the key themes identified in the literature relating to the acceptability of medicine. The purpose of this map is to demonstrate the connections between the themes and reflect how the acceptability of medicine is addressed in the literature.

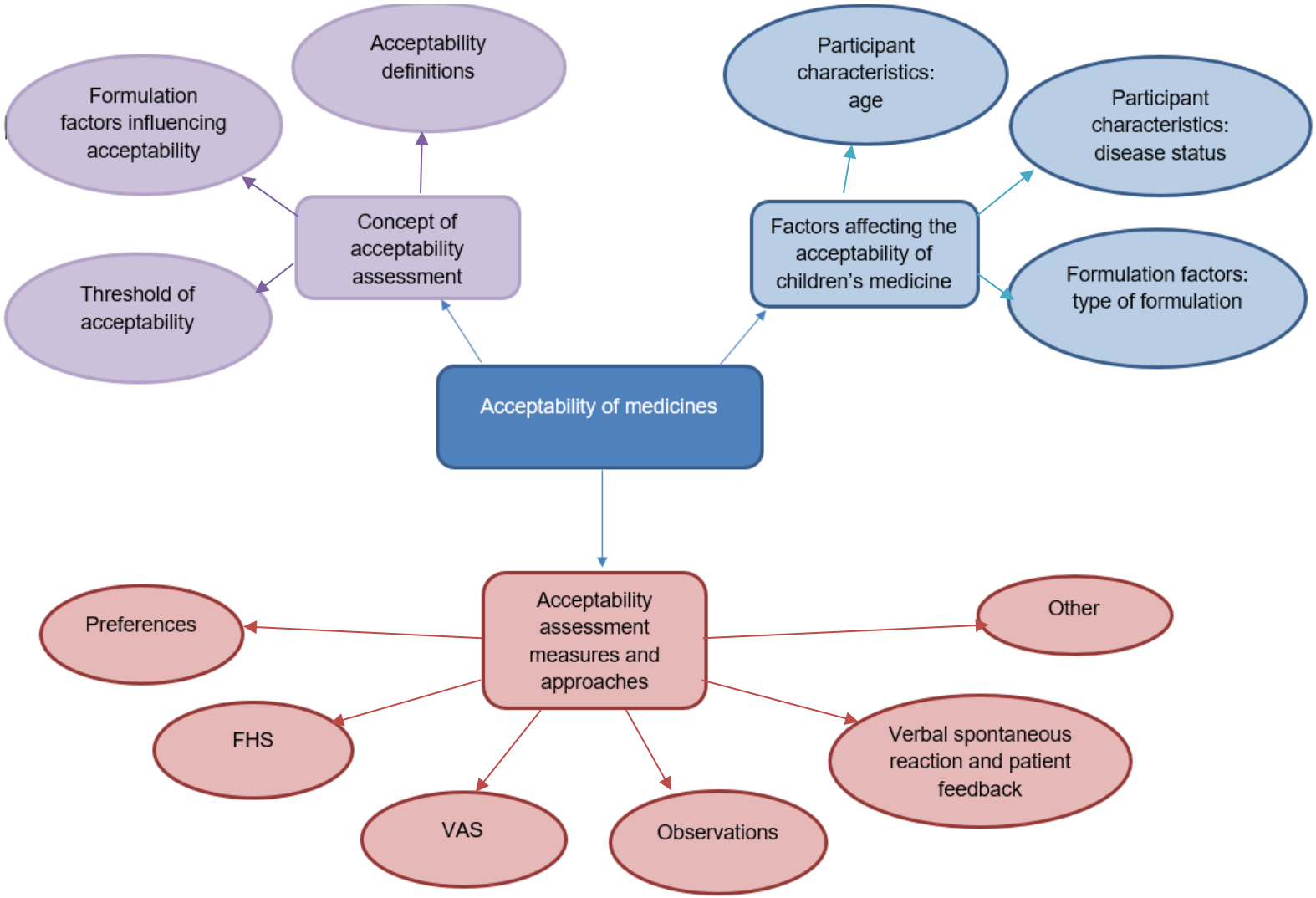


Figure 2.2: Conceptual map of the key themes and sub-themes of the integrative literature review.

Although the EMA (2013) and WHO (2007) guidelines were not included in the main review, the definition of acceptability presented in this guideline is used as the 'gold standard' definition when presenting the findings of the review and the discussion.

2.4.2 Data extraction

Structured summary tables were created and key details from the literature were inputted; these details included author, year, participant age, who provided the assessment, outcome measures used for acceptability, threshold level of acceptability and method of measurement of acceptability (Table 2.3). The papers presented in Table 2.3 are organised in chronological order (most recent to oldest publication dates).

2.4.3 Overview of the papers in the review

All 64 papers were empirical studies, with 27 using a randomised crossover design, 15 using a randomised control trial (Angwa et al, 2020; Hofmanova et al, 2020; Klingmann e al, 2020; Purchase et al, 2019; Thompson, 2009; Kendall, 2001; Geltman, 2009; Cadwgan, 2017; Nahirya-ntege, 2012; Cristofides, 2005; Orlu, 2017; Mekmullica, 2003; Blume, 2018; Klingmann et al, 2018; Cohen, 2005), six using a prospective research design (Moniot-ville, 1998; Akhavan-Karbasi, 2010; Block, 2006; Amirav, 2014; Coleman, 2002; Jagani, 2016), three employed survey designs (Mulla, 2016; Valovirta, 2009; Wallace et al, 2019), two employed a single subject experimental design (Babbitt, 1991; Beck, 2005), two observational studies (Cohen, 2009; Ruiz et al, 2020), interview (Venebles, 2016), one observation and interview (Giralt et al, 2019), one interview and questionnaire (Bryson, 2014), one comparison study (Arapostathis, 2010), and one online survey (Lloyd, 2011). Six did not specify the study design further than empirical (Giralt, 2017; Verrotte, 2011; Polaha, 2008; Nasrin, 2005; Strehle, 2010; Pakalnis, 2003).

The dates of publication ranged from 1984-2020, with 40 (63%) papers published since the year 2008, showing an increase in the number of published papers reporting on the methodology/methods used to assess acceptability in paediatric formulations in the last decade. The majority of studies were conducted in the UK, Europe and

American countries, this is generally in line with the focus on recent European initiatives, however an increase in the number of studies conducted globally in the last year, particularly in African countries such as South Africa, Kenya and Uganda reflects the efforts of global initiatives to improve acceptability (see Table 2.3).

Table 2.3: Data extraction table (presented in chronological order, most recent first).

Author (Year) Country	Formulation type	Drug content	Participant age range	Person(s) undertaking acceptability review	Outcome measurements used to assess acceptability	Threshold level of acceptability	Measurement or result of acceptability
Angwa et al. 2020 Kenya	Dispersible tablets. Oral suspension.	Amoxicillin.	2-59 months.	Caregiver.	Structured questionnaire. Observation of children's behaviour-perception of taste compared to other formulations.	Good acceptability defined as perception of taste of the formulation as same or better and expression of willingness of caregivers to use amoxicillin tablet in future.	Dispersible tablets: 55% of caregivers perceived taste to be better than other medicines compared to oral suspension. Oral suspension: 60.5% believed drug tasted the same as other medicines.
Hofmanova et al. 2020 United Kingdom	Tablets.	Placebo.	4-12 years.	Child and Researcher.	PRO- 5-point hedonic scale. Ability to take-ease of swallowing, taste intensity, mouthfeel. Hedonic perception: preference test.	Marks on 5-point scale were translated to scores from 1-5 (1= negative, 5= positive). Comparison of tablets was done using statistical analysis on SPSS.	62.4% of children swallowed at least one tablet. Success of swallowing was age related. Children who completely swallowed tablet tended to give higher scores for ease of swallowing. Researchers recorded negative facial expressions as indicative of aversion to tablet: lips pressed together, wrinkling nose, browns pulled together, voice disgust, eyes squeezed shut and head shake.
Klingmann et al. 2020 Germany	Orodispersible film vs syrup.	Placebo.	2 days-12 months.	Two independent blinder raters.	Observation: Amount of product taken.	Acceptability defined as aggregate of two variables: everything swallowed or chewed/ partially swallowed.	Threshold endpoints transformed to statistics.

				Caregivers.	Palatability.	Pleasant (positive hedonic pattern), no change (neutral hedonic pattern), and unpleasant (negative hedonic pattern).	ODF- 143/150 (95.3%) Syrup- 121/150 (80.7%).
Ruiz et al. 2020 France	Oral suspension. Oral solution. Suppository. Capsule. Tablet. Coated tablet. Effervescent tablet. Oral lyophilizate.	Paracetamol.	Birth-2 years 3-5 years. 6-8 years 9-11 years 12-14 years 15-17 years	Caregiver for outpatients. HCP for inpatients.	Observation: Result of intake. Patient reaction. Time needed to prepare. Time needed to administer. Methods to ease/achieve administration.	Dose fully taken, partly, or not at all. Positive, neutral or negative reaction. Preparation and administration time: short (<1 minute), medium (1min-2.5mins), long (>2.5min). Dividing dose, use of food/drink, patient reward, use of restraint	Multivariate mapping and clustering provided a score which resulted in either: positively or negatively accepted.
Giralt et al. 2019 Kenya	Pellets.	Lopinavir/ ritonavir.		Researchers. Caregivers.	Observations in home and clinic. Semi-structured interviews.	Qualitative findings- acceptance high where formulation was regarded as: easier to administer and easier to store than liquid.	Caregivers own beliefs (including competence and autonomy, future aspirations related to children's health, self-experience and perceived HIV-related stigma). Mechanisms (including practical issues- storing/administrating, access to support, establishing a routine).
Purchase et al. 2019	Tablets.	Levofloxacin.	Children <5 years.	Caregiver. Researcher.	Questionnaire containing items relating to:	Whether formulation was swallowed.	82% caregivers thought tablet was acceptable.

South Africa					caregiver opinions about drug administration and acceptability. Drug administration (5-point likert scales) Observations	Caregiver responses.	92% felt volume of dispersion as acceptable. 82% children swallowed dose. 12% refused dose. 1% spat it out.
Wallace et al. 2019 Ghana	Vaccine.	-	Parents of children aged 12-35 months.	Parents.	Caregiver Vaccine Acceptance Scale (CVAS)	Caregiver attitudes and beliefs: Vaccine awareness. Vaccine benefits. Past behaviour. Vaccine efficacy and safety. Trust.	Benefits showed strongest association with vaccine uptake. Awareness weakest association. Past behaviour and trust: null association. Efficacy and safety most consistent in significance of associations.
Blume. 2018 South Africa	Oral liquid.	Antibiotics	6 months.	Caregivers.	5-point nominal scale Observation.	Behavioural responses to medicine not defined.	Children were scored to “swallow well” in 77-78% of the observers’ opinion and the tool developer. 12% of children who showed negative behaviour were described as showing “refusal” by the observer, but “spitting” by the tool developer. Substantial concordance between the observers’ scores and the caregiver (68%).
Klingmann et al. 2018 Germany	Mini tablets Syrup	Placebo	6-12 months 2-5 years.	Researcher.	Observation	Acceptability is defined as an aggregate of the evaluation criteria swallowed and chewed.	Swallowability: 16.1% children swallowed all 400 minitablets compared to 31.2% children swallowed all syrup.

							68.8% chewed and/or had left-over tablets, only 51.6% had left-over syrup. 53.9% of children that chewed tablets went on to completely swallow them all. When administered 100 minitablets, 41.9% of children chewed/had leftovers. Of these, 92.3% ultimately swallowed them all. 3.8% had less than 50% of minitablets left; 3.8% had more than 50% of minitablets left.
Lopez et al. 2018 United Kingdom	Multiparticulates.	-	Children (4-12 years).	Researcher. Participants.	Observations of facial expressions. Swallowing the formulation. 5-point Hedonic scales. Willingness to take everyday	Ability to use as required and swallow the formulation.	Swallowability: 92% in children Researchers observations of negative expressions: pursed lips (57%) children, nose wrinkle (30%), eyes squeezed (21%) Children less likely to show acceptance (72%). 5-point hedonic scale (grittiness, mouthfeel, taste, sample volume).
Cadwgan et al. 2017 United Kingdom	Patch vs liquid.	Hyoscine skin patch or glycopyrronium liquid	Median 4 years.	Children. Parents.	Self-report interview and five-point scale. Treatment satisfaction questionnaire for medication (TSQM).	Tolerated, Favoured, Convenient.	Patches well tolerated by children; however, liquid has fewer negative side effects for parents. Patches thought to be favoured because more effective and convenient (administering liquid 3x per day an issue) Neither medicine clearly preferred.
Giralt 2017	Pellets.	10mg Lopinavir	>3 years	Parents	Interview Observations	Caregiver factors that contribute to	Information, motivation, self-efficacy, skills, health beliefs, mental health, coping styles,

Kenya						administering medication. "factors that affect the ongoing treatment adherence".	caregiver-infant relationship will all influence acceptability and adherence.
Klingmann 2017 Germany	2mm minitablets unit dose. Equivalent syrup dose.	Placebo	6 months-5yrs Age group 1: (6-23months) Age group 2: (2-5 yrs)	Children	Observation	Aggregate of the evaluation criteria swallowed and chewed according to evaluation criteria from previous study. Swallowed minitabs or either completely swallowed or partially swallowed syrup.	26.8% of children who took minitablets chewed or left some. 43.5% of children left syrup. Children preferred drink over food to accompany tablet.
Orlu et al. 2017 United Kingdom	Orodispersable tablets.	Placebo	6 age groups-6 months-5 years 6-12months (n=8); 1 year (n=25); 2 years (n=33); 3 years (n=20); 4 years (n=11); 5 years (n=13)	Caregivers Nurses Children >3 years	Direct observations Questionnaires 5-point hedonic scale age adapted questionnaires	Successful administration of ODT. Responses on 5point scale by children >3yrs. Responses on 5-point MAS by parents and caregivers.	78% children rated dosage form as <3 on 5-point scale, 63% reported they 'very much liked' it. 72% expressed willingness to take an ODT again. Caregivers: (child<2yrs) 79% scored 5 on MAS; (child >2yrs) 86% scored 5 on MAS; (child >5yrs) 52% scored 5 on MAS.
Jagani et al. 2016 United Kingdom	Tablets/liquid/capsules.	Range of medication	6-17 years	Children	Age-adapted, self-report diaries to record difficulty/ease of swallowing 6-point facial hedonic scale (0-not difficult, 6-most difficult).	Difficulty/ease of swallowing. Taste/flavour preference.	Pill Glide found to be safe, easy and effective to help children older than 6 years take solid medicines.

Kekitiinwa et al. 2016 Uganda	Pellets. Syrup.	Lopinavir/ ritonavir	3.months- 13 years	Caregivers	Questionnaires: preferences	Caregiver preference. Older children preference. Reported problems	Infants 1-4 years caregiver preferences decreased after 12 weeks. Older children's preference for pellets continually decreased. But preference still higher than alternative formulation after 48 weeks across all age groups.
Medeiros et al. 2016 Brazil	Oral formulations	Captopril. Furosemide	Hospitalised children: ≤6 years. 0-6, 6-12, 13-24, 24+ months	Caregiver/ researcher	7-point FHS and observation	Childs' overall liking Spontaneous reactions	No significant differences were observed for flavours or age groups between the two medicines. Mint flavour had the most negative reaction (40% rejection), neutral and strawberry taste did not differ significantly. Strawberry was most highly accepted (60% + 70%) for both formulations.
Mulla et al 2016 United Kingdom	Tablets vs oral liquid	Xaluprine	3-16 years	Children and parents (if under 6 years)	5-point hedonic scale (pictorial)	Acceptability (not defined).	77% children rated the taste of the formulation 'okay' to 'good', 82% reported it was 'easy to take all the time'
Ranmal et al. 2016 United Kingdom	Solid oral dosage forms	-	6-9 years	Children Caregivers	3 questionnaires: children, young people (10+) and adults 3 item, 5-point scale questionnaire Direct comparison of dosage forms	Acceptability defined as ability and willingness to take the formulation	All ages show a preference for tablets over capsules, tablets rated most acceptable.
Venebles et al. 2016	Non-oral formulations	Inhaled, ocular, dermal,	0-18 years	Children and parents/carers	Interviews	Barriers: age appropriateness, child	88 reported barriers across 148 non-oral formulations reported.

United Kingdom		parenteral, nasal				acceptability, preference issues	65% participants reported at least one barrier to non-oral medication.
Kluk et al 2015 Poland	Minitablets	Lactose, crospovidone, magnesium sterate, blue food clouring	2-3 years	Paediatrician	Observed and recorded	Acceptance defined as swallowing in A or B categories. (A= smooth swallowing/ swallowing with choking reflex or cough, B = biting or chewing followed by swallowing).	Median palatability score was 2.6. 83% children able to swallow 5 or 10 minitablets with fruit jelly as an aid.
Amirav et al. 2014 Israel	Inhaled	Respimat-generated radiolabelled aerosol	0-12 months	Parents	Observation	Acceptance defined as no mask rejection and remaining asleep	77% of infants successfully accepted the medication without waking. (1 woke during the observation, 1 did not go to sleep at all, 1 was excluded for other variables).
Bryson 2014 United Kingdom	Not stated	Not stated	3-11 years	Child Primary caregiver Hospital clinical and technical staff	Interviews and questionnaires Focus groups	Preferences.	Development of a Medication Adherence Prediction Tool (MedAPT) questionnaire. Child's age, medical condition, taste/palatability. Colour, dose form, complexity of routine, and availability of choice contributing factor.
Musiime et al. 2014 Uganda	Minitabs Syrups tablets	Lopinavir/ritonavir	3 months- 13 years	Caregivers	Observation/feedback comments	Ingestion. Taste. Swallowing. Amount.	More problems reported with taking syrups than minitabs. Taste was most common issue with all formulations; worst in minitabs than tablets (50% vs 0%), similar with minitabs and syrup (53% and 67%). Difficulty with swallowing reported for 20% minitabs, 60% syrups, 0% tablets.

							Caregivers preferred minitabs over syrup.
Ogutu et al. 2014 Kenya	Two forms-dispersible oral formulation	Dihydroartemisinin/ Piperaquine	6-59 months	Parent/caregiver	Caregiver questionnaire	Adherence. Ease of use. Acceptability.	Caregivers generally preferred the dispersible tablet (dissolved in a small volume of water or milk) compared to syrup formulation
Thompson et al. 2013 United Kingdom	Lozenges	Amylmetacresol	6-12 years	Clinician Children	Observed spontaneous reactions using 7-point FHS. Children completed FHS themselves	End point of 4-7 on FHS. Secondary end-point facial reactions.	Score of >4 for 85.3% of subjects for strawberry and 49.0% for orange. Willingness to take again: strawberry (94%) orange (56%).
Nahirya-Ntege et al. 2012 Africa	Syrup vs scored tablets	Nvirapine, Zidovudine, abacavir, Lamivudine	2.9 years	Caregivers	Questionnaires	Preference.	74% of caregivers expected to prefer tablets, and 27% expected child to prefer tablets. After 8/24 weeks, 94-97% caregivers preferred tablets and reported that 57-59% of children did.
Spomer et al. 2012 Germany	Minitablets vs syrup	Placebo	0.5-6 years	Children	Observation	Acceptance defined as swallowing and chewing for minitablet, not defined for syrup	Minitablet acceptance was higher or equal to syrup in all age groups.
Van Riet-Nales et al 2012 The Netherlands	Oral doses. 4mm tablet. Powder. Suspension. Syrup.	Placebo	1-4yrs	Parents	Observation and VAS (0-10). Result of intake. Report preference of child and themselves.	Intake and preference. Mean VAS scores	Children's mean VAS scores. Tablet (9.39); powder (8.84); suspension (8.26); syrup (8.35)
Lloyd et al. 2011 United Kingdom	Tablets vs transdermal patches	Methylphenidate	Median 12yrs	Parents/carers	Online survey	Preference (not defined).	Caregivers preferred transdermal patches compared to oral medications

Rodd et al. 2011 Canada	Oral drop vs oral filmstrip	Vitamin D	1.9-4.3 weeks	Parents	Observation and questionnaire for parents 10-point likert scale	Acceptability defined as ability and willingness to take formulation. Acceptance and preference. Infant acceptance was assessed using reactions to administration.	Overall preference of 85.4% observed for filmstrips (Not clear how this was calculated).
Verrotti et al. 2011 Italy	Solution vs granule formulation	Valporate	Average 6.7 years	Parents Children	Palatability: 5-point facial hedonic scale (children) Ease of administration/ tolerability or persistence to medication: interview with parents	Tolerability. Ease of administration. Palatability.	Palatability found to be the most important objective in treatment. Granule formulation was found to positively influence convenience of use Granules preferred over solution after 6 months by all participants.
Akhavan-Karbasi et al 2010 Iran	Rectal vs oral doses	Acetaminophen	6 months to 6 years	Parents	10-cm visual analogue scale	Satisfaction.	No significant differences in parental satisfaction between rectal and oral routes
Arapostathis et al. 2010 Greece	Gel vs needle vs needle-free injection	Anaesthetic	6-11 years	Children	Verbally asked/patient reported	Preference. Acceptance.	64 of 87 children stated they preferred the local injection (with needle) to INJEX (needle-less).
Strehle et al. 2010 United Kingdom	Oral drop	Vitamin K	Infants	Midwives	Questionnaire	Acceptability (not defined).	56% midwives reported use of oral drops as ‘quite unacceptable’ or ‘completely unacceptable’, 33% undecided and 11% ‘not very acceptable’

Cohen et al. 2009 France	Oral	Antibiotics	Children mean 2.9 years.	Parents	Questionnaire. Questions addressing: If entire treatment taken. Taste (5-face scale filled in by parents or child if old enough to understand). Reason for stopping treatment early if applicable. Spitting out product. Whether parents would accept to treat their child again with the same medication.	Main endpoint was taste assessment (5= very good, 1 = very bad). Faces 5-3 were considered a 'satisfactory taste', faces 2 and 1 were considered to cause problems for palatability. Compliance to treatment was considered good if at least 90% of product was taken.	When both parents and children answered the taste scale, correlation between taste assessment was good (74.2%).
Geltman et al. 2009 United States	Sprinkles vs drops	Iron supplement	5-7months	Parents	Questionnaire	Ease of administration.	Parents in oral drop group more likely to report difficulty integrating administration into daily routine than parents in sprinkles group.
Thompson et al. 2009 United Kingdom	Minitablets	Placebo	2-6 years	Clinician	Observed	Ability to swallow.	46% of children aged 2 years swallowed tablet. 53% children aged 3 years; 85% children aged 5 years swallowed the minitablet.
Valovirta & Scadding	ODT's vs Oral solution	Desloratadine	0-12 years	Parents	Questionnaire	'Preference measured against current medication- direct	Parental preference ranged from 26% Netherlands- 65% in Spain.

2009 [online] France, Italy, the Netherlands, Spain						comparison of formulations.	
Munck et al. 2008 France	Granules or capsule	Cfc and Creon (C10)	6-36 months	Parents	Which treatment did you prefer?	Preference.	51% parents preferred CfC for practicality reasons and/or because their child had fewer symptoms 23% preferred C10 because of practicality or less gastrointestinal symptoms No statistical significance between results
Polaha et al. 2008 United States	Pill or liquid	Any	Not stated	Child Parent	Self reported: Medication Acceptance Survey (assesses child/adolescent liquid / pill medication history and acceptance as well as parental interest in pill swallowing training.	Medicine Acceptance Survey.	30-40% of youth had rejected/refused a pill or liquid formulation. Half were unable to swallow a standard size pill or small capsule.
Lottman et al. 2007 Denmark	Two different oral formulations	Desmopressin	5-15 years	Patients/children	Diary card data 100mm VAS for “ease of use”	Comparison of patient preference for desmopressin melt and conventional tablet. Ease of use. Compliance. Preference.	55.7% preferred melt formulation, 44.3% preferred tablet. Patient preference highly correlated to age but not dose. Compliance 94.5% in MELT and 88.9% tablet.

Block et al. 2006 United States	Oral suspension	Cefdinir Amoxicillin/ clavulanate	6 months-6 years	Parents	6-point scale measuring medication satisfaction, ease of use, taste, if parents would use it again.	Not defined.	Preferences defined by ease of administration, better taste, and caused less gastrointestinal distress.
Herranz et al. 2006 Spain	Sustained-release tablet	Valproate	5-14 years	Children Parents	Not stated.	Preferences over alternate formulations.	Preferences found for 'chrono VPA once daily'
Beck et al. 2005 United States	Oral tablets	Methylphenidate	4-9 years	Clinician	Observation.	Acceptance defined as child allowed pill to be in mouth within 10 seconds of verbal prompt. Distress: 3-point rating scale (observed and filled in by therapist)	All children were able to swallow mock tablets with a therapist following training. 7/8 children continued this at home
Cohen et al. 2005 United States	Oral disintegrating tablets	Ondansetron 4mg or placebo	5-11 years	Children	Not defined.	Acceptability not defined Taste. Sensation. Willingness to take in the future.	None of subjects rejected or spat out medication. 12 children found the active tablet to not be as 'good' tasting compared to placebo.
Cristofides et al. 2005 Canada	Sprinkles	Placebo	Infants 4-18 months (mean 11.76 months)	Not defined	Not defined. (Adherence and side effects).	Adherence.	3% were adherent100% of the time. 40% adherent 75% of the time. 65% adherent 50% of the time.
Nasrin et al. 2005 Bangladesh	Dispersible tablets	Zinc	3-59 months	Caregiver	Questionnaire, using comparison to other medicines as	Acceptability measured on child's behaviour when given the medicine- not defined.	93.1% reported tablets were equally or more acceptable as other medicines

					better, same, or worse.		
Bukstein 2003 United States	Chewable tablets vs inhaler	Motelukast sodium tablets and inhaled cromolyn sodium	6-11 years	Parents and children	Questionnaire using 6-point rating scale	Preference and satisfaction. Satisfaction assessed using 7 questions including overall satisfaction on treatment outcome and medication used, convenience and difficulty in administration	Parents and children preferred oral formulation compared to the inhaler
Macdonald et al. 2003 United Kingdom and Ireland	Conventional tablets Amino acid tablets	Protein substitutes.	8-25 years Median = 15 years	Patients	Visual Analogue scale	Acceptability defined as palatability, smell, ease of swallowing and gastrointestinal intolerance.	In phase A patients scored mean-57, in phase B where the amino acids made up 40% of the protein substitute patients scored mean 82. 70% patients preferred the amino acid tablets.
Mekmullica et al. 2003 Thailand	Coated capsules	Typhoid vaccine	4-12 years old	Children	Observation	Success defined as subjects being able to swallow all three capsules.	Success rates 84.4% - 100% dependant on age.
Pakalnis et al. 2003 United States	Nasal spray	Sumatriptan	5-12 years	parents	Questionnaire	Satisfaction (not defined). Tolerated (not defined).	Bad taste, difficulty in use and off-label use all noted as concerns.
Coleman et al. 2002 United Kingdom	Tablet	Micronutrients	1-16 years	Children Family	Likert scale 1 (liked)-7(disliked)	Opinion about medication: Appearance. Smell. Texture. Taste.	Smaller tablets were generally swallowed, larger tablets generally chewed

						Size. Acceptability.	
Patchell et al. 2002 United Kingdom	Creon 10,000 vs Creon 8000	Panceatic enzyme replacement	3-17 years	Children	Questionnaire	Preference with reference to ease of swallowing, presence of an aftertaste and feeling of fullness after taking the medicine.	87% preference for creon 10,000
Brand et al. 2001 The Netherlands	Spacer devices	Nebuchamber vs babyhaler	6-59 months	Parents	Diary and visual analogue scale to answer certain questions	Overall preference and acceptability of child (not defined).	Parents preference on acceptability of nebuchamber in older children but not younger. No statistically sig differences on VAS scores for two treatments.
Kendall et al. 2001 United Kingdom	Nasal spray	Diamorphine vs intramuscular (IM) morphine	3-16 years	Children Parents Staff	Wong Baker facial pain scale. Visual analogue (or OR both). Observation	Patient's reaction defined as no obvious discomfort, mild reaction, winced or withdrew, cried, screamed. Acceptability defined as acceptable, stressful, very stressful or unacceptable	Patients reacted worse to the IMr treatment compared to nasal spray. 80% showed no discomfort with nasal spray compared to 9% of IM. Acceptability significantly greater with spray than IM treatment. Judged as 'acceptable' in 98% patients in spray compared to 32% in IM by staff. Judged as acceptable in 97% cases for spray and 72% in IM for parents. Patients prepared to have the treatment again (94% for spray and 59% for IM).
Kraus 2001 United States	Liquid formulation. Medibottle vs oral syringe.	Acetaminophen (Tempra syrup)	2-14 months	Independent healthcare raters.	Validated infant medication acceptance scale (MAS)	Rated on five behavioural elements: cry, facial expression, body movement or level of agitation, reaction to placement	Medibottle had advantages over oral syringe. Infants showed greater acceptance of medibottle with

						of drug in the mouth, and swallowing of drug.	higher MAS scores (9.0 compared to 7.5).
Weinberg & Naya 2000 South Africa	Tablets vs inhaler.	Zafirlukast and inhaled beclomethasone dipropionate.	12-17 years	Children	Questionnaire.	Preference and ease of use (not defined).	70% children preferred tablets. Reasons being ease of use (71%)
Moniot-ville et al. 1998 France	Oral suspension	Roxithromycin.	2-8 years	Researcher	Observation. 6-point scale.	Acceptability defined as child smiling or without making a face.	Acceptability was good, fairly good or acceptable in 70.5% children
McCrindle et al. 1997 Canada	Tablets. Powder.	Cholestyramine.	10-18 years	Children	Logbook.	Ease of use. Compliance (% of expected medication amount actually taken during the study interval).	Form of the medication increased compliance by 25% in 42% of participants. 13 favoured pills and 3 favoured powder.
Dagan et al. 1994 Israel	Oral suspensions	Antibiotics	18-22 months	Parents	Three or five-point scales.	Acceptability (not defined). Acceptance defined as willingness to swallow and occurrence of vomiting. Satisfaction defined as extremely satisfied and satisfied on the scale.	Percentage satisfaction was reported as 89% amoxicillin, 81% trimethoprim, 74% sulfamethoxazole and 67% cefuroxime axetil.
Cloyd et al. 1992 United States	Sprinkles vs syrup	Valporate	5-16years	Parents Children	Questionnaires.	Preference.	75% of parents and children preferred sprinkles to syrup

Babbitt 1991 United States	Oral capsules	Range of prescribed medications	3.5-17.5 years	Parents	Observation. Parent satisfaction ratings.	Acceptance.	Swallowing skill acquisition clinically significant to treatment acceptance
Sjovall et al. 1984 Finland	Suspension or syrup	Penicillin	3-12 years	Children	5-point FHS. Own spontaneous judgement.	Taste Preference	Younger group less able to discriminate between formulations than older group. In group younger than 6 years it was concluded that the FHS could not be used to discriminate between formulations as the results were similar for all tests. Older children able to discriminate in both verbal and scale methods.

2.4.4 Concept of acceptability assessment

2.4.4.1 Acceptability definitions

Although all papers in this review aimed to evaluate the acceptability of formulations in paediatric populations, 22 papers used 'acceptability' or 'acceptance' as an outcome measure (Babbit, 1991; Dagan, 1994; Moniot-ville, 1998; Kendall, 2001; Brand, 2001; Coleman, 2002; MacDonald, 2003; Beck, 2005; Nasrin, 2005; Araposthathis, 2010; Strehl, 2010; Rodd et al, 2011; Spomer et al, 2012; Amirav, 2014; Ogutu, 2014; Kluk, 2015; Ranmal, 2016; Mulla, 2016; Venebles, 2016; Angwa et al, 2020; Klingmann et al, 2020; Giralt et al, 2019). Even within these 22 papers, a common definition of acceptability was not applied. Ten papers provided definitions or criteria to assess 'acceptability' but these definitions widely varied (Table 2.2). Criteria included "no rejection" (Amirav, 2014), "child smiling" (Moniot-ville, 1998) and "swallowed with ease" (Kluk, 2015); four definitions included the word 'willingness' (Dagan, 1994; Rodd, 2011; Ranmal et al, 2016; Angwa et al, 2020). Two of the 64 papers defined 'acceptability' as the "ability and willingness to take the formulation" (Rodd, 2011; Ranmal, 2016), and one paper used "willingness to swallow" (Moniot-ville, 1998).

Table 2.4: Summary of acceptability definitions

Author (year)	**Acceptance/Acceptability definition**
Dagan (1994)	"willingness to swallow" and "occurrence of vomiting"
Moniot-ville (1998)	"child smiling" or "without making a face"
Beck (2005)	"child allowed pill to be in the mouth"
Rodd (2011)	"ability and willingness to take formulation"
Spomer (2012)	"swallowing" and "chewing and subsequently swallowing"
Ranmal (2016)	"ability and willingness to take formulation"
Amirav (2014)	"no rejection"
Kluk (2015)	"swallowing with ease"
Giralt et al (2019)	"formulation easier to administer and store"
Klingmann (2018)	"an aggregate of the evaluation criteria: everything swallowed or chewed and swallowed"
Angwa (2020)	"perception of taste" and "willingness of caregivers to use"

Given that acceptability is understood to be a multi-dimensional construct, the majority of papers used a variety of outcome measures to assess acceptability (see Table 2.4). In thirty-six papers, two or more terms were used to assess acceptability (i.e. a combination of terms presented in Table 2.5). Four papers did not define any criteria or provide a definition about the assessment used to evaluate the acceptability of the formulation. The most common alternative assessment terms were preference,

amount swallowed/swallowability, ability to use/usability, and taste (Table 2.5). Patient preference, for example, is an individual's evaluation of a specific element (in this case, formulation) over another element, and can only be used when more than one product is being assessed. Whilst there is an argument for the use of patient preference in health care decision making (Bryson, 2014), this will only provide the relative comparison rather than the actual acceptability of the formulation. Whilst factors such as 'swallowability' and 'usability' should be evaluated as part of acceptability assessment, it should be recognised that these factors alone cannot provide the full extent of acceptability.

Table 2.5: Alternative acceptability terms

Outcomes used to measure domain of acceptability	**Frequency of use in papers**	**Author/year**
Preference	23	Klingmann et al (2017); van Riet-Nales et al (2012); Kekitiinwa et al (2016); Herranz et al (2006); Musiime et al (2014); Block et al (2006); Sjovall et al (1984); Cloyd et al (1992); Lottman et al, (2007); Macdonald et al (2003); Ogutu et al (2014); Munck et al (2008); Jagani et al (2016); Nahirya-Ntege et al (2012); Rodd et al (2011); Valorvita et al (2009); Patchell et al (2002); Weinberg et al (2000); Bukstein et al (2003); Lloyd, et al (2011); Venebles et al (2016); Brand et al (2001); Arapostathis et al (2010); Bryson et al, (2014); Hofmanova et al (2020).
Amount swallowed/ swallowability	9	Klingmann et al (2017); Musiime, et al (2014); Lopez et al (2018); Coleman et al (2002); Jagani, et al (2016); Thompson et al (2009), Kluk et al (2015); Dagan et al (1994); Purchase et al (2019); Klingmann et al (2018); Patchell et al (2002); Hofmanova, et al (2020); Klingmann, et al (2020).
Ability to use/ usability	7	Lopez et al (2018); McCrindle et al,(1997); Lottman et al (2007); Ogutu et al (2014); Ranmal et al (2016); Weinberg et al (2000); Cadwgan et al (2017); Angwa et al (2020); Hofmanova, et al (2020.
Taste	6	Musiime et al (2014); Sjovall (1984); Cohen et al (2005); Coleman et al, (2002); Jagani et al (2016); Patchell et al (2002); Angwa et al (2020); Hofmanova et al (2020).
Child facial expression/ behaviour	6	Blume et al (2018); Medeiros et al (2016); Beck (2005); Rodd et al. (2011); Nasrin et al (2005); Kendall et al (2001); Ruiz et al (2020).
Satisfaction	6	Strehle et al (2010); Akhavan-Karbasi (2010); Dagan (1994); Orlu (2017); Bukstein et al (2003); Cadwgan et al (2017).
Reported problems	5	Kekitiinwa et al (2016); Bukstein (2003); van Riet-Nales et al (2012); Kendall et al (2001); Blume et al (2018).

Adherence to treatment	4	Cristofides (2005); Giralt (2017); Orlu, (2017); Strehle (2010).
Ease of administration	3	Block (2006) et al; Geltman (2009 et al); Verrotti et al. et al (2011).
Willingness to take	3	Cohen et al (2005); Dagan (1994); Ranmal et al (2016); Angwa, et al (2020).
Tolerability	3	Verrotti et al. (2011); Cadwgan et al (2017).
Successful administration	2	Ogutu et al (2014); Geltman et al (2009).
Compliance	2	Lottman et al (2007); Macdonald et al (2003).
Palatability	1	Verrotti et al. (2011), Klingmann et al (2020).
Time taken	1	Ruiz et al (2020).

2.4.4.2 Formulation factors influencing acceptability

Overall acceptability is reported to be 'multidimensional'; the combination of several factors including palatability, swallowability, ease of administration, appearance, smell, administration device and convenience of administration (Ruiz et al, 2020). Therefore, whilst some alternative terms may reflect an overall evaluation of the product, some (swallowability, usability, taste and palatability) are individual factors that cannot accurately provide an overall acceptability measure. Therefore, focussing on only one or two of these in the evaluation of paediatric medicines fails to account for the complexity of acceptability (Vallet, et al 2017; Kozarewicz, et al 2014; Ranmal et al, 2016), and will provide incomplete acceptability assessments.

Three of the alternative assessment factors (swallowability, taste and palatability), which account for almost a third of the outcome threshold levels used to assess acceptability, are specific to oral formulations and would not be meaningful if used in non-oral formulations. Consequently, whilst the EMA (2013) has defined acceptability, the implementation of this definition in the actual acceptability assessment of medicinal formulations has not been reported in twenty-two papers included in this review that were published after the definition was established (EMA, 2013). The criteria used to determine acceptability varies both between and within studies on oral and non-oral formulations and therefore it seems that the concept of 'acceptability' is open to interpretation.

Within all 64 studies different stakeholders provided acceptability assessments; parents/caregivers were the most commonly used assessor (n=22 studies) (Rodd et al, 2011; van Riet-Nales, 2012; Kekitiinwa, 2016; Musiime, 2014; Blume, 2018; Block, 2006; Giralt, 2017; Geltman, 2009; Ogutu, 2014; Akhavan-Karbasi, 2010; Munck, 2008; Babbitt, 1991; Nahirya-Ntege, 2012; Nasrin, 2005; Dagan, 1994; Valovirta,

2009; Lloyd, 2011; Pakalnis, 2003; Amirav, 2014; Brand, 2001; Angwa, 2020; Wallace et al, 2019). Children were the primary assessor in 12 studies (Klingmann, 2017; McCrindle, 1997; Sjovall, 1984; Cohen, 2005; Lottman, 2007; Macdonald, 2003; Jagani, 2016; Mekmullica, 2003; Spomer, 2012; Patchell, 2002; Weinberg, 2000; Arapostathis, 2010).

Health care staff including nurses, clinicians and researchers in seven studies (Moniot-ville, 1998; Beck, 2005; Kluk, 2015; Thompson, 2009; Strehle, 2010; Klingmann et al, 2018; Kraus, 2001) and a combination of children, parents/caregivers, and staff in 22 studies (Angwa, 2020; Hofmanova et al, 2020; Klingmann et al, 2020; Ruiz et al, 2020; Giralt et al, 2019; Purchase et al, 2019; Bryson, 2014; Orlu, 2017; Herranz, 2006; Lopez, 2018; Cloyd, 1992; Coleman, 2002; Medeiros, 2016; Verrotti et al, 2011; Thompson, 2013; Polaha, 2008; Mulla, 2016; Ranmal, 2016; Bukstein, 2003; Venebles, 2016; Kendall, 2001; Cadwgan, 2017), and one study did not specify (Cristofides, 2005).

Although children and caregivers were almost equally likely to be asked to provide acceptability assessment, caregivers were more likely to provide the assessment for children under the age of 6 years old. Typically, children between the ages of 6-18 years old reported their own acceptability assessment. However, there were some exceptions with children aged from 4 years old providing their own feedback in some studies (Mekmullica, 2003; Ogutu, 2014; Lottman, 2007), and parents providing acceptability assessments for older children and teenagers up to <13 years old (Munck, 2008; Babbitt, 1991). Further clarification about the age at which children and adults should provide feedback on acceptability is required if acceptability testing is to be standardised.

In 10 studies (Herranz, 2006; Cloyd, 1992; Coleman, 2002; Lottman, 2007; Verrotti et al, 2011; Mulla, 2016; Ranmal, 2016; Bukstein, 2003; Venebles, 2016; Kendall, 2001) both children and caregivers provided feedback. Whilst the EMA (2013) outlines that it expects acceptability testing to be conducted in children themselves, clarification on who should provide the response to the testing is required. It should not be overlooked that the acceptability definition includes both the ability and willingness of the patient to use and their caregiver (defined as ‘user’) to administer as intended. Therefore, it

could be argued that, in children of an appropriate age and capacity where a parent/caregiver is required to administer the medicine, only the responses of both child and caregiver would provide holistic acceptability assessment. Having two acceptability end-point assessments may also reduce bias of using one method to report acceptability assessment.

2.4.4.3 Threshold of acceptability

Clarification is also required regarding what limit of acceptance of a medicine is deemed as a success or acceptable. No criteria as such exist, and information regarding at what point a formulation is classed as acceptable is missing from the studies in the review. Within the papers there was at least two ways that researchers attempted to provide a threshold for acceptability. The first way is by calculating the proportion of participants who expressed a preference or similar positive reaction to the medicine and then arbitrarily defining a threshold limit of acceptability as somewhere between 0-100%. The second is by using a scale approach, and defining the limit of acceptability as a category, so acceptability for each participant is categorised independently.

Apart from the arbitrary limit of 'preference', only sixteen studies provided information about a statistical threshold to define acceptability (Crisofides, 2005; Lottman, 2007; Strehle, 2010; Valvorita, 2009; Moniot-ville, 1998; Weinberg, 2000; Cloyd, 1992; Blume, 2018; Orlu, 2017; Mulla, 2016; Kendall, 2001; Nasrin, 2005; Dagan, 1994; Rodd, 2011; Lopez, 2018; Araposthathis, 2010). Within these sixteen studies, one study reported acceptability to be between 50%-100% adherence (Cristofides, 2005), this was the lowest accepted limit reported. Similarly, another study considered a medicine was acceptable when 55.7% of their participants expressed a preference for it (Lottman, 2007). Conversely, Strehle (2010), reported that 56% of midwives reported the treatment to be "unacceptable", this was the only study to report the unacceptability as opposed to the acceptability of a treatment.

One study considered 65% to be acceptable (Valvorita, 2009), whereas the remaining 12 studies considered a preference of 70% or above to be acceptable. Both Moniot-ville (1998) and Weinberg (2000) reported that 70% of children had a preference, after these four studies reported percentages of 75%-78% acceptance (Cloyd, 1992;

Blume, 2018; Orlu, 2017, Mulla; 2016). The remaining six papers judged acceptability as between 80% and 100% (Kendall, 2001; Nasrin, 2005; Dagan, 1994; Rodd, 2011; Lopez, 2018; Araposthathis, 2010).

Alternatively, twelve studies used the point score or faces on the scales as a way to measure acceptability. On the 7-point scales (Thompson, 2013; Medeiros, 2016), a score of 4 or above, typically including the middle or neutral point/face e.g. “indifference” (Medeiros, 2016) was regarded as an acceptable score by the researchers. Similarly, on the 6-point scales, scores of 3 and above, i.e. “somewhat satisfied” (Bukstein, 2003), or “okay” (Moniot-ville, 2016) were regarded as acceptable. The 5-point scales provided slightly more variance, with five studies (Cohen, 2008; Mulla, 2016; Orlu, 2017; Ranmal, 2016; Hofmanova et al, 2020) regarding scores 3-5 as acceptable, including one study which further grouped these into a “neutral” score (3), and a “positive score” (4, 5) (Ranmal, 2016). However, one study (Sjovall, 1984) only acknowledged a score of 4 or 5 to be acceptable. Two studies (Lopez, 2018; Verrotte, 2016) did not specify which scores they recognised as acceptable. Going forward, researchers should provide a rational for the reason they have decided which point or response equates to acceptability, and a universally agreed minimum level of acceptability would assist researchers in the reporting of their acceptability studies.

2.4.5 Factors affecting the acceptability of children’s medicine

2.4.5.1 Participant characteristics: age

Articles were included in the review if the age of the study participants were children aged between 0 and <18 years; one study focussed specifically on neonates <4.3 weeks (Rodd et al, 2011); and 38 studies spanned across at least two age groups (Table 2.6). Seven of these studies reported that they further subdivided these age groups during data collection (Klingmann et al, 2017, Ogutu, 2014, Lopez, 2018; Ruiz et al, 2020; Klingmann et al, 2018; Angwa, 2020; Hofmanova, 2020). Two of the studies included in this review included participants over the age of 18 years; 8-25 years (Macdonald, 2003), the findings that could be isolated for <18 year olds from these studies were included, one paper did not specify ages but reported they were children (Polaha, 2008).

Despite the age guidelines issued by the WHO (2007) which sub-divides the paediatric population based on pharmacokinetic characteristics, practicality and age preferences, it is clear that almost half of studies did not stratify their sample in line with these guidelines. Whilst this may not necessarily have an impact on the administration of drugs (as the majority of drugs are administered on a weight basis), the acceptability and appropriateness of a formulation will almost certainly be influenced by the variability observed across ages, including child development, ease of administration and patient/care giver adherence (WHO, 2007). Therefore, the results from the papers which assessed acceptability across more than one age group, particularly those ranging from newborn/infants, may not provide an accurate representation of the acceptability of the product in each individual age sub-group.

Table 2.6 Participants' age range

Age	**Number of studies**	**Author**
Newborn/neonate/<4weeks	1	Rodd et al (2011)
Infant 0-23 months	9	Dagan (1994); Strehle (2010); Blume (2018); Amirav (2014); Munck (2008); Cristofides (2005); Geltman (2009); Klingmann et al (2020); Kraus, (2001).
Child 2-12 years	21	van Riet-Nales (2012); Kluk (2015), Thompson, 2009; Nahirya-Ntege (2012); Cadwgan (2017), Lopez (2018), Araposathis (2010), Verrotti et al (2011); Thompson (2013); Ranmal (2016); Bukstein, (2003); Cohen (2005); Beck (2005); Mekmullica (2003); Lloyd (2011); Pakalnis (2003); Giralt (2017); Angwa (2020); Hofmanova, (2020); Bryson, (2014); Cohen, (2009).
Adolescent 12-18 years	1	Weinberg (2000)
Infant to child	14	Spomer (2012); Klingmann (2017); Orlu (2017); Block (2006); Moniot-ville (1998); Akhavan-Karbasi (2010); Nasrin (2005); Sjovall (1984); Ogutu (2014); Medeiros (2016), Valovirta (2009); Purchase et al, (2019); Wallace et al (2019); Klingmann et al (2018).
Infant to adolescent	6	Kekitiinwa (2016); Musiime (2014); Coleman (2002); Venebles (2016); Brand (2001); Ruiz et al, (2020).
Child to adolescent	10	Herranz (2006); McCrindle (1997); Cloyd (1992); Lottman (2007); Macdonald (2003); Babbitt (1991); Jagani (2016); Patchell (2002); Kendall (2001); Mulla (2016).
Not stated	2	Polaha (2008); Giralt et al (2019).
Total	64	

2.4.5.2 Participant characteristics: disease status

Acceptability of formulations is also likely to be influenced by disease status. Studies that included both healthy volunteers and patients were included in this review. In the reviewed papers, patients were enrolled from a range of pathologies, including asthma, arthritis and outpatient wards. In future studies where patients are all or part of a study population, the patient characteristics should be reported to at least disease level. Healthy volunteers evaluating the acceptability of formulations (either placebo/vitamin) accounted for participants in 12 studies (Klingmann, 2017; Orlu, 2017; van Riet-Nales, 2012; Cristofides, 2005; Macdonald, 2003; Thompson, 2009; Rodd et al, 2011; Strehle, 2010; Spomer, 2012; Nasrin, 2005; Klingmann et al, 2018; Bryson, 2014). In 49 studies, samples comprised volunteers/patients already taking medicine, testing both active and placebo formulations (Pakalnis et al, 2003; Cohen et al, 2009; Ogutu et al, 2014; Kekitiinwa, 2016; Herranz, 2006; Musiime, 2014; Blume, 2018; Block, 2006; Giralt, 2017; McCrindle, 1997; Sjovall, 1984; Cohen, 2005; Cloyd, 1992; Coleman, 2002; Geltman, 2009; Lottman, 2007; Moniot-ville, 1998; Medeiros, 2016; Akhavan-Karbasi, 2010; Verrotti et al, 2011; Munck, 2009; Beck, 2005; Jagani, 2016; Kluk, 2015; Thompson, 2013; Polaha, 2008; Nahirya-Ntege, 2012; Mekmullica, 2003; Dagan, 1994; Mulla, 2016; Valorvita, 2009; Patchell, 2002; Weinberg, 2000; Bukstein, 2003; Lloyd, 2011; Venebles, 2016; Amirav, 2014; Kendall, 2001; Cadwgan, 2017; Brand, 2001; Arapostathis, 2010; Angwa et al, 2020; Hofmanova et al, 2020; Klingmann et al, 2020; Ruiz et al, 2020; Giralt et al, 2019; Purchase et al, 2019; Wallace et al, 2019; Kraus, 2001). Three studies did not define patients' disease status or treatment administered (Lopez, 2018; Babbitt, 1991; Ranmal, 2016).

The EMA has stated that it is preferable for acceptability studies to be conducted in the most relevant patient population as part of clinical trials (Kozarewicz, 2014). Additionally, testing the acceptability of a medicine that a patient has already been prescribed may increase the real-world application to the medicine. Therefore, those studies which test in a clinical population and are representative of the population the formulation is targeted to, may provide better validity. However, that is not to say that testing in a non-clinical sample is not beneficial; the testing of new, prospective formulations is necessary to develop and improve on existing products and formulations. Similarly, some aspects of acceptability, such as the size of a tablet could

be considered as disease-agnostic, and therefore there is merit in studying in 'healthy' children too.

2.4.5.3 Formulation factors: type of formulation

All papers included in this review measured the acceptability of medicines, both oral and non-oral, in a paediatric population. Twelve studies focussed solely on or compared the acceptability of non-oral formulations, five of these studies compared non-oral formulations with oral formulations including patch vs liquid (Cadwgan, 2017); patches vs tablets (Lloyd, 2011); tablets vs inhalers (Bukstein, 2003; Weinberg, 2000); gel vs injection vs needless-device (INJEX) (Arapostathis, 2010) and the remaining studies assessed/compared only non-oral formulations including vaccines, inhalers, rectal administrations, nasal spray, and spacer devices (Brand, 2001; Kendall, 2001; Amirav, 2014; Pakalnis, 2003; Venebles, 2016; Kraus, 2001; Wallace et al, 2019). Fifty-one studies evaluated the acceptability of oral dosage formulations, the most common being tablets, suspensions, dispersible tablets, films, and syrups. Of these 51 studies, 25 of them assessed the acceptability of one dosage form (Cohen et al, 2009; Hofmanova, 2020; Orlu, 2017; Herranz, 2006; Blume 2018; Lopez, 2018; Cristofides, 2005; Block, 2006; Giralt, 2017; Cohen, 2005; Coleman, 2002; Moniot-ville, 1998; Babbitt, 1991; Beck, 2005; Kluk, 2015; Thompson, 2009; Thompson, 2013; Mekmullica, 2003; Nasrin, 2005; Dagan, 1994; Strehle, 2010; Patchell, 2002; Ranmal, 2016; Purchase, 2019; Giralt, 2019), whereas 26 evaluated or compared two or more types of dosage form such as film vs syrup or dispersible tablet vs suspension etc (Akhavan-Karbasi et al, 2010; Medeiros et al, 2016; Ogutu et al, 2014; Angwa, 2020; Klingmann, 2017; van Riet-Nales, 2012; Kekitiinwa, 2016; Musiime, 2014; McCrindle, 1997; Cloyd, 1992; Geltman, 2009; Lottman, 2007; MacDonald, 2003; Verrotti et al, 2011; Munck, 2008; Jagani, 2016; Polaha, 2008; Nahirya-Ntege, 2012; Rodd et al, 2011; Mulla, 2016; Spomer, 2012; Valorvirta, 2009; Bryson, 2014; Klingmann et al, 2018; Ruiz et al, 2020; Klingmann, 2020).

The types of formulations assessed in acceptability studies will have an influence on the assessment criteria used, for example studies that compared more than one medicine typically used preference (Klingmann, 2017; van Riet-Nales, 2012) to evaluate acceptability, whereas studies that investigated tablet size or palatability generally opted to use swallowability (Lopez, 2017; Jagani, 2016). The formulation

type will impact on the criteria used to assess the acceptability of the medicine product. Therefore, this limits the extent to which acceptability can be compared within or across studies.

2.4.6 Acceptability assessment measures and approaches

The methods used to measure the acceptability of formulations varied widely in this review. The following section will provide a general outline of the prevalence of each method identified, followed by a more comprehensive overview of the most common assessment methods used.

Overall, 19 different methods for assessing the acceptability of medicines in children were identified across the 64 papers. The most common methods were patient or caregiver preference, observations, questionnaires and scale methods (Table 2.6). Preference was reported in 24 studies; of these, reports were made by parents in eight studies (Kekitiinwa, 2016; Brand, 2001; Ogutu, 2014; Munck, 2008; Nahirya-Ntege, 2012; Rodd et al, 2011; Valovirta, 2009; Lloyd, 2011), by children in eight studies (Klingmann, 2017; Macdonald, 2003; Patchell, 2002; Ranmal, 2016; Weinberg, 2000; Arapostathis, 2010; Sjovall, 1984; Hofmanova, 2020) and by parents and children together in eight studies (Cloyd, 1992; Lottman, 2007; Bukstein, 2003; Venebles, 2016; Cadwgan, 2017; Herranz, 2006; Kekitiinwa, 2016; Bryson, 2014).

In 22 studies, 'preference' was paired with at least one other assessment method, including: questionnaires (Cadwgan, 2017; Valovirta, 2009; Nahirya-Ntege, 2012; Rodd, 2011; Bryson, 2014), visual analogue scales (Van-Riet Nales, 2012; Brand, 2001; Akhavan-Karbasi, 2012; Lottman, 2007; Macdonald, 2003), Facial Hedonic Scales (Verrotte, 2011; Jagani, 2016; Hofmanova et al, 2020); observations (Rodd, 2011) and self-report diary methods (Lloyd, 2011; Jagani, 2016). In six papers (Herranz, 2016; Sjovall, 1984; Cloyd, 1992; Munck, 2008; Arapostathis, 2010; Kekiniitwa, 2016) preference was used as a lone method of assessment. In 16 papers (Van Riet-Nales, 2012; Kekitiinwa, 2016; Sjovall, 1984; Cloyd, 1992; Lottman, 2007; Macdonald, 2003; Munck , 2008; Jagani, 2009; Nahirya-Ntege, 2012; Valovirta, 2009; Weinburg, 2000; Bukstein, 2003; Lloyd, 2011; Venebles, 2016; Cadwgan, 2017; Arapostathis, 2010) preference was used to assess the acceptability of one dosage

form over another e.g. intradermal patch vs liquid (Cadwgan, 2017) or tablets vs patches (Lloyd, 2011). In two papers (Patchell, 2002; Brand, 2001), preference was used to evaluate two different types of the same formulation (for example, in Brand's (2001) study the comparison was between inhaler spacer devices (Nebuchamber vs Babyhaler). The remaining paper asked participants to evaluate preference between a new sustained release tablet compared to their typical medication (Herranz, 2006). Questionnaires were also commonly used as a method of acceptability testing in 19 papers. Specific questionnaires such as the 'Treatment Satisfaction Questionnaire for Medication (TSQM)' (Cadwgan, 2017), and the 'Medicine Acceptance Scale (MAS)' (Kraus, 2001; Polaha, 2008; Orlu, 2017) were used. These are discussed in section 2.4.6.6. One online questionnaire used a discrete choice experiment approach to explore factors that affected the health-related quality of life in children with ADHD (Lloyd, 2011). Similarly, the Caregiver Vaccine Acceptance Scale (Wallace, 2019) was used to elicit caregiver attitudes and beliefs. Studies which used questionnaires were most likely to ask parents to complete them alone (n=11 studies) (Valorvirta, 2009; Pakalnis, 2003; Blume, 2018; Block, 2006; Geltman, 2009; Ogutu, 2014; Akhavan-Karbasi, 2010; Nihirya-Ntege, 2012; Rodd et al, 2011; Angwa, 2020; Wallace et al, 2019). This was followed by parents and children completing together (n=7 studies) (Herranz, 2016; Cloyd, 1992; Cadwgan, 2017; Bukstein, 2003; Mulla, 2016; Ranmal, 2016; Hofmanova, 2020), children alone (n=2 studies) (Weinberg, 2000; Patchell, 2002) and parent and researcher or researcher alone (n=2 studies) (Orlu, 2017; Medeiros, 2016). In six studies, questionnaires were used as the sole instrument to measure acceptability (Nahirya-Ntege, 2012; Cloyd, 1992; Geltman, 2009; Ogutu, 2014; Strehle, 2010; Pakalnis, 2003) but they were coupled with preferences in six other studies (Kekinittawa, 2016; Valorvirta, 2009; Patchell, 2002; Ranmal, 2016; Nasrin, 2005; Lloyd, 2011). Finally, scale methods such as Facial Hedonic scales (Cohen, 2008; Orlu, 2017) and Likert scales (Rodd, 2011) were used alongside questionnaires to measure acceptability. The remaining questionnaires were all developed for the purpose of the individual studies, and had different 'acceptability' end points, for example, the questionnaire developed by Bukstein et al (2003) measured 'preference' as a primary outcome for acceptance.

Finally, observations were also used as a method of acceptability assessment and were typically undertaken by parents (n=8 studies) by observing children's behaviour

and facial expressions (van Riet-Nales, 2012; Musiime, 2014; Blume, 2018; Giralt, 2017; Babbitt, 1991; Rodd et al, 2011; Amirav, 2014; Angwa, 2020) or healthcare staff (n=10 studies) (Orlu, 2017; Lopez, 2018; Moniot-ville, 1994; Medeiros, 2016; Beck, 2005; Kluk, 2015; Thompson, 2009; Hofmanova, 2020; Klingmann, 2020; Klingmann et al, 2018). In six papers, observations were used as a lone method of assessment (Amirav, 2014; Spomer, 2012; Klingmann, 2017; Klingmann, 2018; Kluk, 2015; Thompson, 2009). They were also used alongside other assessment methods, including; Visual Analogue Scales (VAS) (Kendall, 2001; Orlu, 2017), Facial Hedonic scales (Blume, 2018; Lopez, 2018; Moniot-ville, 1998); Cohen, 2008); and Feedback/Preferences (Giralt, 2017; Musiime, 2017; Babbit; 1991). In four studies, (Orlu, 2017; Lopez, 2018; Ruiz et al; 2020; Giralt et al, 2019) observations from health-care staff were used alongside caregiver observations. See section 2.4.6.4 for further details on observations.

Table 2.7: Frequency of acceptability measurements

Method or instrument for data capture	**Frequency**
Observation	27
Preference	22
Questionnaires	24
Online	1
Treatment satisfaction questionnaire measurement (TSQM)	2
Medicine Acceptance Scale (MAS)	3
Caregiver Vaccine Acceptance Scale	1
Facial Hedonic Scale	
3 point	1
5 point	9
6 point	3
7 point	2
Visual Analogue Scale	
100mm	6
Likert Scale	
5 point	3
7 point	1
10 point	1
Baker Wong Pain scale	1
Verbal self-report (child)	4
Diary/Logbook (completed by child)	4
Interview	
With child	3
With adult	1
With both	5

2.4.6.1 Preferences

Preferences were a common method used to evaluate how acceptable a formulation was in the review. Twenty-two studies (Van Riet-Nales, 2012; Kekitiinwa, 2016; Herranz, 2006; Sjovall, 1984; Cloyd, 1992; Lottman, 2007; Macdonald, 2003; Munck, 2008; Jagani, 2009; Nahirya-Ntege, 2012; Rodd et al, 2011; Valovirta, 2009; Patchell, 2002; Weinberg, 2000; Bukstein, 2003; Lloyd, 2011; Brand, 2001; Cadwgan, 2017; Arapostathis, 2010; Venebles, 2016; Hofmanova, 2020; Bryson, 2014) used preferences of both parents and/or children to provide part, or all, of the assessment of the medicinal products. Preference has previously been found to be closely related to adherence of treatment in children. The Children's Medication Preferences (CHIMP) study (Bryson, 2014) conducted at Alder Hey Children's Hospital reported that choice (preference) of a formulation and associated factors have an influence on medication acceptability due to the premise that one formulation will not suit all children. Preference was found to be highly associated with medicine acceptance in children when they were given the choice, provided that an acceptable option was available (Bryson, 2014).

In the current review, preferences were used as the endpoint or sole measure of evaluating the acceptability of a formulation in twelve of the 22 studies that used preferences. Five of these had parents or caregivers provide their own preference or their child's perceived preference (Munck, 2008; Nahirya-Ntege, 2012; Valorvita, 2009; Lloyd, 2011; Brand, 2001). Three studies used the preference of the child and their parents (Musiime, 2014; Cloyd, 1992; Bryson, 2014), and three studies used the preference of the children alone (Herranz, 2006; Patchell, 2002; Hofmanova, 2020). The remaining studies used preferences along with other evaluation end-points including the ease of use of the formulation (Lottman, 2007; Weinberg, 2000); compliance to treatment (Lottman, 2007; Macdonald, 2003), acceptance (Rodd, 2011; Ranmal, 2016; Arapostathis, 2010); satisfaction (Bukstein, 2003; Block, 2006), and appropriateness (Venebals, 2016), swallowability (Jagani, 2016; Kekitiinwa, 2016).

Ultimately, preference has been demonstrated to distinguish between formulation type within a trial (tablet type/liquid type) (van Riet-Nales, 2012), alternative existing formulations (a new sustained release tablet compared to the typical tablet used to treat the children (Herranz, 2006), taste of oral formulations (Block, 2006), size of oral

tablet (Valovirta, 2009), oral vs non-oral routes (Weinberg, 2000; Lloyd, 2011), and between injection type (Arapostathis, 2010). This provides evidence that this method of assessment is useful and can account for the range of formulation factors and individual differences in children.

Preferences were reported for oral formulations when compared with inhalers in two studies (Bukstein, 2003; Weinberg & Naya, 2000), reasons given were ease of use. Whereas preference was reported for other non-oral formulations, such as patches (Lloyd et al, 2011). Similarly, preference was marginally higher for alternative oral dosage forms such as filmstrips (Rodd et al, 2011) and melt formulations (Lottman et al, 2007) when compared with tablets, this was found to be reflective of compliance with treatment with higher percentages found for alternatives over tablets (Lottman et al, 2007). Parental preference differed depending on a number of factors, preferences were found to be variable depending on the country where the study was conducted e.g. preference was found to be 26% in Netherlands and 65% Spain (Valorvirta & Scadding, 2009) between ODT's and oral solutions, this could be due to cultural differences. Similarly, the age of the child seemed to influence parents' preference for formulation (Brand, 2001; Lottman, 2001). This could be due to the influence of parents' perceptions or beliefs relating to their child's age and their child's abilities to take different formulations. In one study parents/caregivers were asked to report which formulation (syrup vs tablet) they expected themselves and their children to prefer. Seventy four percent of caregivers expected to prefer tablets, but only 27% expected their children to prefer tablets. Following the study, parents were again asked to report which formulation they preferred, 94-97% of parents expressed a preference for tablets, and reported that 57-59% of their children preferred tablets (Nahirya-Ntege et al, 2012). This is something that should be considered when parents are asked to provide acceptability assessments as proxy. Past experience, understanding and perceptions will all impact parents' beliefs about the age at which children can, or should, take different medications.

2.4.6.2 Facial Hedonic Scale (FHS)

Hedonic scales refer to the pleasure or the perception of pleasure, of a given substance or experience. Researchers may select hedonic scales based on characteristics of their target population, for example, the details on the face (gender,

colour of hair or skin) and/or the number of faces to choose from. Also, the wording of the anchor phrases (the words used beneath categories or anchors on scales to explain what they relate to) can be selected dependent on the target population. Hedonic scales differed between studies on a number of aspects, e.g. number of points, faces used, facial expressions, colours, and the anchors/phrases included. A 5-point scale was the most common scale (n=9 studies) (Dagan, 1994; Cohen, 2005; Mulla, 2016; Lopez, 2018; Verrotti, 2011; Strehle 2010; Orlu, 2017; Ranmal, 2016; Hofmanova, 2020), 7-point scales were used in two studies (Thompson, 2009, Medeiros, 2016), 6-point scales were used in three studies (Moniot-ville, 1998, Jagani, 2016; Bukstein, 2003), and 3-point scales were used in one study (Dagan, 1994) (see Table 6). A 5-point hedonic scale was used with children as young as 3 (Orlu et al, 2017) and 4 years old (Hofmanova, 2020; Cadwgan et al, 2017).

Eleven studies in the review used a 'faces' scales and, of these, 7 used a simple emoji-based image (Cohen, 2005; Mulla, 2016; Lopez, 2018; Jagani, 2016; Bukstein, 2003; Ranmal, 2016; Thompson, 2009), and one used a more realistic drawing of a child's face (Medeiros, 2016), three papers only explained the scale and no further details regarding the images on the scale are available (Hofmanova, 2020; Strehle, 2010; Moniot-ville, 1984). Figures 2.3 a-f show a selection of ‘faces’ used in some of the studies. When focusing solely on the emoji-based faces there are considerable differences between the characteristics of the faces. Although all faces include eyes and a mouth, some also include a nose, eyebrows, hair, hands, tears and all have slightly different expressions or intensity of expression (such as degree of downturn of the mouth). Some include other elements such as 'thumbs up and down' and noses being held to suggest distaste. The more realistic faces portray gender specific features. None of the studies provided information on how these faces/facial expressions or the accompanying text were chosen, and it is unclear whether any particular scale is more meaningful or relatable to children.

Figure 2.3 Facial Hedonic Scale (Cohen, 2008)

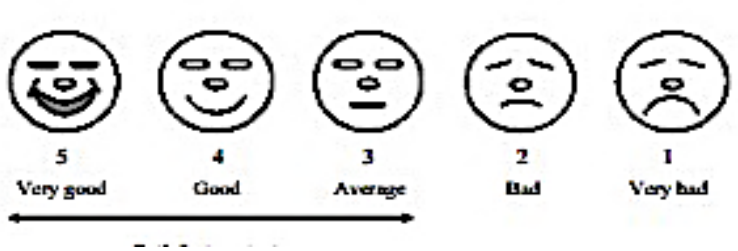


Figure 2.4: Facial Hedonic Scale (Ranmal, 2016)

Figure 2.5: Facial Hedonic Scale (portrait) (Lopez, 2018)

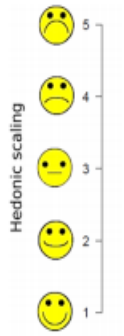


Figure 2.6: Facial Hedonic Scale (Mulla, 2016)

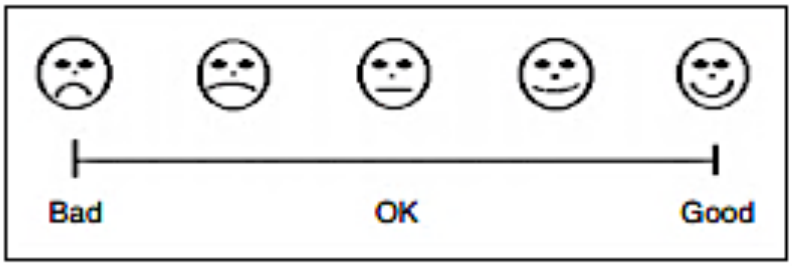


Figure 2.7: Facial Hedonic Scale (Medeiros, 2016)

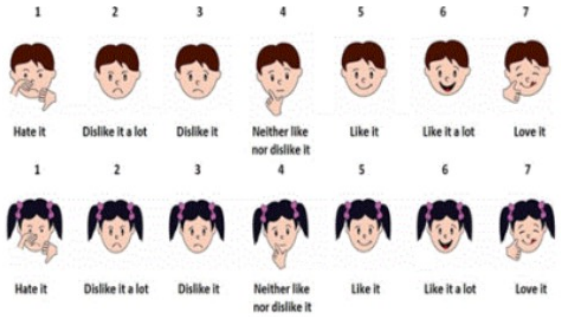


Figure 2.8: Facial Hedonic Scale (Thompson, 2013)

Different characteristics were measured across the studies (Table 2.8). Two FHS in the current review were reported as 'age-adapted' (Orlu, 2017; Ranmal, 2016). However, both studies used 5-point scales and the 'age adaptation' referred to the anchor phrases next to each face. Hedonic scales are sometimes used with 'anchor phrases' or verbal descriptors when used in child populations, this helps mitigate some of the issues with the understanding or comprehension of the interpretation of the scale. The anchor phrases used in the studies in this review were highly dependent on what the scale was measuring. For example, a scale with the 'Ease of Swallowing' as an end point for acceptability used "easy to take-not easy to take" as endpoints (Lottman et al, 2007), whereas a scale measuring 'Taste' as an endpoint, used "Very good-Very bad" (Cohen, 2008). The phrases/anchors varied widely across all of the FHS used, even when the endpoints of the scale were the same. Two of the studies used FHS to exclusively measure "overall satisfaction" (Dagan, 1994; Strehle, 2010). Even between these two studies, the terminology differed, with Strehle (2010) using "Very good (1) - Very bad (5)" and Dagan (1994) using "extremely satisfied-extremely unsatisfied".

Table 2.9: Characteristics of measures use

Author (year)	Age	Measuring	Number of points/ measurements	Anchors (words and numerical)	Level of acceptance
Facial Hedonic Scale (FHS)					
Dagan (1994)	18-22 months	Acceptance/compliance "willingness to swallow and occurrence of vomiting" "satisfaction"- defined as 'extremely satisfied/satisfied' "acceptability"- not defined	3-point/ 5-point	"pleasure" "without problems" "refusal"	"satisfaction" Above 50%
Thompson (2013)	6-12 years	Taste/mouthfeel liking	7-point	"super bad" to "super good"	Anything rated >4
Medeiros (2016)	6 years and below	Overall liking	7-point	'hate it' - 'love it'	"acceptance to indifference"- Rated points 4-7
Moniot-ville (1998)	2-8 years	Acceptability- "refusal of medication"	6-point	Bad (0) - Good (6)	Points 3-6
Jagani (2016)	6-17 years	Ease of swallowing	6-point	Not difficult (0) - most difficult (6)	% decrease before and after treatment
Bukstein (2003)	6-11 years	Patient preference, satisfaction, adherence, safety	6-point	Smiling face (6) - 'frowning face' (1)	Somewhat satisfied (3)- very satisfied (5)
Cohen (2008)	Avg. 2.9 years	Taste	5-point	Very good (5) > Very bad (1)	Points 3-5
Sjovall (1984)	3-12 years	Taste evaluation	5-point	Smiling face – unhappy face	4,5
Mulla (2016)	3-16 years	"overall acceptability"- Taste, smell, incident of vomiting, ease and willingness to take	5-point	Bad (1)- Good (5)	"okay" (3)- "good" (5)
Lopez (2018) (online)	4-12 years	Appearance, ease of swallowing, mouth-feel, taste	5-point	Extremely liked (1) - Extremely disliked (5)	Not defined
Verrotte (2016)	Avg. 6.7 years	Palatability	5-point	Not defined	Not defined
Age-adapted FHS					
Orlu (2017)	3-5 years	Whether the child liked taking the tablet Willingness to take again	5-point	Very much liked (5) - not at all (1)	Points 3-5

Ranmal (2016)	6-9 years	Liked/disliked, willingness to take again, ease/difficulty to take	5-point	Negative (1) - positive (5)	Neutral (3) - Positive score (4 + 5)
Nominal Scale (CareCAT)					
Blume (2018)	0-5 years	Swallowing	5-point	Swallows well (1) - Not taken (5)	Not defined
Visual Analogue Scale (VAS)					
Brand (2001)	6-59 months	“ease of handling spacer” “control of asthma symptoms” “overall preference”	100mm (10cm)	Not defined	Clinically relevant if the VAS score preceded 60%, Statistically significant if VAS score preceded 95%, 50% not included as it “did not show a preference”
Van Riet-Nales (2012)	1-4 years	Acceptability	100mm (10cm)	Very unpleasant (0) - not at all unpleasant (10)	Not defined
Kendall (2001)	3-16 years	Acceptability of treatment to patients	100mm (10cm)	Acceptable, stressful, very stressful, unacceptable	Not defined
Lottman (2007)	5-15 years	Safety, ease of use	100mm (10cm)	I find it very easy to take (0) - I find it very difficult to take (10)	80% compliance
Akhavan-Karbasi (2010)/ Scholnik (2002)	Avg. 6.7 years	Satisfaction of route of administration	100mm (10cm)	Not defined	Level of satisfaction was compared between patients in the two different routes of administration groups.
Macdonald (2003)	8-25 years	Efficacy, safety, ease of use	100mm (10cm)	Very easy to use (0) - very difficult to use (100)	80% compliance

Three studies (Mulla, 2016; Ranmal, 2016; Moniot-ville, 1998) presented their scales with a negative anchor such as, “very unpleasant” or “not satisfied” on the left-hand side of the scale and the positive anchor on the right. Five studies (Orlu, 2017; Lopez, 2018; Cohen, 2008; Bukstein, 2003; Jagani, 2016) presented the positive anchor/face on the left and the negative on the right. Five did not specify (Dagan, 1994; Thompson, 2013; Medeiros, 2016; Sjovall, 1984; Verrotte, 2016). Moreover, there were also differences observed between the anchor and corresponding number on the scale. Six studies (Ranmal, 2016; Orlu, 2017; Mulla, 2016; Cohen, 2008; Bukstein, 2003, Moniot-ville, 1998) presented the negative face/phrase corresponding to the lowest number on the scale (0, 1), whereas the remaining two studies (Jagani, 2016; Lopez, 2018) presented it the opposite way.

One study (Sjovall, 1984) used the hedonic scale alongside the question ‘Which one of these figures do you think has tasted this medicine?’, and the children were then asked to indicate the figure on the form. This differs from the use of the hedonic scale in other studies which ask the child to indicate *their own* liking for the medicine by using the hedonic scale to do so (Thompson, 2013). The effect of the accompanying question to the results of the FHS is still relatively under-researched, and the impact of this could be beneficial in providing best practice recommendations to industry.
There is little research or evidence regarding which scales for the acceptability of medicine assessment are preferred by or are more suitable for children, and the reliability and validity of one scale over another for children has not been tested and is still unclear. The Wong-Baker FACES Pain Rating Scale used in one study (Kendall, 2001) has been validated for use in children. However, despite the number of hedonic scales used to measure the acceptability of medicines, it is still unclear whether any scale is more valid or reliable as this information is generally missing or not reported in the papers.

2.4.6.3 Visual Analogue Scales (VAS)

Visual Analogue Scales (VASs) are presented as a horizontal line, usually 10cm (100mm), with two opposing limits on either end. In the current review all the VAS included were 100mm which provides some consistency across paediatric acceptability testing (Figure 2.4). Six VAS were used, either as the sole measure

(Macdonald, 2003), or alongside another method (Van Riet-Nales, 2012; Akhavan-Karbasi, 2012; Brand, 2001; Kendall, 2001; Lottman, 2007).

Relating to the comprehension of VAS, phrases attached to the scale should be meaningful to research participants. In the current review, four of the six studies provided accompanying phrases (Van Riet-Nales, 2012; Lottman, 2007; Macdonald, 2003; Kendall, 2001). However, two studies did not define phrases (Akhavan-karbasi, 2010; Brand, 2001) The phrases were all different and matched the purpose of each study. For example, in the study by Macdonald (2003), the phrases 'Very easy to use' to 'Very difficult to use' were employed to measure ‘Ease of Use’ of a medicinal product. Whereas 'Very unpleasant' to 'Not at all unpleasant' was used to measure the acceptability of oral dosage forms in Van Riet-Nales’ (2012) study.

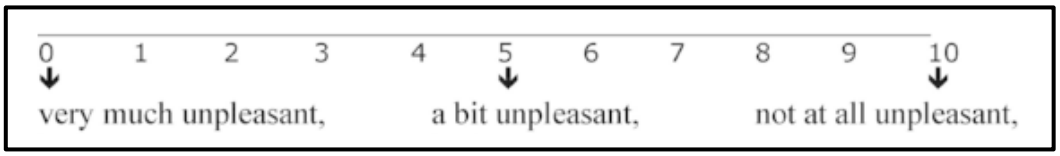


Figure 2.8: Example of Visual Analogue Scale (van Riet-Nales, 2012).

In the studies which used a VAS, two used a VAS to measure acceptability in a population group over the age of 6 years old (Akhavan-Karbasi, 2010; Macdonald, 2003), whereas the remaining four studies included children aged 5 years or younger (Brand, 2001; Van Riet-Nales, 2012; Kendall, 2001; Lottman, 2007). Only one study (Macdonald, 2003) which recruited children aged 8 years and older, relied solely on children completing the VAS with no proxy reports from parents. The remaining five studies all had parents act as proxies to complete (Van Riet-Nales, 2012; Akhavan-Karbasi, 2012; Brand, 2001; Kendall, 2001; Lottman, 2007). Whilst having parents to act as proxy reporters overcomes the issue of whether the VAS can be understood and appropriately used by a child in acceptability assessments, it further accentuates the discussion regarding whether the parent or child should be the one to provide the acceptability assessment. Studies did not report advantages or limitations of using VAS in child populations, however this is discussed in section 2.5 in context of wider literature.

In five studies, the VAS was used alongside another assessment method to evaluate acceptability (Van Riet-Nales, 2012; Akhavan-Karbasi, 2012; Brand, 2001; Kendall,

2001; Lottman, 2007). However, the study which used the VAS as a lone acceptability assessment method (Macdonald, 2003) made use of alternative outcome measures rather than the VAS scores, such as 'compliance to treatment' to assess the overall acceptability of the new formulation. Preference was used in all five of the remaining studies alongside the VAS, as well as self-report diary methods which were used in one study (Brand, 2001); observations were used in two studies (Kendall, 2001; Van Riet-Nales, 2012); verbal self-reporting was used in one study (Van Riet-Nales, 2012); and the Wong-Baker FACES Scale which was also used in one study (Kendall, 2001).

2.4.6.4 Observations

Observations of children's facial reactions, body language and/or amount of ingested product have also been used in testing the acceptability of medicines. Observations vary between studies as to who provides the observation assessment, which behaviour is observed to measure acceptability, and what observed behaviour is regarded as acceptable. Ten studies used parent observations to assess the child's acceptability of the formulation (Blume, 2018; Giralt, 2017; Amirav, 2014; Kendall, 2001; Spomer, 2012; Babbit; 1991; Cohen, 2008; Orlu, 2017; Rodd, 2011; Angwa, 2020). Eight relied on the researcher or clinician to provide the acceptability assessment from the observation (Lopez, 2018; Beck, 2005; Kluk, 2015; Thompson, 2013; Moniot-ville, 1998; Klingmann, 2018; Mekmullica, 2003; Klingmann et al, 2018). Eight studies used both caregiver and researcher observations to provide two separate acceptability assessments (Blume, 2018; Kendall, 2001; Orlu, 2017; Moniot-ville, 1998; Klingmann et al, 2020; Ruiz et al, 2020; Giralt, 2019; Purchase et al, 2019). Only two of these studies provided information regarding the coherence between the two assessors, Orlu (2017) reported that caregiver and nurse observations showed excellent agreement to a figure of 95%, however no further details were provided. Whereas Blume (2018) reported that caregiver scores marginally differed to researcher observation scores, this study also video recorded the observation which allowed the researchers to standardise the scores provided in a blinded test a week later. This found that the scores were reproduced 81% of the time between observers. Five studies used the child's facial expression/reaction to judge acceptability of the formulation (Thompson, 2013; Lopez, 2018; Moniot-ville, 1998; Kendall, 2001; Giralt, 2017). Lopez (2018) evaluated issues with the palatability of a product based on negative facial expressions, whereas Moniot-ville (1998) and Kendall (2001) evaluated

positive (e.g. a smile) and negative facial expressions to assess the acceptability of a formulation. Seven studies observed the child's ability to swallow, or swallowability of, a formulation as an outcome measurement for acceptance (Kluk, 2015; Orlu, 2017; Klingmann, 2018; Blume, 2018; Spomer, 2012; Van Riet-Nales, 2012; Mekmullica, 2003). Lopez (2018) compared researcher observations to patient reported outcomes and reported that patient reported outcomes provided better discrimination between samples, and individual evaluation of a range of attributes including taste, texture and sample volume. Whereas the observation could only provide the overall judgement of acceptability.

The majority of these studies measured the ability to swallow using terms such as "swallowed" to denote the formulation as being acceptable, and "refusal/not swallowed" as not acceptable. However, differences were observed with some endpoints. For solid oral formulations, Klingmann (2018) regarded 'chewing or biting' the formulation as acceptable, whereas others regarded this as not acceptable (Kluk, 2015; Beck, 2005; Spomer, 2012). Similarly, a 'choking reflex' was also regarded as 'acceptable' by Kluk (2015), provided the whole dose was subsequently taken, whereas in Medeiros' (2016) study this was not acceptable. The remaining studies measured oral acceptance by observing physical behaviour with physical negative behaviour including turning head away, blocking with hands, clamping mouth shut (Beck, 2005), and crying (Rodd, 2011; Medeiros, 2016).

Variance between the criteria for observations was also noted (Table 2.10), and three studies (Amirav, 2014; Mekmullica, 2003; Spomer, 2012) did not specify which criteria the observations were based on further than success or failure. Giralt (2017) reported that the observation was carried out systematically using detailed checklists, however no further information is supplied. Typically, acceptability in observations is based on an individual's own judgement of a behaviour such as "acceptable, stressful, very stressful and unacceptable" (Kendall, 2001), or "facial expression" (Lopez, 2018), it is possible that the subjectivity of the observer will impact on how the behaviour is scored/judged, and therefore impact on the acceptability score provided. Having two external observers or recording the testing as in Kluk's (2015) and Blume's (2018) studies would allow for the retesting/scoring of the study and the inter-rater reliability of scores.

Observations were paired with questionnaires (Rodd, 2011; Orlu, 2017), hedonic scales (Lopez, 2018; Blume, 2018; Cohen, 2008; Moniot-ville, 1998, Orlu, 2017; Medeiros, 2016), VAS (Kendall, 2001; Van-Riet Nales, 2017), interviews/patient feedback (Giralt, 2017; Babbit, 1991; Rodd, 2011; Klingmann, 2018; Van-Riet Nales, 2017), Likert scales (Rodd, 2011) and Wong Baker FACES Pain rating scale (Kendall, 2001). Interestingly, the majority of studies paired observations with another form of acceptability evaluation, only one study (Mekmullica, 2003) did not.

The use of more than one evaluative measure to assess acceptability may be necessary to provide a more reliable measurement of acceptability.

Table 2.10: Characteristics of observation studies

Author (year)	Behaviour(s) observed	Acceptance threshold
Observed by researcher/clinician		
Thompson (2013)	Spontaneous facial reaction	Sucked lozenge for 1 minute or spat out
Lopez (2018)	Negative facial reaction	Pursed lips, nose wrinkle, brow bulge, eyes squeezed
Moniot-ville (1998)	Facial reactions/ swallowability	Smile = good or fairly good No face= acceptable Made faces/complained= poor Refusal= very poor
Van riBeck (2005)	Physical behaviour	Acceptance= child allowed tablet to me in mouth for 10-seconds; Swallowability= child swallowed within 30 seconds; Chewed; expelled= removed/spat out tablet; Avoided= turning head, blocking with hands, clamping mouth shut
Kluk (2015)	Ability to swallow	Acceptable: Smooth swallowing; swallowing with choking reflex or cough Not acceptable: biting or chewing; spitting out or refusal to take; choking without swallowing
Orlu (2017)	Ability to swallow	Successful administration of ODF Total score on Medicine Acceptance Scale (MAS) (3 or above = acceptable)
Klingmann (2018)	Swallowability	Acceptable: “swallowed” or “chewed and subsequently swallowed” Acceptability: defined as ‘everything swallowed’ or ‘partially swallowed’
Observed by parent/caregiver		
Kendall (2001)	Pain Facial reaction	Smiling to crying ‘no obvious discomfort, mild reaction, winced or withdrew, cried, screamed’ ‘acceptable, stressful, very stressful, unacceptable’
Cohen (2008)	Pain (Observational Pain Scale) Nausea	Nausea, dizziness, discomfort
Giralt (2017)	Infant's response	Adherence and handling of medicine
Amirav (2014)	Behaviour	“did not awaken” “cry” “demonstrate fear”
Medeiros (2016)	Overall liking	Positive reaction: Easy administration, sucking motions, licking lips, smile, stop crying, opening the mouth asking for more, nod positively No reaction: Had no reaction, does not woke up, woke up without crying. Negative reaction: Retching, nod negatively, cover mouth with hands, facial grimacing, crying, spitting, kicking, turning the head, refusing to swallow, cough
Blume (2018)	Swallowing	“swallows well”, “refusal”, “spitting”, “vomiting”, “medication not taken”

Spomer (2012)	Swallowability	Swallowed- acceptable chewed, spat out, choked on, refused- not acceptable
Van-Riet Nales (2012)	Swallowability	Full dose swallowed, part-dose swallowed, dose not swallowed
Mekmullica (2003)	Ability to swallow	Successful swallow of formulations
Rodd (2011)	Infant medication acceptance scale	Reaction to supplement in mouth Swallowing of supplement Crying Facial expression
Babbitt (1991)	Noncompliance /nonacceptance	Mild inappropriate behaviour
Angwa (2020)	Perception of taste	Children's expression/reaction
Klingmann (2020)	Amount taken/palatability	"everything swallowed" or "chewed/partially swallowed"
Ruiz et al (2020)	Result of intake Patient reaction Time needed to prepare/administer Methods used to achieve administration	Dose fully taken, partly, or not at all. Positive, neutral or negative reaction. Short (<1 min), medium (1-2.5 min), long (>2.5min) Dividing dose/using food or drink/patient reward/ restraint
Giralt (2019)	Easier to administer and store	n/a

2.4.6.5 Verbal spontaneous reactions and patient feedback

Verbal spontaneous reactions and patient feedback were used to assess the acceptability of formulations in four studies (Arapostathis, 2010; Medeiros, 2016; Cadwgan, 2017; Thompson, 2013). This feedback is often provided immediately after a formulation is administered (spontaneous) or following a question or prompt by the researcher (feedback). These reactions provide information about the subjective acceptability of a formulation to the individual. Additionally, understanding what aspects of the medicine are not acceptable and/or are disliked by participants is crucial to adapting the medicine for that individual (Table 2.11).

Verbal reactions and feedback have been considered useful and effective ways to evaluate taste. However, some limitations with using these methods have been reported such as children being unable to articulate appropriately and the lack of standardisation of the verbal feedback. For example, one study (Thompson, 2013) measured children's responses to the questions "would you be happy to take it (the medicine) again?" and "would you be happy for mum or dad to give you this flavour medicine when you get a sore throat?". Differences were observed in responses to these two questions, despite the same medication being evaluated, 94% said yes to the first question but only 86% said yes to the second question. Whilst this difference was not statistically significant, it provides some evidence that the interpretation and understanding of a question may elicit different results depending on how the question is asked (Thompson, 2013). However, Sjovall et al (1984) compared spontaneous verbal judgements with results of a 5-point hedonic scale measuring the acceptability of a penicillin medication and found that for children under the age of 6 years old, verbal assessment discriminated between the formulations better than a hedonic scale, but that for children older than the 6 years no difference was shown between the two methods. Additionally, one study correlated verbal feedback to a rank score between 1 (very good/or similar) – 5 (very bad/or similar) (Sjovall, 1984) which allows for the testing and evaluation of these verbal judgements in a more statistical manner that allows judgements to be made across studies.

Table 2.11: Spontaneous verbal reactions

Author (year)	Verbal reactions	Age of children
Positive verbal reactions		
Medeiros (2016)	"good," "I want", "liked", "tasty", "very good "or “better than the last one”	<6 years
Cadwgan (2017)	‘good’ ‘very good’	Avg. 4 years
Negative verbal reactions		
Medeiros (2016)	complain and say "bad"	< 6 years
Thompson (2013)	‘disliked’	2-6 years
Cadwgan (2017)	‘thought I was going to choke’ ‘itching’, ‘unpleasant taste’	Avg. 4 years
Sjovall (1985)	Not defined	3-12 years

2.4.6.6 Other measurements and tools

Other tools have been used and adapted for the evaluation of acceptability of medicines in a paediatric population. The Caregiver Children’s Acceptance Tool (CareCAT) is a single page diary with a 5-point nominal scale. It allows the evaluation of the acceptability of medicine based on observable behaviour which can be used as a longitudinal measurement of behavioural responses to treatment duration for up to four weeks (Blume, 2018). The tool (Figure 2.9) consists of one positive behaviour (swallows well) and four negative behaviours (refusal, spitting up, vomiting, not taken), which caregivers complete when their child is given the medicine. The tool was developed to be used in clinical practice by health professionals and by parents/ caregivers for ‘at home’ use, within the study reliability of this scale was tested and reported to be a reliable tool to assess acceptance (Blume, 2018). It is intended to estimate the ‘general acceptance’ of a medication in a child population.

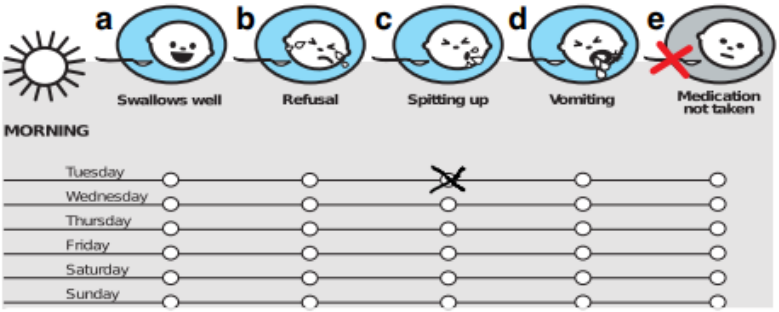


Figure 2.9: CareCAT (Bloom, 2018).

Similarly, The Medicine Acceptance Survey (MAS) (Kraus et al, 2001) is a 10-point summative tool which evaluates five behavioural responses in children when administered medicine (Figure 2.10). These responses are crying, facial expressions, body movement, reactions, and ingestion of the drug. The MAS was developed for caregivers/parents to use on infants, and so some of the responses (crying/body

movements) may be specific to infants. Whilst the MAS has content validity, internal reliability and interrater reliability, its efficacy and use outside of an infant population is unknown. Nevertheless, it has been adapted and used in newborns (Rodd et al, 2011) and in a population of older children/ adolescents (Paloha, 2008).

Item and observed behavior with examples	Points
Cry	
Not crying, not screaming	2
Crying or screaming but can be comforted	1
Crying or screaming, cannot be comforted	0
Facial expression	
Happy or positive face	2
No facial distress	1
Abnormal facial expressions, signs of distress Example expressions: facial grimacing, "scrunching up" face, squinting eyes, looks of anger, distress, or fear	0
Body movement, level of agitation	
Normal movement, calm Example behaviors: patient comfortable, normal activity	2
Restless, mild agitation Example behaviors: mild head turning, mild avoidance movement of arms or hands, mild restless movement of feet	1
Thrashing about, hysterical Example behaviors: head turning, avoidance movement of arms or hands (pushing away, covering mouth with hands), kicking	0
Reaction to placement of drug into mouth	
Allows drug to be introduced into the mouth	2
Resists placement of drug into the mouth Example behaviors: does not willingly open mouth, purses lips	1
Refusal of placement of drug into the mouth Example behaviors: refuses to open mouth, tightly clenches mouth or jaw closed, pushes or thrusts tongue outward	0
Swallowing of drug	
Swallows drug without loss	2
Spits out drug (partial loss of dose)	1
Spits out entire dose or throws up	0

Modified with permission from reference 1.

Figure 2.10: Medicine Acceptance Scale Adapted for Children/Adolescents (Paloha, 2008)

Existing patient reported outcome measurement tools have been used to evaluate the taste, suitability and age-appropriateness of medicines in a paediatric population. These measures include Likert scales, the Treatment Satisfaction Questionnaire for Medication (TSQM) (Cadwgan, 2017) and the Wong-Baker FACES Pain Rating Scale (WBFP) (Kendall, 2001). The TSQM was initially developed for use in adult populations to evaluate treatment for chronic diseases, however, it has recently been used in paediatric populations (Cadwgan, 2017). It has been tested for reliability and validity in adult populations and scores highly on internal and construct validity, however reliability and validity is not reported in this study for children. The TSQM is a 14-item scale which aims to evaluate four key domains: effectiveness, side effects, convenience and global satisfaction. In Cadwgan's (2017) study, parents were asked to complete the TSQM through observation of their children.

Additionally, Wong Baker FACES Pain Rating Scale (WBFP, 2009) is a validated tool and was established as a self-assessment scale to measure the amount of pain an child may be in. It was originally developed with children, at least 3 years or older, to help them communicate their pain and improve assessment so that pain could be addressed and managed.

Figure 2.11: Wong-Baker FACES pain scale

In research use and to maintain the validity of the scale and its results, the Wong-Baker FACES Pain Rating Scale should solely be used for pain assessment. The developers highlight that the scale should not be used in the assessment of emotions, moods, comfort or otherwise. However, one study in this review (Kendall, 2001) used the W-BFP Scale to measure the reduction of pain caused by the treatment as an indirect assessment of acceptability. Whilst the tool was used correctly (i.e. to measure pain), the extent to which a measure of pain can be used as an acceptability measure is debatable.

That being said, measures such as the TSQM (2017) that evaluate more than one aspect of a concept may provide a more accurate picture of the overall acceptability of a medicine by accounting for the many different aspects that result in the "overall acceptability". Ranmal (2016) used a multidimensional measure (Figure 2.12) to evaluate the overall acceptability of a formulation, accounting for personal preference (like/dislike), how easy or hard it was to take, and how likely the child would be to take the medicine in a real-life setting. Rather than using one end point such as preference or swallowability to evaluate the overall acceptability, this type of measure recognises that acceptability is the combined result of a number of different factors.

Figure 2.12: Ranmal (2016).

2.5 Synthesis and Discussion of Review Findings

In order to situate the findings of the review and draw conclusions, in this section the key findings from the reviewed papers are integrated into wider literature. The review demonstrates that whilst there are attempts in the literature to define acceptability, no common definition is applied. In line with current regulatory definitions (EMA, 2013), some studies used the willingness and ability of children and caregivers to administer and take medicines (Rodd et al, 2011; Ranmal et al, 2016; Angwa, 2020). However, this definition of acceptability is open to interpretation (Ranmal et al, 2018), and it was common for individual studies to use their own definition of acceptability that reflected the specific purpose of the study. For example, studies that compared medicines opted to use preference (Klingmann, 2017; van Riet-Nales, 2012), whereas studies that investigated tablet size or palatability generally opted to use swallowability (Lopez, 2017; Jagani, 2016). The way that acceptability is defined or understood within the papers impacts on the criteria used to assess the acceptability of the medicine product. Whilst few studies provided the criteria used to assess acceptability, those that did were highly variable, ranging from criteria such as acceptance or rejection of a medicine, to a child's body language such as "child-smiling" (Moniot-ville, 1998) or "swallowed with ease" (Kluk, 2015). This variability limits the extent that acceptability can be compared within or across studies.

Overall acceptability is understood to be the combination of multiple factors, including appearance, palatability, swallowability and ease of administration (Korarewicz, 2016). However, there needs to be some guidance on which aspects of acceptability should be evaluated for which medicines e.g. swallowability, palatability and taste for oral

formulations; pain and appearance of medicine for injections etc. Focussing on only one or two of these factors in the evaluation of acceptability of paediatric formulations fails to account for the complexity of acceptability (Vallet et al, 2017; Kozarewicz, 2014; Ranmal, 2016). The simultaneous consideration of a number of these factors may provide a solution if conducted in a standardised manner. Similarly, whilst there was variance in the criteria used to assess acceptability, a universal threshold of acceptability is also dramatically lacking an evidence-base. Within the literature there were two main ways that investigators attempted to provide a threshold of acceptability. Firstly, the proportion of participants that express a willingness to take the medicine or provide a preference is transformed to a statistical limit, and an arbitrary percentage is recognised as acceptable (between 50%-100%). The approach of using a statistical limit to assess acceptability is observed within veterinary practice to judge palatability of medicine for animals, the EMA (2011) proposes a numerical limit of 80% (dogs) and 70% (other species) to judge whether a medicine can be regarded as acceptable or not. A requirement for a statistically agreed limit for the acceptability of medicine in children has been previously highlighted as necessary (Mistry & Batchelor, 2017). The second method used to provide a threshold of acceptability is through the use of a scale measure and defining acceptability as a point score or face on the chosen scale (Thompson et al, 2013; Medeiros et al, 2016). Again, guidance should be provided around which face or number on the scales is deemed to be acceptable as the current review highlights the variance between the accepted points.

This review provides evidence that formulation developers and researchers are beginning to include children and young people in the evaluation and development of medicines for children, as called to do so by the EMA (2013). Whilst this demonstrates that steps are being taken to make medicines more acceptable for children, further work is still required. Specifically, further clarification is required regarding the age that children should be included in studies. Differences were observed in the current review, and few studies followed the age guidelines issued by the WHO (2007). Differences were observed for ages of children providing their own acceptability assessments and studies where adults/caregivers were used as proxy. Typically, children between the ages of 6-18years old reported their own acceptability assessment, however there were some exceptions with children aged from four years

old providing their own feedback in some studies (Mekmullica et al, 2003; Ogutu, 2014; Lottman, 2007), and parents providing acceptability assessment for older children and teenagers up to 13 years old (Munck et al, 2008; Babbitt, 1991). Further clarification about the age at which children and/or adults should provide feedback on acceptability is required if testing is to be standardised. Both healthy children and patients were tested in the studies included in the review. Following guidance from the EMA that testing should include the most relevant patient population (Kozarewicz, 2014) means that those children of the relevant age and disease status would be appropriate for testing. Patients' past experiences in taking medicines and the nature of this treatment may also impact on children's perceptions of acceptability (Giralt, 2017), therefore, whilst not every child may be a current patient, almost all children have taken some form of medication over their lifespan. Similarly, some features of acceptability, such as tablet size or appearance, can be considered disease-agnostic (FDA, 2015), and therefore testing in healthy populations of the appropriate age would also be beneficial rather than just testing adult populations.

This review provides evidence that the measures that are used to assess the acceptability of medicines in children are widely varied and dependent on a number of factors. Methods used to assess acceptability differed depending on the focus of the study (see Table 2.7), as well as researcher decisions about the child's age and assumed understanding, and the formulation and associated formulation factors (route of administration, dosing frequency) (Figure 2.13). The variance between these factors may mean that it is not possible for one global measure to evaluate acceptability of medicines in children as it is important that the measure used is suitable for the intended purpose (Mistry and Batchelor, 2018). However, this review highlights a number of issues with the currently used measures, not least that the children who are asked to use these measures have neither been included in their development and nor in the decision making when choosing a scale to use in practice.

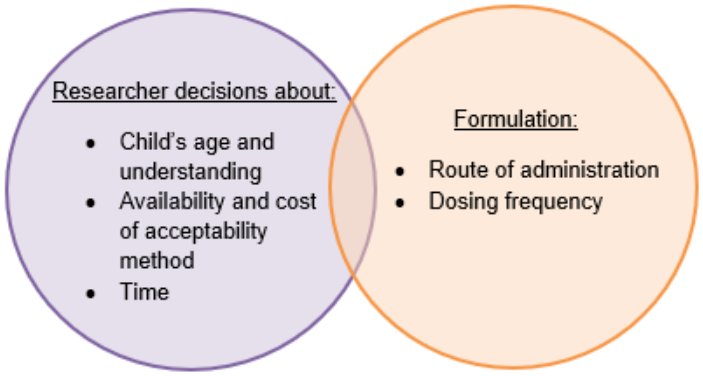


Figure 2.13: Current practice: criteria that impact on the development and selection of methods used to assess the acceptability of medicine in children.

Of the scales used to assess acceptability, Facial Hedonic Scales (FHS) were the most common and were demonstrated for use in children as young as four (Hofmaova, 2020; Cadwgan, 2017). Hedonic scales are sometimes used with phrases or verbal descriptors when used in child populations and this is said to mitigate some of the issues with understanding and comprehension of the scales. FHS were age-adapted in two studies (Orlu, 2017; Ranmal, 2016), this related to the phrases used along with the images. However, Sjovall (1984) compared spontaneous verbal judgements with the results of a five-point hedonic scale measuring the acceptability of penicillin medication and found that for children under the age of six years old, verbal assessment discriminated between the formulations better than a FHS. For children over six years, no difference was observed. No studies provided information about how or why scales or response images were designed or chosen, and there is a gap in the literature about which image is the most meaningful or relatable to children. Similarly, the structure of the studies is also left up to the discretion of the researchers, as mentioned earlier studies differed on the presentation of the scales. Some displaying positive anchors/responses to the left of the scale, and others presenting these on the right. Similarly, studies on numerical scales also differed, with some presenting the negative face/phrase corresponding to the lowest number on the scale (0, 1), whereas other studies presented it the opposite way. It is not clear whether such issues have an impact on the outcome of assessment. Whilst this was not discussed within the papers, this has been explored in food preferences, and no differences were observed for presentation (Peryam & Pilgrim, 1957; Mistry & Batchelor, 2017). Visual analogue scales provide continuous data and may be better suited to comparing differences between samples, however Mistry & Batchelor (2017) report VAS are restricted by the age at which children are able to comprehend and use them. This is

reflected by the results of the current review which noted that parents/adult helpers completed the scale with the child in all but one study that used a VAS. Although not reported in the review papers, it is important to note that VAS can be misused when the anchor phrases and responses on the scales are not meaningful to participants (Bartoshuk, 2005). The degree to which the anchor phrases and responses were meaning to the children is unclear.

In order for age-appropriate and acceptable medicines to be developed for children, the measures that are used to evaluate the acceptability of medicines must be shown to do just that. It has been demonstrated in pain studies that when given the choice children have opted to use hedonic scales over VAS (Luffy, 2003). Similarly, Bracken et al (2018) evaluated the age-appropriateness and acceptability of four different assessment tools with children and found children had preferences for specific scales and identified issues with the use of others. This provides evidence that different measures may be better suited to evaluate different aspects of acceptability of medicines (Preston, 2017).

Based on the synthesis of the findings from this review it seems reasonable that a third domain should be added to the existing criteria used to assess the acceptability of medicine in children. This domain should relate to children and caregivers and should consider issues such as including children's voices, acknowledging their understanding and considering factors such as including them in assessment of acceptability. Adding this third domain could be a move towards better practice in developing and selecting appropriate methods (Figure 2.14).

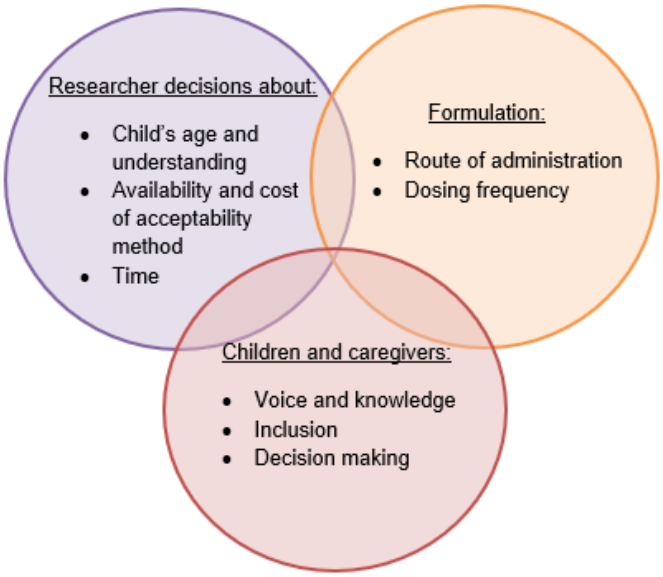


Figure 2.14: Proposed best practice: inclusion of criteria that should influence the development and selection of methods used to assess the acceptability of medicine in children.

2.5.1 Conclusion

The purpose of the review was to address the broad question about the methods used to assess the acceptability of medicine formulations for the population of children under the age of 18 years. It has highlighted the knowledge deficits and the potential benefits of inclusion of children in developing acceptability measures. The inclusion of children in research about children, particularly in a topic as subjective as medicine acceptability, has the potential to help industry and developers to obtain a better understanding and improve knowledge of age-appropriate formulation development. Obtaining the unique perspective of children about the appropriateness of measures used to evaluate the acceptability of medicine can only enhance understanding where multiple viewpoints are required (Figure 2.14).

The literature review chapter has presented and discussed themes around the development of medicine for children and young people, the understanding of the acceptability of medicine, and the methods used to conduct acceptability testing with children and young people.

This chapter has suggested that the current understanding of the acceptability of medicine is fragmented, which ultimately impacts the extent to which the methods that are used to evaluate acceptability can be deemed reliable or appropriate for use with

children and young people. These limitations originate from the fundamentally adult-focussed assumptions that drive pharmaceutical development, and health care more generally (Tariq, 2013). There is an increasing recognition that children should occupy a more active role within research (Coulter, 2004), particularly where they can provide new types of knowledge in topics that concern them, such as their own healthcare (Stafford et al, 2006).

The study presented in this thesis builds upon such work that has included children's opinions and experiences of their own healthcare and complex health issues (Lidskog, 2008; RCHP, 2012). It does so by providing children with the opportunity to engage in research for the co-construction of knowledge to improve the understanding of the acceptability of medicine, and the methods used to evaluate acceptability.

Chapter 3
Methodology

3 Methodology

The review in Chapter 2 highlighted a gap in knowledge regarding the acceptability of paediatric formulations. It also demonstrated the limited and "fragmented" knowledge that exists about the best methods to conduct acceptability testing in paediatric populations (Ranmal et al, 2018, p18). This chapter will detail the research methodology that was employed to begin to address this gap in knowledge, prior to a detailed discussion in Chapter 4 of the methods employed in the current study to answer the research questions.

This chapter begins by describing the generic qualitative research approach that underpins this project and examines the use of employing this approach over other, more specific, qualitative research methodologies. This chapter concludes with a critical examination of the ethical arguments for the competence and inclusion of children in research that concerns them.

3.1 Aim

The aim of this study was to:

1. Explore the experiences of children in relation to medicines, to incorporate their views to develop a better understanding of the acceptability of medicine, and to relate this to the tools that are used to assess the acceptability of medicines.

3.1.1 Objectives

The objectives of this study were to:

1. Explore children's experiences of medicines to gain a better understanding about what is acceptable to children in formulations.
2. Evaluate with children methods used to assess the acceptability of medicine.
3. Use this new information to propose ways that existing tools used to assess acceptability of formulations in a paediatric population can be re-designed to better reflect children's perspectives on the acceptability of medicine.

3.2 Generic Qualitative Approach

A generic qualitative approach is reportedly best defined in the negative (Kahlke et al, 2014), as it is "not guided by an explicit or established set of philosophic assumptions in the form of one of the known qualitative methodologies" (Caelli et al, 2003, p4) as seen in phenomenology, grounded theory or ethnography (Richard and Morse, 2007). Rather, generic qualitative research draws and builds on a range of tools, techniques, traditions and ideas from different approaches (Crotty, 1998), whether related to their epistemological, theoretical (Neergaard et al, 2009), or methodological stances (Hunt, 2009). Drawing on the strengths of established methodologies, this approach remains flexible and reflexive. This approach aligns with the underpinning principles of the current study which involves exploring the ways in which children can be involved in this research, accounting for their personal preferences and strengths.

As the current study sought to understand and explore children's thoughts, feelings and perspectives, it was decided that employing a generic qualitative approach which carefully considers the positioning and engagement of children would be most appropriate in the current study. Qualitative research approaches have been previously found useful when undertaking research with young children, as they allow for a flexible approach that can be adapted to the individual children's interests, needs and levels of engagement (Rogers & Evans, 2008). Additionally, qualitative research is described as an approach that explores social phenomena from the perspective of insiders, attempting to understand how people interpret and make meaning of their experiences and construct their worlds (Merriam, 2002;2009), by providing them with the means to express their voices (Lapan et al, 2012). These characteristics make it a suitable method of gaining a better understanding of children's thoughts and opinions of the acceptability of medicine.

Before deciding on a generic qualitative approach, number of other qualitative methodologies were considered- of particular note was phenomenology. However, each of the other methodologies had limitations in terms of their appropriateness for the current study. Whilst phenomenological enquiry is concerned with the "lived experience" of the individual, this approach focusses on the inner dimensions of the phenomena, the cognitive and psychological processes, inner qualities and structures (Percy, 2013, p13). The current study was interested in the children's interpretation of acceptability in relation to their outward behaviours, their understanding and

construction of the term acceptability of medicine, and the appropriateness of the ways in which it is assessed.

In terms of its design, generic qualitative research studies aim to understand how individuals interpret, construct, or make meaning of their worlds and experiences (Merriam, 2002). It relies on an interpretive approach (Marshall & Rossman, 2006) creating opportunities for the researcher to "access to another's reality" (Silverman, 1983; 17). As expressed by Berger and Luckman (1967), the reality of children's experiences lies in their own construction, and therefore gaining an understanding of the reality of their world aligns to a social constructionist perspective. For this reason, the voices and explanations of the children are key to interpreting the data and the subjective interactions within this study are the primary means of accessing the social constructs.

The epistemological position adopted in this study is primarily influenced by Guba and Lincoln's (1985) conception of Naturalistic Inquiry, later acknowledged as a form of constructivism (Guba and Lincoln, 1988). This assumes that knowledge is maximised when the gap between the researcher and the participants is minimised, and, as a result, facilitates a better grasp on the socially constructed meanings. Therefore, generic qualitative research seeks to produce knowledge *with* individuals whose experiences are of interest to research (Clark, 2004), asserting that we "cannot know reality apart from our interpretations of it" (Clark, 2004; 473). Therefore, it is proposed that the adult academic will not be able to know the reality of a child without engaging with them to co-construct knowledge about their own lives and experiences.

From this perspective, data can be seen to be both individually and socially constructed. Consequently, this study focusses on the construct of the acceptability of medicine from the perspectives of children. Therefore, core to this research was the necessity of providing children with the means to express and present their experiences, perceptions and opinions, while accepting that knowledge of social reality will always be influenced in some way by the interpretations of the researcher (Schutz, 1967; Gadamer, 1976; Patton, 1990).

The researcher, therefore, is an integral component to this approach, “attempting to interpret phenomena in terms of the meanings people bring to them” (Denzin and Lincoln, 2005, p3). Therefore, whilst the aim was to reduce the impact of the researcher on the study, it is acknowledged, as Schensul (2012) proposes, that the researcher will influence the study. This influence is related to the fundamental beliefs of the researcher, including their epistemological, ontological and theoretical orientation, that these beliefs may have influenced the assumptions brought to the research, and in turn, may have affected how the study was conducted. In order to minimise the extent of this influence, Flick (2007) suggests that the researcher be reflexive, considering their influence on the participants, data collection, practice and outcomes. This focus on reflexivity can be seen throughout the thesis.

3.2.1 Challenges

Conscious of the challenges associated with the use of generic qualitative research, particularly for neophyte researchers, Kahlke (2014) outlines three main critiques with generic qualitative approaches: theoretical void, lack of a robust literature/quality debate, and method slurring. Each of these is interlinked.

The “theoretical void” that critics argue lies at the heart of much generic qualitative research arises because without clear alignment to or articulation of the underpinning specific epistemological and theoretical approaches the research framework is unclear. However, this criticism has been addressed in this study as although not theory driven, this research is, as Kahlke (2014) states, not “atheoretical” (p13) and its epistemological grounding is clearly stated. This study is grounded within a social constructivist epistemology acknowledging that human experience is both constructed and contextual as well as allowing for shared realities (Thorne et al, 1997). This epistemological positioning fits well with the research question, aims and objectives of the study but also the positioning adopted in relation to the participatory and child-centred approach.

The argument of generic qualitative studies lacking a robust literature review or having a clear approach to study quality are also charges that can be refuted. The literature review presented in Chapter 2, provides a clear, comprehensive and robust review of

the literature. Also, the decision to adopt a generic qualitative approach was not taken lightly and it resulted from a considerable and conscientious reading of the methodological literature to ensure that a clear understanding of the impact of epistemological decisions on subsequent choices about methods. Rather than having a pre-determined framework to work within such as is available to researchers undertaking phenomenology for example, each choice has been considered carefully. This has required broad reading, the thinking through of issues and drawing on a number of different sources in order to identify and define the research methods. Rather than relying on pre-existing methodological rules or assumptions (Chamberlain, 2000) which has been reported to hinder the "thinking through" process (Kahlke et al, 2014, p44), the research choices have been reviewed and examined. Particularly in relation to the congruence of the methodology and methods, research questions, and the researchers own philosophical positioning. This has been extremely valuable to the development of the researcher and to the overall quality and robustness of this research study.

The third major critique that Kahlke (2014) discusses is that of method slurring. This criticism is linked to the opinion, not always well-grounded, that generic qualitative research mixes methodologies without due consideration of the potentially varying and incompatible underpinning epistemological and methodological values and assumptions. This can create issues related to the congruence of the research when the epistemology, methods and techniques are not working in harmony. However, the research methodology and methods were selected carefully, ensuring cohesion and harmony between these choices and throughout the research process. This aligns with Kahlke (2014) who refers to this as "building" (p46) the research framework, as opposed to a post hoc fitting together of the research questions, methods, methodology and theoretical underpinnings. Generic qualitative research is not, therefore, "free-floating theorising" (Thorn, 2004; p4), but instead a "critical examination within methodological guidelines that are consistent with [the researchers'] understandings and intended applications to practice".

The following sections of this chapter attend to the subjectivity of the researcher and the impact of her own beliefs and standings on the approach to this research, data collection methods, and the interpretive nature of the data analysis. This is followed

by a section considering the conceptualisation of children and the arguments for their involvement within research.

3.3 Researcher Positioning, Subjectivity and Reflexivity

An underpinning principle of this study was to facilitate the involvement of children in research in age appropriate ways that accounted for their strengths. This was crucial to being able to fulfil the aim of this study to explore the experiences of children in relation to medicines, to incorporate their views to develop a better understanding of the acceptability of medicine, and to relate this to the tools that are used to assess the acceptability of medicines. This, therefore, required the researcher to think in a new way, working outside of existing methodologies and resisting the traditional methods often employed to conduct health research with children. To achieve a more coherent understanding of the acceptability of medicine, Denzin and Lincoln's (2000) statement is drawn on, that this improved understanding is only made possible by employing "many perspectives, [and] hear[ing] many voices" (p. 1054).

The role of the researcher and their values within any research is becoming more widely recognised. Throughout life, knowledge is often constructed based on our own previous experiences, contextual, and cultural values (Greene and Hill, 2005). In terms of research, these experiences and values are drawn on to construct, for example, our participants' identities. In research with children, these values are often shaped as pre-existing ideas about childhood, which ultimately impact on which approaches, and methods used in the research process. Aligning with the idea that "the research process… cannot be considered as independent of the researcher" (Emond, 2005; 126), the methods, approaches, and theoretical framings used are linked to the researcher(s) and their fundamental perspectives. Davis (1998) emphasises the importance of reflexivity in research with children, asserting that this encourages the researcher to question their assumptions, ideas and conceptions of childhood, and children as a population.

Throughout this study the researcher's role as a researcher, academic, children's leader, and companion has had to be continually evaluated. However, before these roles are addressed, it seemed fitting to consider the positionality of the researcher.

The researcher is a white female in her early 20s who has consistently worked around children in some manner for the last 6 years. She grew up in a large family full of much younger children with whom she has always played and interacted. The interest in children's research originated from previous practice studying developmental psychology, and the underlying cognitions, experiences and behaviours that take place during childhood and adolescence. This is furthered by her experience of working with a range of children from many different backgrounds and has also provided a particular perspective on the varying ways that children communicate, express themselves and behave. As a researcher, the positionality adopted is one of an early career researcher establishing her research profile, and conscious that she is still developing within health sciences and pharmaceutical research.

All of these experiences and factors mean a personal and somewhat unique set of perspectives are brought to this research which will inform a particular interpretation when researching the social world of the children. Particular meanings or interpretations may be attached during social situations with children based on the researchers own psychological experience and values of working with children, and therefore it was crucial that this was something to be aware of when attempting to understand or interpret children's behaviour, language and creations.

Given the researchers experience of working with and interacting with children, she felt reasonably prepared and confident about being able to communicate with the children in the study and able to create an informal and friendly environment that the children would be able to trust. There were a few instances during data collection that would support this, for example, when one of the children in one of the school settings referred to the researcher using her name 'Beth', as opposed to "Miss"- which is typical of school age children within a school setting. Similarly, when returning to one of the initial groups for the second workshop and having two of the children wave and run to greet the researcher when they saw her arrive at their group. These displays of behaviour perhaps show that the children who took part in the study did not *only* view her as a researcher, but also a friendly person, someone to trust and confide in. In this sense, this positioning meant the researcher remained "human" (Stanley and Wise, 1993;157).

However, it has been argued that the display of emotions can influence a researchers' interpretation of a situation (Widdowfield, 2000). This was something the researcher was conscious of, particularly when setting boundaries between herself and the children. The balance of roles between researcher and trusted adult was something that was worked hard on ensuring, conscious that becoming too 'friend-like' might negate the ethics of the research study, and too 'researcher-like' would not be beneficial to the collection of meaningful data. Assurances were taken in that the children were able to talk to the researcher *like* a friend, whilst at the same time asking questions about the study and remaining aware that she also had research duties to complete. This is particularly significant when considering the statement that "meaningful relationships" require a de-emphasis of "researcher only" knowledge (Bryne, 2009;68). As Hadfield-Hill and Horton (2014;148) explain, "we are never just researchers, just doing research".

The analysis of the interactions with children and the data collected is partially the interpretation of the researcher. Where children did not provide an explanation or assign meaning to certain aspects of their drawings and creations, it was attempted to interpret the possible meanings conveyed by the exploring children's interests, motivations and individual differences. It is acknowledged that their drawings and creations can be complex to interpret, and attention is drawn to the interpretation of the images being "just that, interpretation" (Rose, 2001, p2).

Referring back to the social constructionist epistemology adopted in this study, the primary objective was not to 'find out' objective truths, as we can never have the same perspective as another (Nagel, 1974), rather, it was attempted to construct an understanding of the concept of the acceptability of medicines. Similarly, with regard to drawings and creations, it is worth noting that there is no 'correct' answer when asking someone "what this means" (Hill, 1997). In particular, there is evidence to support that it may not the 'finished' product or its explanation that is meaningful in children's drawings, but instead the process of the drawing or creating, and the actions, language and explanation that accompany this (Ring, 2001).

The focus on reflexivity is particularly significant when considering what Dahlberg et al (1999) call 'meaning making' with children. This is the shared construction or

development of the underlying meaning of something such as a discussion, painting or creation. Here the earlier point that the views and voices of the children are not 'found out' or uncovered is emphasised (Mauthner et al, 1998), and that the researcher, along with the children, research methods and data, are interdependent and interconnected when developing the meaning of a drawing, idea, or concept (Mauthner and Doucet, 2003).

Furthermore, it is also crucial to acknowledge that whilst referring to the individuals in this study under the umbrella term of 'children', that the child population is not homogenous and individual children's perspectives on issues may be varied and complex. These individual perspectives are significant in themselves, and it is accepted "that children, as adults, may have different perspectives on the same issues" (Dockett and Perry, 2007;49), and that these are reflective of the individual contexts. Therefore, the aim of a continually reflexive approach in this thesis was to enable the researcher to step outside of her adult presuppositions and adopt an open-minded and child-centred positionality. This leads on to the following section which highlights particular situations and issues that need to be considered when conducting research with children.

3.4 Research with Children

It is recognised that there are a number of methodological issues to be accounted for in research with children. Firstly, within the literature there is considerable discussion regarding whether research with children should be conducted differently to research with adults (Punch, 2002). Traditional research approaches have long viewed children as "transitional objects" (Maconochie, 2008, p2) to be studied, with the researcher conducting research "on" them (Hill et al, 1996), rather than "with" them (Mauthmer, 1997). These traditional approaches grounded in positivist methodologies have focussed on the acquisition of large-scale quantitative data conducted and interpreted by adult researchers (Barker and Weller, 2003). This approach fundamentally disregards the child as possessing their *own* views and opinions and is instead underpinned by adult assumptions and interests (Hood et al, 1996; Valentine, 1999), which ultimately prevent adults from listening to children (Hendrick, 2000). However, over the last three decades there has been profound change in the way in which

children, their competencies, and rights, are represented at the social, political and academic level (Pagani, 2018).

The reconceptualization of children as competent social actors (Pagani, 2018; James and Prout, 1990) who have the ability to valuably contribute to matters that affect them (O'Keane, 2008), has changed their role within research both theoretically and methodologically. This view of children, emanating from regulatory changes in 1989 (UNCRC), along with work in the field of the new social studies of childhood, has worked to reposition children within society (Mayall, 1996) and particularly in research (Gallacher and Gallacher, 2008).

There is a new appreciation for children as 'valuable contributors' to research (Willumsen, 2014; p332). With a recognition that children have a specific view on the world (James and James, 2001); that they may identify different issues to adults or view issues differently (Maconoshi, 2008), and that these views are worth listening to (Alaned, 2001). It is also recognised that children communicate in many different ways (Barker and Weller, 2003), and this has led to a critical examination of traditional research methods which are typically adult-focussed and a search for new methods that can serve as tools or frames that allow children's experiences to be articulated and engaged with within research (Veale, 2005; Hill, 1996).

Since these changes, researchers have attempted to account for children's preferences by employing arts-based techniques and methods which Crivello et al (2009) regard as being 'fun'. Whilst there is some discussion about using "fun" methods in the literature, the current study aligns to the perspective of Ford & Carter (2013) that the research and outcomes are still regarded as serious, even if the methods used are labelled as fun. In addition, there is then the discussion about what is "fun" and for whom? Conscious of these issues, the methods used in the current study are *typically* child-centred, and the children within the study had the option to interact, or not, with the methods and activities.

Despite the challenges associated with designing child centred research, this was something thought to be crucial in the current study. As Christianson (2004) suggests, by using methods that are child-centred and that children are already familiar with, we

are able to enter their 'culture of communication' (p166). Children are therefore better equipped to participate *meaningfully* within the research. This is reportedly due to overcoming the adult-focussed assumptions that are ingrained in traditional research methods (Bradding and Horstman, 1999), and providing opportunities for children to present their actual experiences and knowledge (Wilkinson, 2015). Epistemologically it has been argued that child-centred methods and approaches to research generate better knowledge than traditional methods (Cahill, 2004), by producing more "authentic knowledge about children's subjective realities" (Grover, 2004; Gallacher and Gallacher, 2008; p502).

Within this study it is recognised that children can, and do, act as knowledgeable beings outside of the control of the researcher (Gallacher and Gallacher, 2008). This study was mindful that traditional methods, conducted with a value on word-based data such as structured interviews or focus groups can generate information with children from which adults "create knowledge" (Gallacher and Gallacher, 2008). Therefore, this study aimed to overcome the sole use of adult-centred word-reliant data collection techniques and instead also use a selection of arts-based methods to generate meaningful child-centred data.

3.4.1 Children's competence

The notion of children's competence is highlighted within academic literature (Horgan, 2016). Traditionally, the assumption of many adults has been that children are not competent enough to express an opinion. However, theories of developmental psychology and socialisation have helped to inform understanding about how the ways in which children think differently to how adults think. For example, Piaget's (1932) theory of cognitive development presents a four-stage process from birth to adolescence. Whilst there has been critique that the hierarchical progression of this theory suggests that "child thought" is valued less than that of the mature adolescent/adult (Maconochie, 2008; p3), ultimately this theory asserts that *children think differently than adults.* The theory states that children can be thought of as "little scientists", who actively create their realities from what they know, their individual experiences and their mental representations of the world. Piaget, like many other

developmental psychologists (Erikson, 1958; Bandura, 1977) believed that children learn best through doing, and actively exploring.

Building on this, socio-cultural psychologists have questioned the use of traditional methods in research with children. Several notable psychologists (Vygotsky, 1978; Donaldson, 1978; Hogan, 2005) have stressed that when subject to clinical interviews, tests and surveys in experimental settings, as opposed to being observed in their natural environments, children also appear less competent. This is not to say that children are not competent, but that the ways in which research is conducted with children does not enable them to present their competency. Hence, when conducting research concerned with understanding children's views and experiences, a methodological approach and methods that account for children's competencies and that can be conducted within familiar settings, is preferable (Alderson, 2004; Kellett and Ding, 2004).

Even accounting for children's preferences and strengths, there are still arguments regarding the reliability and validity of children's accounts. When working with children in research, researchers generally have to account for a number of considerations that are relative to the stages of development and cognitive capabilities of the children in the study. For example, the use of appropriate language, concepts and speed of questioning can all affect children's responses (Lamb et al, 1999; Scott, 2008). Children are also thought to be more suggestible than adults and may feel more pressured to conform to adult instruction and questioning (Flewitt, 2005; Tangen, 2008). Therefore, simply the presence of the adult researcher may influence the children in their behaviour and responses. However, this notion could be applied to any participant and not only children; adults are prone to many memory biases such as social desirability and third-person bias. Therefore, the issue is trading the benefits against the drawbacks of involving children in research. It is argued that even considering the potential for bias and influence, children are still better placed than any other person to tell us about their experiences, thoughts, opinions and views on the acceptability of medicine and the appropriateness of the methods used for evaluating the acceptability of medicine.

The study aligns to the principle that children are capable of providing both valid and insightful information, providing they are approached appropriately and that their data are interpreted carefully (Livingstone & Haddon, 2009). Therefore, it is important to consider factors related to the conduct of the researcher during the conduct of research with children. Recommendations from Zaman (2005) are drawn on, who argues that both observation and the opportunity for children to express their opinions and perceptions are necessary to provide a more accurate picture of children's behaviour and beliefs. Useful techniques for generating a coherent understanding include the 'think aloud' method, where children are asked to commentate on their activity, the 'active intervention' where the researcher asks relevant questions during the task or activity, and 'laddering' in which the researcher asks the children why they like or dislike something (Zaman, 2005).

Whilst this work was grounded in doing research with children, this was limited to the data collection phase. The methods that were used have been used with children in other areas of research (IDS, 2009) and have been used by researchers when interacting with children in their everyday lives (Literat, 2013; Biggeri and Anich, 2009; Chung and Gerber, 2010; Third et al, 2014; Driessnack, 2005). These methods are valued for their ability to uncover and access children's views, and ultimately, enable the inclusion of children's voices within research. In future research building on this work, the aim would be to include children across more phases of the research process, such as design, analysis and dissemination.

3.5 Conclusion

This chapter has provided a background to the underpinning philosophical, theoretical and methodological constructs that this study is grounded in. Reflexive considerations of the researcher's role and the perceived positioning of the children with the study have been considered.

This study uses a variety of methods to engage with children to learn and understand about their views, beliefs and experiences with medicine, and to try to improve the methods used to evaluate the acceptability of paediatric formulations. Their perspectives could lead to the development of more appropriate and effective methods

of assessment, which in turn would help to create better medicines for children. The methods are discussed in detail in Chapter 4.

Chapter 4

Methods

4 Methods

Building on the previous chapter in which the methodological grounding of this study was outlined, this chapter presents a detailed account of the empirical data collection for the current study. Firstly, it begins with a brief overview of the data collection process followed by an in-depth description of each stage including accessing the population, obtaining demographic information, the context of the data collection, the methods used to collect data, the development and use of the workshops, the ethical considerations and, finally, the methods of data analysis.

4.1 Design

4.1.1 Overview

This study draws on the growing body of literature using mixed methods in healthcare research with children (Tariq, 2013). The research makes use of a range of qualitative methods including participant observation, participant-centred workshops, drawing activities, discussions with children, ranking exercises and scale measures. These methods were decided on as they are well suited to the child-centred nature of the study and lend themselves to the wide range of children and settings encompassed within this study. The methods were refined throughout the study following their application in practice and feedback from the children who participated in the study.

The data collection process involved workshops and one-to-one sessions using a variety of visual and creative methods as well as activities and discussions with children. One of the primary drivers was to create a responsive research environment, which allowed children the opportunity to express dissent and/or preference when it came to participation in any or all activities. This approach presented the opportunity to minimise influence as the researcher, encourage shared control of the data collection and provide an environment that facilitated children's choice of methods and amount of interaction with each method. The flexible nature of the workshops encouraged a child-led process that was responsive to the children's behavioural and verbal cues relating to factors such as enjoyment, understanding, method preference, and dissent.

4.1.2 Target population and inclusion criteria

The target population was children aged 5-12 years within the North West of England who met the inclusion criteria (see Table 4.1). No specific exclusion criteria were identified.

Table 4.1: Inclusion criteria

Table 4.1: Inclusion criteria
• Children aged between 5-12 years • Attending one of the identified settings for recruitment • Physically and cognitively able to give informed assent and whose parent/caregiver physically and cognitively able to provide informed consent for their participation • Sufficient fluency in English to be able to understand and engage in the study

The EMA guideline (2013) categorises children within different brackets and stipulates that school children within the 5-11 age bracket, other than newborns, are most affected by pharmacological differences such as drug absorption, distribution, elimination and excretion (EMA, 2013). It felt important to focus on this age range as the children in this age range are both most affected and are a very under-researched group in terms of their experiences and perceptions of the acceptability of medicine. However, despite this under-representation, they have appropriate cognitive and motor skills, are able to express their opinions and perspectives and have reading and comprehension abilities. A typically developing child begins to be able to read, recognise and understand simple words and stories at age 5 years (Morris et al, 2015). Since engagement in the study required the children to be able to understand the questions and purpose of the study and provide their written consent to take part, the age of 5 years old seemed a reasonable age for the lower age limit of eligibility for inclusion in the study. Although the EMA guideline notes the upper age of those school children who are 'most affected' as being 11 years, this study included children who were up to 12 years old.

4.1.3 Settings

Key settings were purposively identified which enabled the recruitment of children who met the inclusion criteria. Two main settings (1. Schools and clubs; 2. Clinical settings) were identified and designed into the study, and a third setting (Museum) was

incorporated into the study at a later date (see Figure 4.1). Each of these three types of setting required data collection to be undertaken in a slightly different way. Each setting was decided on in order to increase the likelihood of recruiting from a wide population, accounting for socio-economic backgrounds, age, gender, children without clinical medicine use and children with experience of taking medicine in hospital. As outlined in the Introduction, Chapter 1, acceptability is a subjective concept and is often dependant on age, gender, background, culture and health status (EMA, 2012).

By recruiting children from clubs and schools it was aimed to recruit children with different experiences of taking medicines and children within specific age brackets. The first clubs contacted were Rainbows and Brownies local to the researcher's home as the researcher had pre-existing contact with them having been leader within Guiding since 2015. Through Rainbows and Brownies, information about the study was passed on to the leaders of local Cub and Scout packs.

In order to account for differences in background and socio-economic status, contact with a school local to the researcher's home was made via email explaining the study and they expressed interest in taking part. Another school also agreed to take part as a data recruitment site. Within this setting data collection was conducted by working with the children within small group-based workshops.

It was also believed important to be able to recruit children who had a depth of experience in taking medicines, and who may have a different health status to children who do not typically attend a hospital. For this reason, one of the selected settings was a Children's Hospital. Within the hospital interviews were conducted on a one-to-one basis.

During the study, the opportunity to take part in a "Meet the Scientist" day as part of the Festival of Science event within the World Museum, Liverpool was provided. The researcher along with three colleagues attended the event and set up a 'station'/table which acted as an information source about medicine development and also a base to recruit children and undertake data collection, the researcher and colleagues facilitating children on a one-to-one basis. This provided the opportunity to recruit children from a variety of socio-economic and cultural backgrounds.

Figure 4.1: Settings used within the study

4.1.4 Sampling

Sampling is the means of selecting a proportion of the target population to represent the wider group. It is more time saving and costs less than collecting information from the whole target population (Polit & Beck 2010). The North West of England, where this study was conducted, was chosen due to proximity to the researcher and because it encompasses a wide and varied area, including a large major city. The overall purpose was to generate an appropriate sample, with boys and girls of different ages to address the research question, aims and objectives (Plano et al, 2008; Hunt & Lathlean, 2015). A purposive approach for the selection of individual settings (schools, Rainbows etc.) was important, as it allowed me to target pre-specified groups, whose experience and knowledge were valuable to the study (Green & Thorogood, 2014).

In order to sample the population within the settings, a convenience strategy was employed (Table 4.2). A convenience sample is "one that is available to the researcher by virtue of its accessibility" (Bryman, 2008, p183). This strategy was decided on given that the researcher had already identified and been granted access to the appropriate settings. This meant that any child within these designated settings, who fitted the inclusion and exclusion criteria, was eligible to participate. The selection of children within the settings depended on their availability on the days and times I visited the setting, whether the children themselves wanted to take part in the study, and in schools/clubs and clinical settings, parental consent was also required. Convenience sampling has limitations, the most obvious disadvantage is that the sample is likely to

be biased (Mackey & Gass, 2005) and not necessarily representative of a whole population.

The debate surrounding the complexities of determining sample size in qualitative research has engaged social scientists from different fields for many years (Blaikie, 2018). Acknowledging the complexities of predicting or stating sample size in qualitative research, as well as the requirement to justify sample size for the purposes of research processes and ethical review committees, the current research project followed recommendations for qualitative research which state that a sample size of 15-20 participants can generate sufficient data (Vasilieou et al, 2018). Therefore, it was proposed that up to 40 children would be recruited from guiding groups (with four groups approached and an expected average of 10 children per group) and an expected 10-20 children from the leisure groups. Between 12-48 children were proposed from two-four primary schools (an expected 6-10 children from each school). Finally, it was expected that 10 children would be recruited from the hospital setting. Achieving the intended sample size was dependant on setting population sizes and availability, such as the number of guiding clubs and schools that agreed to participate. Therefore, it was intended that a minimum of 80 and maximum of 120 children would be recruited for this study.

In total, two schools and four groups agreed, and one hospital was included. The addition of the museum event offered an opportunity to collect both data from children from a different setting and increase the number of children recruited. The recruitment via the museum event allowed sample sizes from the remaining settings to be lower whilst ensuring sufficient data was generated.

Table 4.2: Sampling

Settings	Sampling of Site	Sampling of Population	Requirements
Schools	Primary school children (both boys and girls, aged between 5-12 years old)	Teachers identified 8 children in total. 4 children from Key Stage 1 (2 boys and 2 girls) and 4 children from Key Stage 2 (2 boys and 2 girls).	Access to school granted by headteacher Child assent required Parental assent required
Clubs	Rainbows & Brownies (All girl groups, aged between 5-12),	Approached each group and recruited children by convenience sampling.	Access to group(s) granted by leader(s). Child assent required Parental consent required.

	Scouts and Cubs (All boy groups, aged between 5-12)	Every child in each group was eligible.	
Hospital	Clinical sample of children (both male and female) between the ages of 5-12 years old from a large regional Children's Hospital.	A member of the clinical team identified children (boys and girls, 5-12 years old) when the researcher was on the ward. Children recruited by convenience sampling as they were on the ward at the same time/day as the researcher.	Access to the ward/hospital granted by Ward/Researcher manager(s). Child assent required. Parental assent required.
Museum	A public 'Meet the Scientist' event (aimed at children between 4-12 years old) at the World Museum, Liverpool provided a setting from which to recruit children.	The audience at the 'Meet the Scientist' event was fluid and entirely voluntary. Families turned up to the museum with the expectation of taking part in activities. Any child who was at the museum on the day could take part in the activities, however only the data from those children who reported their age as between 5-12 years old was included in the study.	Access to the museum event was provided by the event organisers. The process of participation for the children from this setting relied on relied on a more limited form of consent/assent than within the other settings. The children were informed about the study before completing the activities, after the completion of the activities the children who wanted to take part in the study 'posted' their activities into a 'letterbox'. Although this was not a written form of consent or assent, this was deemed to be consent on behalf of both child and parent/carer.

4.1.5 Recruitment

For the children recruited from the clubs and schools, they and their parents were provided with information and consent sheets by either the researcher or a gatekeeper in each group e.g. a teacher or leader. They were given at least a week to read through information sheets and consider taking part in the study. The researcher went back to each organisation at least one week later to collect signed consent forms. Before the visit back to the clubs and schools, a gatekeeper was contacted at each site to see if any parents or children had any questions, and if they did, to ensure they knew when the second visit was scheduled at each particular site. On the day of visit to collect consent forms from the guiding groups the researcher was available to both parents and children to answer any questions that they had. During this time, their rights to say no or withdraw from the study were reiterated. However, if a parent or child did not want to participate, they tended to tell the gatekeeper (contact at each group) who then updated me. At the school, no parent had further questions about the study and

those who wanted to take part returned their and their child/ren's signed consent sheets to the school to be collected on the day of data collection. Before data collection commenced with any child or group, it was ensured that all consent and assent forms from both child and parent were provided. It was further ensured that each child at the group knew what they were taking part in by verbally asking and receiving a positive verbal or behavioural response (e.g. head-nod).

At the hospital, children were recruited 'on the day'. This meant that although information sheets and consent forms were provided and available to the parents and children to answer any questions, the decision about their participation was made on the same day. This compressed timeline for decision-making was undertaken as the study was deemed to have a low-sensitivity (i.e. was not believed to be upsetting or cause harm) and the aim was to make participation possible without adding burden to the children and parents. Gaining consent and assent on the same day aimed to make the research process as short and least time consuming as possible for these participants, and to ensure that the parents and children were not required to make any unnecessary trips to or from the hospital for the sake of the research. Prior to recruitment a relevant healthcare professional identified eligible children using the inclusion criteria for the study and checked with the child and parents if they were interested in talking to me about the study. They then introduced the researcher to the identified parents and children and time was given to answer any questions they had about the study. The parents and child/ren were then given between 10-15 minutes (longer if needed) to read through the information sheets and decide if they would like to take part. If they wanted to take part, they were given the option to either complete the research on the same day at a time convenient to them or take part on another day that the child/parent were scheduled to be in the hospital. Once the child/parent had decided about their involvement in the study, consent and assent forms were signed and collected by the researcher. No research took part before the forms were signed.

Within the hospital setting it was more challenging to recruit children than in the non-clinical settings. Reasons for lower numbers than anticipated being approached included the compressed timeline for recruitment following ethical approval and study end, the fact that recruitment coincided with 'winter pressures' within the hospital which

meant that the clinical settings were very busy, as well as the availability of healthcare professionals on the wards to introduce the researcher to the children. The initial proposed number of children to be recruited from the hospital was ten. However, within the available time frame only six children were identified within the agreed recruitment settings who were eligible and were approached to be recruited. Of these six children, only three participated. Of the three children and parents who were initially interested in participating in the study but who did not go on to participate, the researcher determined it would be unethical to ask for consent and assent due to the physical stress that the researcher observed the child was experiencing related to their hospital treatments. Two of the children's parents declined to consider their child's involvement due time constraints as their child was very preoccupied with treatment. These issues meant that recruiting the target of ten children from the hospital was not possible and therefore, this sample was lower than expected.

Similarly, children attending the World Museum were also recruited 'on the day'. In this setting, information sheets and consent forms were not provided as this event favoured a more fluid approach. Since the event was not pre-bookable by the public, neither the research team, nor the organisers, had any means of direct contact with the parents or children. Therefore, it was assumed that the people who turned up on the day were informed about the event, and that there would be activities they could part in. Information posters detailing the study were displayed, and flyers were available around the stand. As the children approached the data collection table, and before they completed the activities, they were told that the activities formed part of a research project and they were asked if they had read the posters. If parents accompanied the children to the activity table, they were also informed of the nature of the research and asked if they had read the posters or flyers. See Section 4.3.2 for full details of the consent/assent process.

4.2 Data Collection Techniques

The study was composed of two phases and on some occasions these phases were undertaken during the same period of data collection (e.g., when a return visit by the researcher was not possible). Phase 1 aimed to generate an understanding of

children's acceptability and perceptions of medicines. Phase 2 built on this to refine ideas and focus on evaluating and refining the tools used to assess acceptability.

As noted earlier, the data were collected in three main settings (clubs and school – via workshops), the museum and the hospital (on a one-to-one basis). Various methods were used (drawing, discussion, activity sheets, booklets and ranking activities) with the children. In this next section, the individual methods are presented, and this is then followed by how these were used within the workshops, at the museum and at the hospital.

4.2.1 Rationale for selection of methods

The overriding concern when choosing methods for this study was to enable the co-creation of knowledge in a two-way 'conversation' with children aged 5-12 years old. Existing methods specific to the collection of data regarding children's acceptability of medicine are typically adult-focussed and then adapted for children; this was not the approach the researcher wanted to adopt, instead it was aimed to use the best possible methods for enabling children's contributions. The Institute of Developmental Studies (IDS, 2009) provides best-practice methods for encouraging participation with children in research, these include mapping, listing, sorting, ranking, diagrams, digital/media use, and photography. Other authors have noted that creative visual methods such as drawing (Literat, 2013; Biggeri and Anich, 2009), storyboarding (Chung and Gerber, 2010) and writing (Third et al, 2014) are useful for engaging children in joint knowledge production, particularly when accompanied with discussion and spoken feedback (Driessnack, 2005).

Prior to the research data collection methods being finalised, the researcher met with Alder Hey Children's Hospital 'Generation R-YPAG (Young Person's Advisory Group)', in order to inform the direction of the study. This is an established and experienced group of young people who regularly provide advice and input into a wide range of research studies. This session was designed to be engaging and informative for the young people whilst producing vital feedback for the researcher, children were offered the opportunity to interact with large A3 sheets, colouring, drawing and writing down their ideas using a selection of drawing materials. The group were also provided with sticky notes, stickers and empty packets of different medicines to evaluate and

use to target their ideas. Eleven young people, aged between 8 and 18 years old, took part in the session. The researcher explained the general area of the research and encouraged small group discussion about different ideas the researcher had about data collection methods as well as other aspects of data collection. In particular, the researcher was concerned with ensuring that the research topic was one of interest to the advisory group, obtaining an idea of how involved the YPAG believed children should be involved in data collection, and testing out preliminary questions and ideas for ease of understanding. Following this initial meeting, the researcher developed participant information sheets and consent forms, which were sent via e-mail to the YPAG facilitator to share with the group. These sheets/forms were reviewed by the YPA group and comments on wording, layout, and images were fed back to the researcher e.g. the group suggested changing the colours of the boxes on the information sheets, in order to make a distinction between the information sheets for the younger age group and the information sheets for the older age group. The group also suggested that removing some text to reduce the length of the information sheets, and increasing the size of text to make it easier for children to read would be better.

Therefore, following the guidance provided by the IDS (2009), experience of working with children and PPI with children, a combination of child-centred qualitative data collection methods were selected and developed to be offered as a choice for data collection. These arts-based methods and activities involved drawing, colouring, discussion activities, ranking activities and scales/ questionnaires. It was intended that the use of these methods within the workshops and when working with individual children would facilitate them sharing and presenting their ideas, opinions and perspectives. Additionally, these methods enabled the collection of different aspects of children's behaviour including visual, verbal and behavioural forms of expression. Table 4.3 provides a summary of research methods used and more detail about each method is presented in subsequent sections.

Table 4.3: Research methods

Method	Objectives and Rationale

Drawing/Worksheets	Used as a projective method- familiar and fun activity for most children in the age group. Different worksheets developed for different ages and preferences.
Discussion	Allowed for building rapport with children and allowing opportunities to express assent and dissent. Child-centred research method- child is the primary focus of interested, child allowed to vocalise and express preferences through direct interaction with researcher. Also allowed for the clarification and exploration of drawings which in turn facilitated data analysis including children's own interpretations and meaning making.
Activity booklets	These included the main activities in an easily accessible and child-centred way. Children are familiar with activity booklets such as magazines and provide a novel and interesting self-contained data collection method.
Ranking activities	Ranking activities are also a fun and child-centred method. They are easy to use, and it has been demonstrated that even very young children can understand them. Ranking activities were used to assist in the collection of data whilst maintaining novelty of the methods.

The methods and the way they were presented to children might have shaped the contributions provided by the children. The rationale for using these methods is outlined in sections 4.2.2-4.2.4. Even though careful decisions were made about the selection of methods and the resources and materials available to children, the researcher has to critically consider how these choices both frame and potentially limit what the children contribute and can create.

Materials such as props can trigger particular responses that might be helpful or could create a focus that is overly directed by the prop (Carter and Ford, 2012). So, for example in this study, the inclusion of potentially legitimate props such as medicine packets, blister packs and syringes could have overly directed the children's attention to focus on these props, potentially limiting children's imagination. The potential for misdirection, constraint or influence on the shaping of data by the use of props has not been a major focus of attention within health research. However, work from other fields, particularly forensic interviewing does provide some evidence of the need to be cautious and consider the influence of props (Poole et al., 2011, 2012). For example, Nigro and Wolpow (2004) note that

whilst props may increase the quantity of data generated, it may decrease the accuracy of data and that prior experience of the props was influential. Work by Salmon (2006) also notes the importance of selecting developmentally sensitive and carefully considered toys as triggers within clinical settings. Other resources such as crayons and pencils result in the creation of two-dimensional outputs whereas the inclusion of collage materials can open up creativity into three dimensions; the use of toys such as Lego might create new opportunities for expression, although what can be built is restricted by the type of bricks, colours and so on (Carter and Ford 2012). The framing of children's contributions by the choice of materials and resources is often overlooked but it is an issue that would benefit from future methodological research.

4.2.2 Drawing and discussion

Drawing has been described as a useful and fairly quick way to gain considerable amounts of data in a short period of time (Malet et al, 2010). Due to the wealth of research on the impact of drawing and the frequent use of drawing in child-centred interviews (Literat, 2013), it was decided this would be one of the main methods of data collection. A number of studies have demonstrated that drawings can be used to help researchers gain an insight into the child's world, facilitating discussion about difficult or complex and important issues that would otherwise be difficult to talk about (Gross & Hayne, 1998; Pipe et al, 2002; Weinle, 2002; Wesson & Salmon, 2001).

To develop child-friendly methods it was important that a variety of media such as drawing materials (pens, pencils, crayons), activity sheets and plain A4 sheets of paper, as well as novel materials such as stickers, glitter and scent pens were provided to facilitate the children's expressiveness (Malchiodi, 1998). A wide range of materials were developed and used in the drawing activities; mindful that the children in the study were different ages, at different developmental stages, and had different preferences and drawing styles. For instance, two activity worksheets were developed aimed at each age group, that were provided at the workshops for the children to interact with.

It was also thought important to provide the children with a wide range of materials to use in the creation of their drawings. It was necessary to consider their own unique

preferences and drawing styles. For instance, drawing skills develop in stages and are dependent on children's age and individual capability (Steel, 1997; Lowenfeld, 1978; Read, 1966). Whilst there are a number of proposed models, each agree on the typical age groups of development. Between the ages of 4-8 children are generally in the "schematic stage" and are still developing their fine motor skills but are beginning to draw more realistic pictures, following a particular schema, and creating stories to go along with their drawings (Steel, 1997). In the current study, the children in the younger age group (5-7 years) within this schematic stage did express a stronger interest for the thicker felt pens, gel pens and glitter pens, and typically chose to talk and discuss their drawings at the same time as they were creating them. Between the ages of 7-12 years, children's spatial perspective generally increases. During this 'preteen stage' children may draw more realistically, detailed and smaller drawings in an attempt to convey their ideas, rather than discussing the meanings out loud (Steel, 1997). For children in this stage fine line pens and sharpened pencils were provided so that they could create more intricate drawings. All of the children expressed particular interest in the scented pens and pencils provided, as they enjoyed the novelty of being able to physically display how their medicines would smell or taste. Figure 4.2 shows the variety of materials provided.

Figure 4.2 Example of the range of materials provided at the workshops

The variety of materials also enabled the children to decide on the tools they used (e.g. crayons/pencils/pens), as well as colours, therefore providing them with some

control within the workshop and over the activities they were completing. The younger children spent a lot of time working on their drawings, whereas the older children tended to draw small but detailed medicines accompanied by a large amount of writing describing what it was illustrating. It is key to note that the researcher was not solely responsible for interpreting the drawings, instead the children were encouraged to either write down or verbalise a short explanation of their drawing; this helped communication and conversation and the understanding of what the children meant.

“Drawing and discussion” was used throughout the workshops, primarily to provoke conversation from the children about their drawings, but it was also used in the other activities such as the ranking exercises to uncover the meanings and decisions underlying their behaviour. Discussion is a method that often accompanies drawing (Driessnack, 2005) and is useful when working with children for a number of reasons. It helps to clarify the researcher’s interpretation of the drawing, it allows the researcher to ask about certain aspects of the drawing that is not necessarily clear to them, and it also allows the child to discuss the aspects of the drawing that are most meaningful to them (Pipe et al, 2002; Wesson & Salmon, 2001). Discussions with children are often more relaxed when conducted in group settings as it facilitates dynamic child-to-child discussion in ways not possible in one-to-one interviews between an adult and a child (Hunleth, 2011). When drawings are used as a projective measure (i.e. focussing on what the child says, rather than what they draw), it helps to build rapport and reduces the defensiveness of the child by redressing the power imbalance between the adult and child (Hennessy & Heary, 2005).

It is also thought that children attribute meaning not necessarily to the picture that they draw, but the action of drawing (Praiser, 2017), for example, in the study one child made straight lines on their drawing whilst making hand gestures depicting a ‘pop’ or ‘bursting’, at the same time as explaining that these lines showed the fizzy medicine bubbling in the bottle. So, whilst the finished image looks like a bottle with lines at the top of it, watching the process, what the child said, and their body language, helps to better represent the intended image, and the researcher’ understanding of its interpretation (see Figure 4.3).

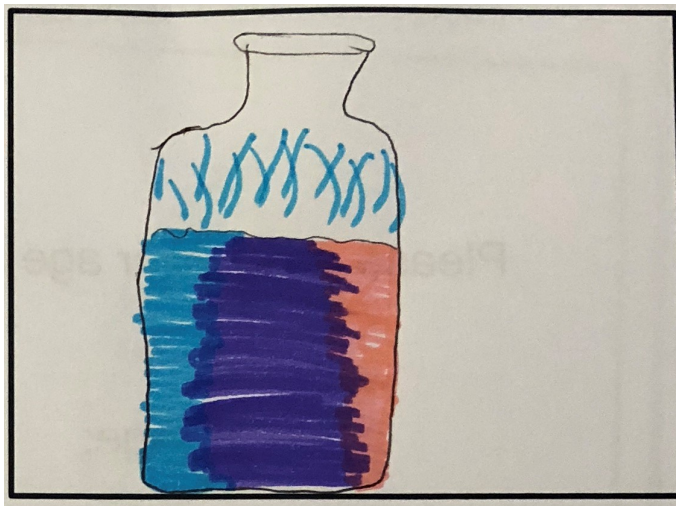


Figure 4.3: Image of a fizzing medicine (Child, aged 12).

Furthermore, children are meaning-makers (Wright, 2007), and make use of many different forms of verbal and non-verbal communication. Often children will demonstrate meaning within their drawings by writing letters, words, numbers and symbols, by physically expressing through movement or body language, and by constructing verbal signs, noises and words in order to convey the intended meaning of their drawings. It has been stated that drawing along with the act of telling, talking or discussing, enrich and inform each other (Kendrick & McKay, 2004). Drawing and discussing affords children the opportunity to create and share meaning using a duality of modes: the non-verbal graphic description which stems from imagery and visual-spatial memory; and the verbal description which involves talking about the drawing, events or graphic details. This crossover of modes is said to increase children's capacity to mentally manipulate and organise images, ideas and feelings (Cox, 2005).

The concept of using speech to accompany drawings is common in health research with children (Gauntlett and Horsley, 2004) and, in clinical and educational settings, drawing and discussion has been reported to produce twice as much information than talking alone (Driessnack, 2005; Patterson & Hayne, 2011). It has been observed that children aged 7-8 years appear to be able to illustrate their feelings and emotions with greater ease than they were able to articulate them (Wetton, 1999). Therefore, this may lead to richer data when both drawing and discussion are used together (Porcellato et al, 1999) as it is recognised that different ideas and perspectives might be presented depending on the methods used (Backett & Alexander, 1991). Horstman

et al (2008) suggest that current understandings of child development and the use of art may assist children in constructing complex ideas or recalling events, therefore, topics or issues that may otherwise have been avoided or ignored may be talked about, and a deeper understanding of the child's actual feelings and perceptions may become known by the researcher. It has also previously been stated that children often know more than their drawings reveal (Griever, 1990), and that drawing alone generates fewer ideas and data than drawing and discussing (Pridmore & Lansdown, 1997).

4.2.3 Activity sheets and booklets

The aim of the worksheets and booklets was to encourage the children to think about medicines and provide some information about which aspects of the medicine were most important. One worksheet was developed for the children aged 5-7 years and one for those aged 8-12 years. The 5-7-year worksheet (see Figure 4.4) is a one-page activity which asks the child to "Create their own medicine", the main activity was the 'Drawing Box' which the children could draw their medicine in. A smaller writing box next to the drawing box provided short sentence starters, typically used in schools with this age group, to facilitate some explanation of the children's drawing. The sentence starters asked the children: I have chosen this shape because… I have chosen this colour because… My medicine tastes like… My medicine smells like…

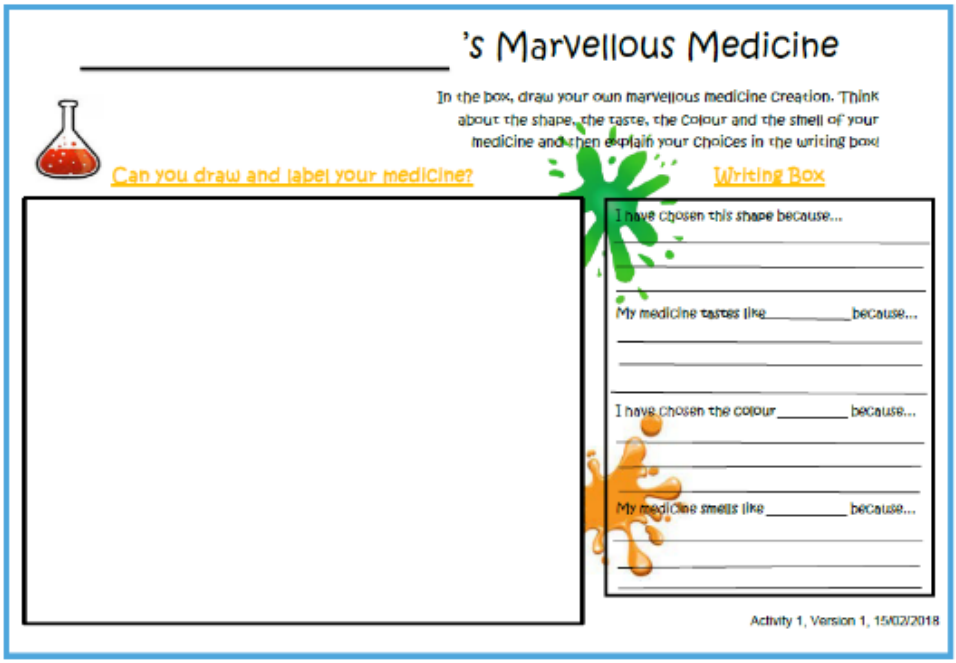
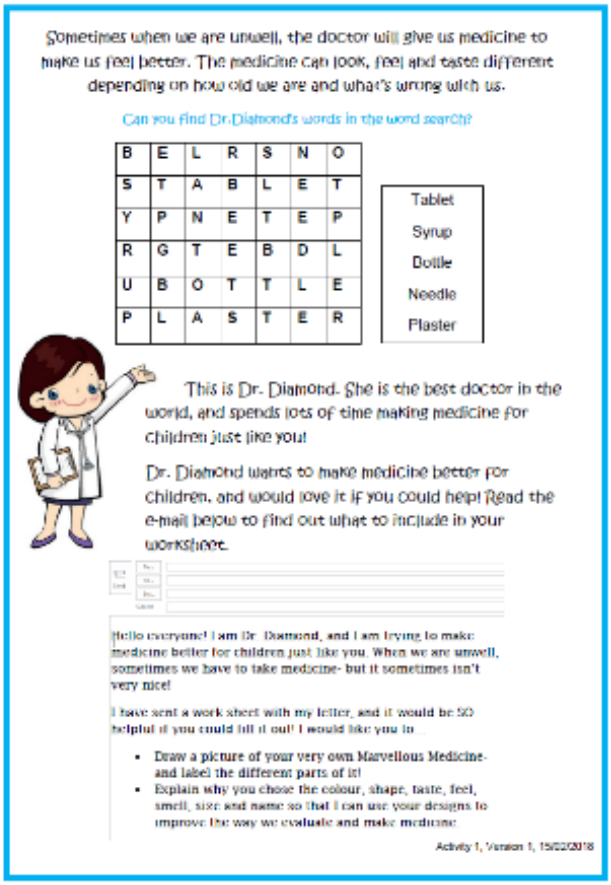


Figure 4.4: Activity sheet for the 5-7-year-old children



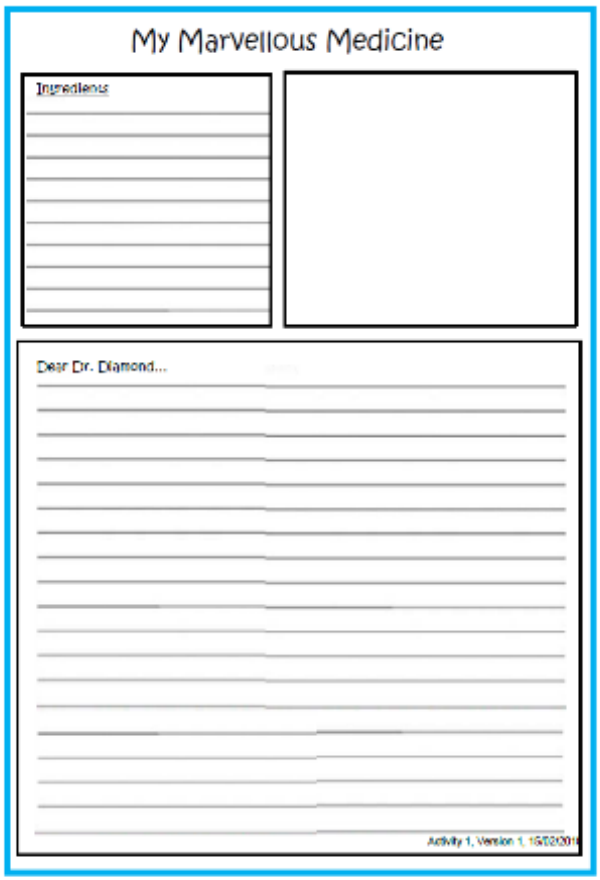


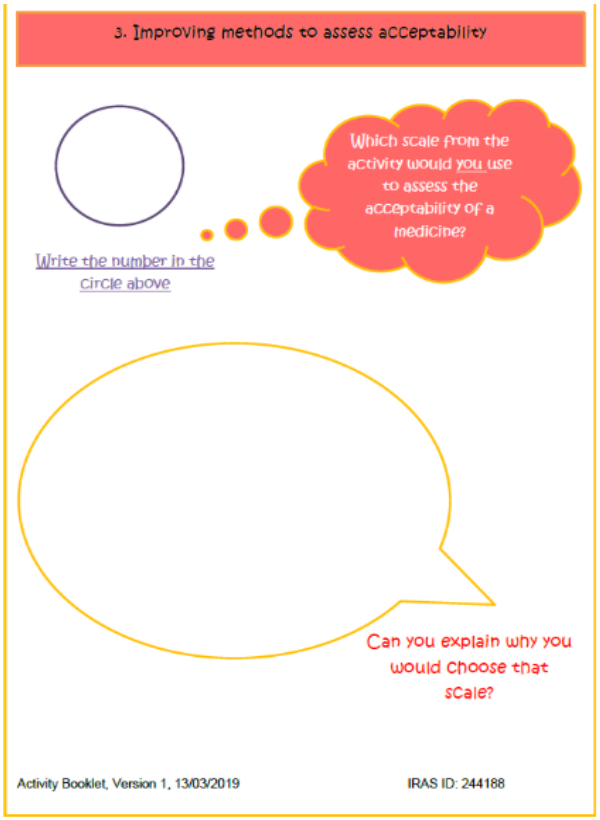
Figure 4.5 Activity sheet for the 8-12-year-old children

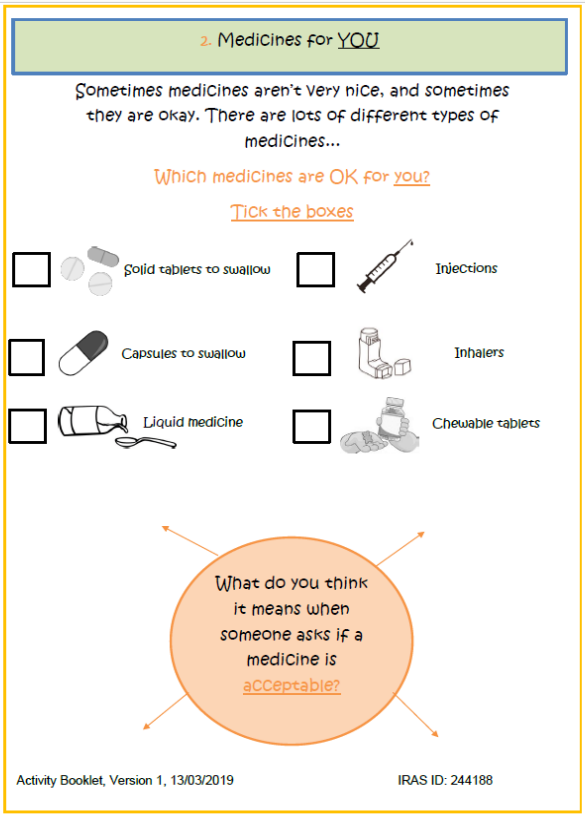
The 8-12-year activity sheet (Figure 4.5) aimed to facilitate the same information from an older age group. This was a two-page activity sheet geared toward older children's reading and writing skills and interests. The first page began with a short description in the form of an e-mail, explaining what the task was. On the back of the worksheet was a small drawing box for the older children to draw in, along with the main activity which asked them to write a paragraph about their medicine. Ideas for them to include were written in the email so they had some direction if they needed it. Children were also provided with blank pieces of paper and template sheets, which were offered as an alternative to the activity sheets, or for the children to use once they had finished. It was up to the children to decide which drawing materials they used, although most of them opted for the activity sheets.

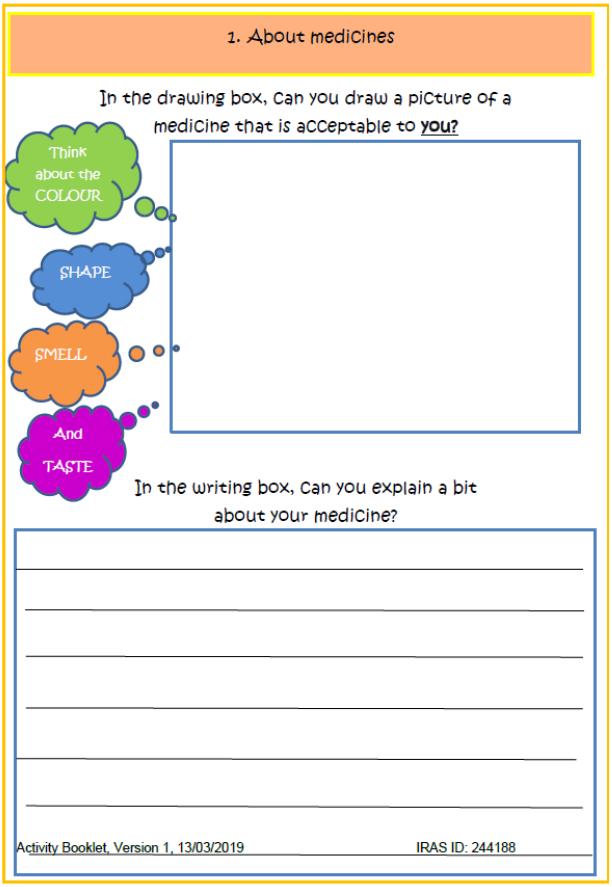
The activity sheets were designed to be a fun and child-centred option for children and a starting point for their engagement in the study. These sheets encouraged children to use their imaginations to create “marvellous medicine” and some guidance was provided as the children were asked to ‘think about shape, taste, colour and smell’ of the medicine. However, there was no expectation or guidance that these marvellous medicines would be either realistic or achievable. Giving free rein to their ideas and creativity mirrors to some extent the notion of ‘blue sky’ research which pushes boundaries and can sometimes be responsible for leaps forward in thinking. The aim of the exercise was to give the children no constraints in them being able to create the best possible medicine and to explore the characteristics and attributes that this marvellous medicine would have. In this activity, the discussions that accompanied these drawings were key to exploring what the children imagined a marvellous medicine to be, and what they believed would be helpful in a real medicine. The children were generally pragmatic and realised that some of the more magical, marvellous and unusual components of their designs might not be reasonable or realistic. However, the activity was successful in stretching their ideas and exploring key aesthetic issues of taste, shape, colour as well as aspects of related to the meaning and motivation for taking medicines.

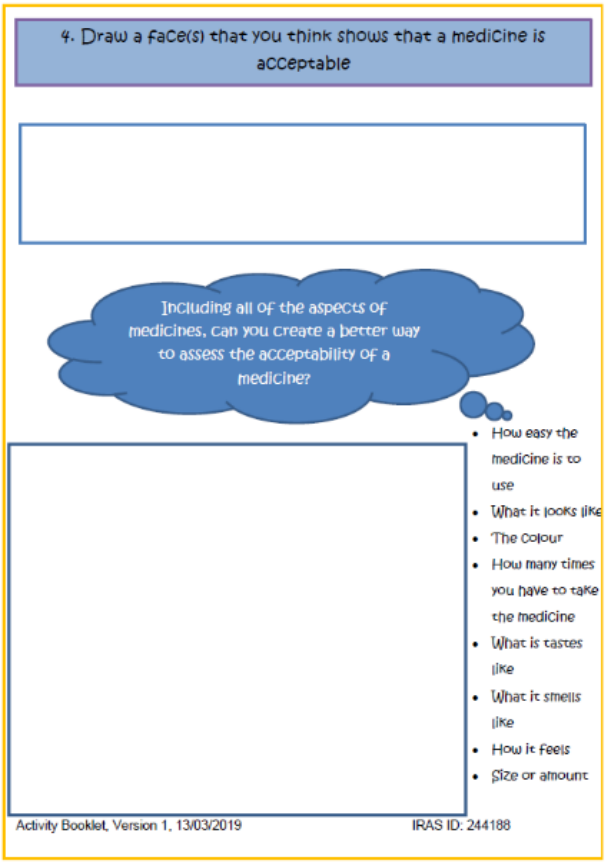
An additional data collection method was created as the workshops progressed, when it was realised that the existing activities would be difficult to use in smaller or more restricted settings, such as within schools and the hospital. An activity booklet was created which included the individual activities from both phase 1 and 2, in a more accessible form. The activity booklet consisted of 6 pages, with a separate activity on each page. The first page was an information sheet, asking the child for their ‘special name’ (pseudonym), their age and to circle if they were a boy or a girl, this was so that it was easy to match the activity booklet to a child and group them correctly into the relevant age and gender. Pages 2 and 3 (see Figure 4.6) aimed to elicit information about the children’s perceptions of the acceptability of medicines and the methods used to evaluate this acceptability. Pages 4-6 (see Figure 4.6) were focussed on refining the ideas from Phase 1 and to further the understanding of children’s acceptability of medicines. Pre-existing tools were evaluated in parallel to activity 3, which asks the children which scale they would prefer to use. In activity 5 the children

are asked to re-design or create a new method to assess the acceptability of medicines.









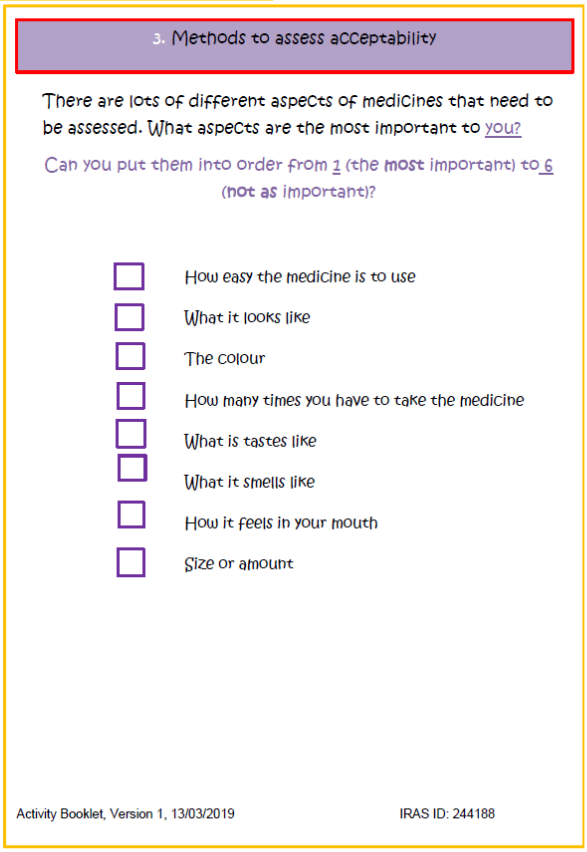


Figure 4.6: Activity booklet, pages 1-5

4.2.4 Ranking activities

Task-based activities such as ranking exercises have been used by researchers in research with children and are said to "enhance children's research imaginations" (Alderson, 2001, p147). Grouping or ranking exercises are used in a number of studies with children (Brooker, 2001), for example Gadd and Cable (2000) demonstrate how happy and sad faces can enable young children to present how much they like or dislike a situation. Ranking exercises are also commended for their ease of use and the ability of the child to rank aspects or issues of the research in order of importance (Clark, 2005). Children under the age of five have demonstrated their ability to understand and use ranking exercises (Maconochie, 2008). However, there is also evidence to suggest that, when used as the lone method with children, ranking exercises can become tokenistic (Clark et al, 2003) or too simplistic, as they typically deal with a narrow range of issues (Bragg, 2007).

In the current study the ranking activities were used as one way to understand which aspects of the medicines were most important, which flavours were preferred, and which acceptability measures were favoured. Small, laminated cue cards with the different aspects of medicine, flavours and scales were given to the children to interact and play with. In some workshops the children put them into their own order on the floor or on tables, whereas in others the children were able to use Velcro to arrange the cue cards on a game board (see Figure 4.7). The ranking exercises were intended to encourage a group consensus regarding which aspects of medicines were most and least important. However, these exercises ended up instead providing a useful prompt to encourage discussion due to the dynamics of the groups. For example, some of the group workshops were conducted in large spaces such as church halls, and this allowed children to break off into smaller groups and discuss the ranking game individually rather than together. Some children chose not to interact with the ranking activity as a 'game', and instead talked about the aspect cards rather than putting them in order.

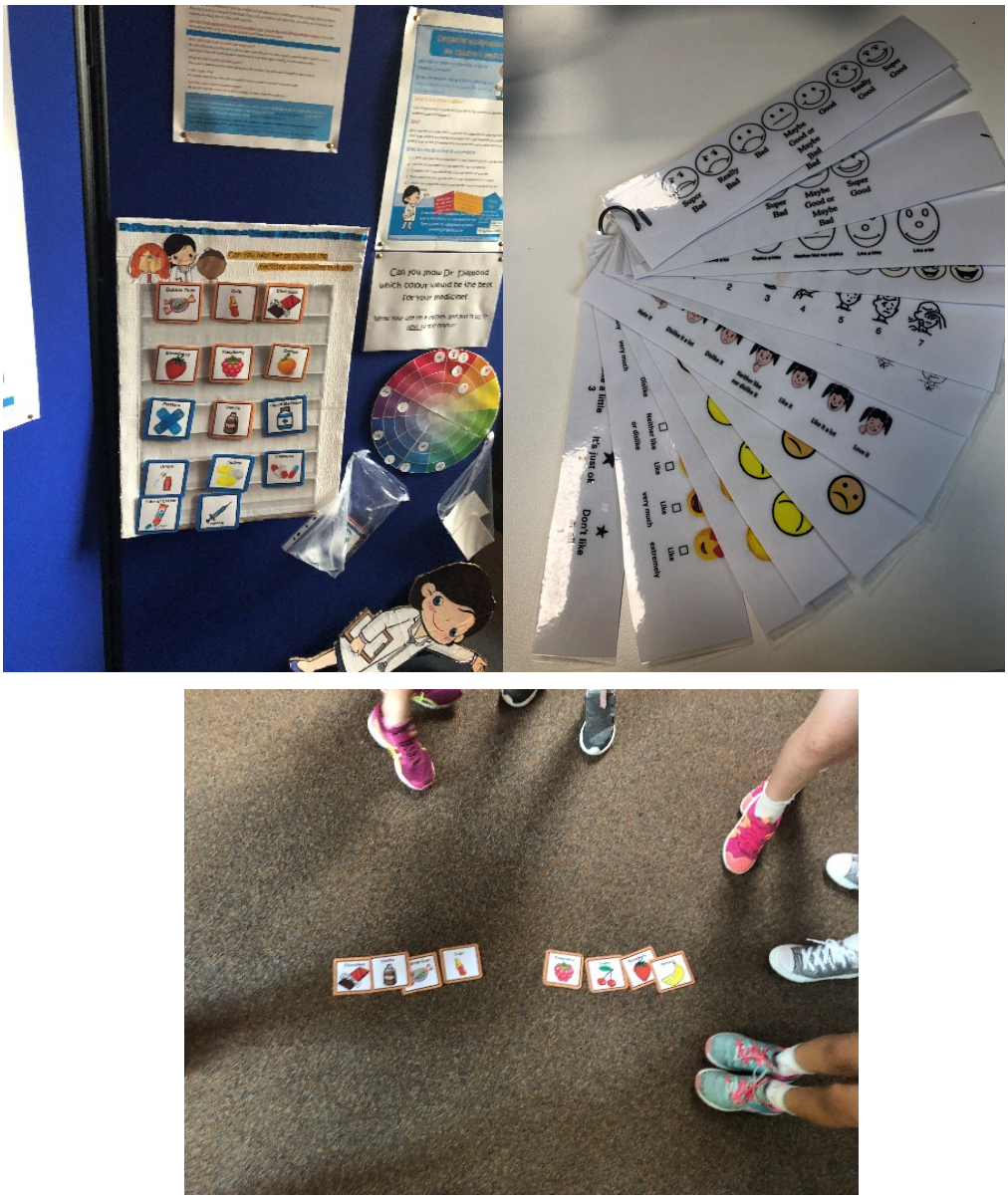


Figure 4.7: Selection of ranking activities used in workshops

4.2.5 Developing and undertaking the workshops

Workshops were chosen as a way of collecting data from the children. Workshops were identified as a valuable approach in settings where the children already knew each other and had established relationships. These were conducted under the general guidance for running focus groups which states that participants should share similar characteristics and be acquainted with one another (Kitzinger, 1994; Krueger & Casey, 2000). The group dynamic created by working with a group of children from the same age and background and who are already acquainted with one another, aims to decrease researcher control over the study and encourage the free expression of ideas from the participants (Kitzinger, 1994; Wilkinson 1998, Madriz, 2003).

Whereas in a traditional focus group or interview the researcher would take control of the discussion by using a structured or semi-structured interviewing schedule, the arts-based activities in the workshops offered prompts within a supportive environment (Kennedy et al, 2001). This provided the opportunity to gain information about the research topic. As Goss (1996) discusses, creating the opportunity for participants with similar characteristics to discuss the issues that they believe are relevant to their lives in relation to the activity, helps to ensure that the knowledge, language and concepts that are outcomes of the workshops are grounded in the voices and experiences of the participants. Arts-based methods were particularly useful for quieter or shy children as the workshop encouraged them to be confident to speak up, as also reported by McDonagh and Bateman (2012). Additionally, as noted by Richardson et al (2009), the children were able to build on each other's responses and often came up with thoughts relating to things that others were saying, which may not have happened in an individual interview.

It was intended that as the workshops progressed opportunities would be taken to review and modify the methods in collaboration with the children. Challenges that arose within the first workshops were evaluated and modified (such as adapting the work sheets and booklets), through discussion with the children and observation of the efficacy and limitations of various methods and approaches.

4.2.5.1 A listener and observant participation approach

The role of the researcher during data collection was varied and dependent on the group sizes and dynamics but it always involved some form of listening and observing the children and their interactions with the activities and, where other children were present, their interactions with one another. Listening and observation skills have been labelled as the basis for attaining a comprehensive understanding of a particular community or viewing social reality through the eyes of the participants (Venne, 2006). The decision to use the term 'listener and observant participation' instead of 'participant observation and listening' is also influenced by work such as Wilkinson (2013), and is based on the value placed on each role, whether that was as a 'participant' or a 'listener/observer'. At the same time as listening to, and observing the children and activities, the researcher was also consciously and intentionally

attempting to minimise her position as an 'outsider' who was there to observe and listen. This was achieved by being involved with the activities, for example, by taking up lying positions on the floor with them when they were drawing, interacting with them during the activities and talking with them rather than at them.

Although there is diversity in the definition of listening, in this instance, listening was understood to be the active process of communication, which involves hearing, interpreting and constructing meanings (Clark, 2005), which is not limited to spoken word. Listening was used within this research to pick up on and encourage a dynamic process of discussion with the children about things they were talking about or highlighting as important to them, as opposed to simply extracting what they were saying. Whilst listening, observing children's behaviours and interactions was also undertaken, mindful that children communicate in many different verbal and non-verbal ways (Edwards et al, 1998). Both the listening and observation helped to construct a more comprehensive understanding of their understanding, knowledge, thoughts and ideas about medicine development and assessment.

Observations of the children were also important in complementing the listener participation by "giving importance to the interpretation of actions and words, in the contexts that they occur" (Grieg & Taylor, 1999, p81). Observation techniques have long been used in early years education as a tool to understand young children's abilities and needs (Smidt, 2002), and are said to become increasingly important the younger a child is (Elfer & Selleck, 1999). The researcher was conscious of the risks of using observation such as her subjectivity as an adult researcher. There was a worry that behaviour, such as facial expressions and decisions (e.g. colour choices) might be interpreted an adult lens and that this might be incorrect or incomplete. Therefore, by actively involving the children in the interpretation and analysis by asking them questions and asking them to explain things, they were able to help clarify whether the observations and preliminary analysis were in line with their own perceptions (Miller, 1997; Clark, 2004).

4.2.5.2 Audio recording the workshops

The main reason for choosing to audio record the groups was to allow the researcher to interact freely with the children rather than having the distraction of having to try and

write down their comments. Recording the children's conversations and interactions with one another also aimed to help facilitate the subsequent interpretation of the physical outputs (pictures and drawings). The use of digitally recorded qualitative data has been commended for its "replayability" (Tessier, 2012, p449) this meant the researcher would have access to the original data that was "neither idealized or constrained" by a specific viewpoint or interpretation (Heritage, 1984, p 238).

Given the size of some of the workshops the audio recordings allowed me to record conversations between children that might otherwise have been missed. Many of the conversations centred on why children made certain decisions about their drawings or ordering, and so during analysis the transcribed audio files helped me to interpret and give meaning to their outputs. By basing the analysis on the significance that the children give to the data, rather than solely on the researcher's interpretation, it was aimed to lessen the chance of misinterpreting their meanings.

Although the audio recorder was minimally intrusive, having the children acknowledge its use was necessary to obtain their informed assent to being recorded. However, it was important that their knowledge of being recorded did not impact their natural behaviour. Before the recording began, the children's comfort and familiarity with the recorder was encouraged, by asking if anyone wanted to press the 'on' button and start or finish our recording. For most groups, the audio recorder was, at first, a novel 'toy' that they each wanted to 'have a turn' at. Throughout the workshop the children lost interest in the device, and it was often only when it was time to turn off the recorder that the children again requested to press the button. Involving the children in the recording helped them to take some ownership of it, and rather than me recording them, it instead became within the children's control.

In some of the workshops, such as the large group museum events, it was not possible to audio record given the setting (a large and noisy environment and the potential for not only recording specific children but also surrounding conversations), and the turnover of children attending the stall and taking part in the study. However, the focus of these busier workshops was on obtaining a large sample of children, as detailed in section 4.2.6. Instead, children were encouraged to write down their ideas and annotate their drawings. Additionally, in some of these busier workshops (e.g., within

the leisure groups when there were larger numbers of children within one room or hall) the children attending generally decided to sit in smaller groups to complete the activities, rather than sit in one large group together. Therefore, audio-recording each of the individual group discussions at all times was not feasible. The researcher carried the audio-recorder around the room with her and recorded only the information provided by the children when she was present. In future studies, it might be useful to provide each smaller sub-group with their own recorder to ensure no data is lost.

See Table 4.4 for detail regarding the number of children who participated in each activity, and contributed to each aspect of the study.

Table 4.4: Detail of number of children who participated in each activity.

	Schools			Clubs				Hospital	Museum	Total
Groups	**S1G1**	**S1G2**	**S2G1**	**R1W1**	**R1W2**	**R2**	**B1**	**Ward**	**Museum**	**Total**
Total	3	3	2	7		4	8	3	81	111
Drawing & Discussion	8			19				3	81	111
Activity sheets	5			19				0	81	105
Ranking activities	8			19				0	Unknown engagement	27
Activity booklets	5			11				3	0	19
Audio recorded	3 recordings.			4 recordings.				3 recordings.	0	10

*Unknown engagement: Due to the conduct of the museum event, not all activities were monitored. Therefore, the ranking activity was presented more as a game or discussion point for children to interact with. No information detailing how many children engaged with this activity were kept.

4.2.5.3 Undertaking the workshops

Each group of activities was planned to last no more than 60 minutes, this aimed to mitigate boredom, and also reflected the time available within the settings. The group sizes ranged between 3-8 children, depending on the original group size and some groups were split into smaller groups in line with guidance suggesting that group sizes of 8 or fewer are appropriate (Horner, 2000).

Phase 1 activities aimed to generate an understanding of children's acceptability and perceptions of medicines, and Phase 2 activities built on these to refine ideas and focus on evaluating and refining the tools used to assess acceptability. In Rainbows and Brownies where phase 1 and 2 were conducted separately, two visits were scheduled with each organisation. The workshops were carried out in a flexible and unstructured manner, each comprised of 3 key parts: introduction, main activity, debrief.

4.2.5.4 Introducing the workshops

Each workshop began by introductions to the children and having them all sit down together. The researcher explained who she was, what the workshop was about and what we would be doing for the next half an hour during the main activities. During the introduction and debrief parts of the workshop, which approximately lasted for 15 minutes each, it was important that the children listened whilst it was explained, primarily so that any questions could be answered, issues identified, and a safe space was provided for children to assent or dissent to taking part. Larger groups were managed by using pre-existing methods such as a 'talking stick' or 'Olivia' (a doll used within guiding groups which is passed around the children for them to hold whilst they talk). This was a particularly helpful technique in the larger workshops and those with younger children.

After the initial introductions and when assent had been gained, workshops began with an open discussion about the general area of medicine, what the children knew about it and if they had ever been given medicine; this aimed to be free flowing to allow for the natural progression of conversation. The children were all eager to share their stories of times when they had taken or been given medicine or stories about someone, they knew who took medicine. The discussions naturally progressed to what the children liked and disliked about medicine, and with some prompting such as "can you tell me more about that?", the children discussed the different kinds of medicines, and the flavours, smells and other aspects that they liked or disliked.

4.2.5.5 Main activity

Following the introduction, the main activities were presented. Each activity was explained the drawing materials were introduced. Whilst most of the groups had their

own supply of materials, all of the children expressed an interest to use the pens and pencils that were provided. The activities are presented in more detail in the previous section 2.4.5.

All of the children chose to interact with the drawing activities first and settled into a space in the room with a selection of pens and pencils to begin their drawings. The younger children actively involved one another in their creations and explained what they were drawing although some children chose to draw without input from their friends. In some cases, children asked for help to draw a shape or colour in, but mostly the children were more interested in explaining to me what they were drawing and why. Once the activity pages were complete, some children opted to continue drawing either on plain paper or by using the templates, and others engaged with different games that were not related to the workshop activities, such as skipping and playing together.

The ranking activity was somewhat structured in some workshops and completely unstructured in others. In larger workshops the ranking activities were left for the children to interact with freely, they talked amongst themselves about where each card should be positioned. In the smaller groups, once the drawing activities were tidied away, we looked at the cards together and discussed some of the medicines. Following this the children were asked to order the cards in whatever way they decided. Most of the time the order of the cards was a straight line with the flavours on one level and forms of medicine (i.e. liquid or tablet or inhaler etc) on another, for example, in one workshop the children separated the flavours into ‘fruits’ and ‘sweets’.

The third activity involved the children interacting with and evaluating different acceptability scales. Laminated scales and examples of currently used methods that are used to assess the acceptability of medicines were provided. The children played with these scales, circled their favourites, completed the example scales and discussed what they liked and disliked about them. The children were provided with post-it notes, stickers, emojis and novel templates such as empty ‘Top Trump’ cards and plain paper to re-design and develop the scales in ways they thought were more appropriate. Whilst the children were completing these activities, questions such as

“why did you choose that game/layout?” and “why have you decided to use (colour)?” were discussed.

4.2.5.6 Debrief

The workshops ended with a short debrief to give the children time and opportunities to ask any questions they had and to play with their friends before going back home or to their classes. The children were all told they could take their drawings home, if they wanted to do this, pictures were taken of their drawings. Most of the children decided to take their activities with them, along with certificates and debrief sheets with more information. They were each given the choice of a sticker and a small gift such as a rubber. Images of the children’s drawings can be found in the Findings (Chapters 5 and 6).

4.2.6 Museum

The World Museum event provided an opportunity to recruit a larger number of children than those attending the school and the clubs. The identification of the museum 'Meet the Scientist' event provided the chance to extend the initial recruitment sites to include this as a third site. These events are described as ‘interactive, hands-on science days for all the family’, and are mainly attended by children between the ages of 4-12 years and their parents/carers. This seemed an ideal setting to recruit children for the study, so an area was provided for the researcher to set up a stall and be one of the 'scientists'. Members of the PMRU team at Alder Hey and colleagues from Edge Hill University accompanied the researcher to ensure that the children taking part on the day understood the study and were fully informed in how their data would be used for the study.

The difference in the conduct of the study between the workshops and museum relates primarily to the participants and data collection techniques. The museum event was a much more fluid environment due to the fact that the event was not pre-bookable, and no prior contact was available with the families. However, as earlier mentioned there was a level of expectation that those present were attending the museum with the intention of engaging with the activities and getting involved in the day. Groups that arrived together such as school trips, families or groups of friends, and individual

children, were able to approach the stall and complete the activities. Therefore, the focus was less on the group dynamic and more about engaging a large number of children in a variety of activities simultaneously. The activities used within this setting were the same as within workshops although since the children had no set schedule for taking part, they could select whichever activity they wanted to. Each activity was clearly labelled and both children and parents were informed about the study before taking part in the activities. The research team present on the day aimed to ensure that each child had the opportunity to discuss with an adult about the study, although it was clear that the children were talking to their parents or guardians about the activities (Figure 4.8).

Once the children had completed the drawing activities, someone from the team of researcher's present would ask the children again if they wanted to take part in the study. If they did, they were able to post their drawing activities into Dr. Diamond's letter box. Following this they were provided with certificates of participation and stickers, along with debrief sheets which contained additional information regarding the study and contact numbers for them to get in touch with the researcher if required.

Figure 4.8: Children discussing with parent and researcher about the activities (permission gained for use of photograph).

4.2.7 Clinical setting (Hospital)

As opposed to the small group workshops conducted within the schools and clubs and the large event held in the museum, the hospital provided an opportunity to undertake one-to-one semi-structured interviews with children. The inclusion of a clinical setting provided an opportunity to recruit children who were likely to have more experience taking medicines than children recruited from the other settings and therefore could provide another perspective on the acceptability of medicines.

The key difference between the workshops and hospital setting was that the data collection methods and techniques were adapted to suit the setting. Children were invited to take part in an interview rather than a workshop, as it was deemed that interviews would be more feasible and appropriate considering the setting. Although the benefits of the workshops could not be engaged in, the children were able to have one-to-one attention from the researcher who was able to tailor the interview to meet that child's particular needs. Semi-structured interviews have long been used in qualitative research with children (Burnard, 2005), and are frequently used by nurses who conduct research within hospitals with children (Baumbusch, 2010). Semi-structured interviews are said to facilitate rich description and personal accounts of children's experiences and perspectives (Lambert & Loiselle, 2008) provided they are conducted in a way that allows for children's spontaneous and in-depth responses (Ryan et al, 2009).

In order to facilitate the rich description and accounts of children's experiences, developing an interview guide is key (Ryan et al, 2009). The activities from the workshops were adapted and developed into an activity booklet (see Figure 4.6), which was used as a semi-structured guide for the interviews. A key benefit of using an activity booklet was that the child had control over which activities they engaged with, this helped to minimise the extent to which the researcher led the interview (Steubert & Carpenter, 1995). Additionally, the same techniques used within the workshops such as listening, observing and discussing were also used, creating a reciprocal environment that aimed to lessen power dynamics.

Each interview followed a similar pattern, the researcher was introduced to the child by a healthcare professional such as a nurse or ward manager who had identified the child as eligible. Following this, the study was explained to both parent and child and information was provided for them to read through (full details of the recruitment process can be found in section 4.1.5). After attaining consent and assent, each interview began with an open discussion about medicines which the children in the hospital generally took point on, explaining what medicines they had and why. In each case, the children were eager to start the activity booklet, and enjoyed having the choice of materials (such as different pens, pencils and crayons) to use. The adapted version of the ranking game worked well, and the children could number the aspects of medicines from 1 to 6 based on how important they were to the individual child. Finally, the children enjoyed interacting with the laminated scales, and used the pens to colour, draw and label the scales depending on their opinions.

Following the completion of the activity booklet, the children were provided with a certificate and a debrief sheet, and each child seemed happy with this. Most children at the hospital chose to take their booklets home with them, and so before I left, I took pictures of their booklets with their permission to use for data analysis. The children were all provided with a choice of sticker and rubber as a small thank you and appreciation for taking part. The parents were provided with a copy of the consent and assent forms in line with the requirements of ethics approval for this setting.

4.2.8 Photography

Supplementary data were obtained through pictures and photographs of the completed activities. Some children opted to take their drawings and creations home, when this happened photographs were taken of each item - with their permission/assent - in order to document them. The photographs were also used to record the context of the drawings, activities and groups, and then used as reference points during analysis to inform interpretation of the children's drawings.

4.3 Ethics

Ethics approval was obtained (FOHS 204) from the Edge Hill University, Faculty of Health and Social Care Research Ethics Committee (FREC) prior to conducting any fieldwork in the settings and ensured that the research was consistent with ethical

guidelines outlined in Edge Hill University's Ethical Guidelines for Undertaking Research with Children and Young People (UREC, 2012). As this study involved the collection of data from children within an NHS hospital, Health Research Authority (HRA) ethical approval was also necessary. HRA approval was granted on (date), following this a research passport form was completed for the participating NHS trust and a local capacity and capability letter of access was provided. Complete adherence to university and NHA policy and ethical documentation was followed at all times, however, as Horton (2008) notes, it is acknowledged that there is more to consider when doing research than described in the guidelines of 'good practice'. Regardless of how ethically well designed or prepared a researcher is, it is recognised that as Morrow and Richards (1996) assert, it is impossible for researchers to foresee what ethical issues may arise throughout the research process, therefore ethics were considered situational and the researcher was responsive to ethics throughout this study.

Many methodological and ethical issues that researchers are faced with when conducting research with children are no different to research with adults, for example, issues related to the risks and benefits of participation, confidentiality, interpreting and disseminating findings, as well as issues of participant protection and withdrawal (Dawson, 2009; Morrow, 2008). However, research with children also generates additional ethical issues such as power dynamics, competence and the inclusion of the child's 'voice'. Power dynamics when conducting research with children have been recognised as a problem (Dorozenko, 2016), with children often perceived as a "powerless group in society" (Morrow, 2008, p16). Whilst it was not the intention to adopt these power roles, the researcher's positionality as an adult academic and the lead researcher in the study, provided a position of power. However, the children were also perceived as 'powerful', as they have knowledge and experience that adults do not have.

Related to this latter point is the notion of children's competence (Horgan, 2016). Children have traditionally been viewed by adults as not competent enough to express an opinion (Maconochie, 2008). However, in the previous chapter it is argued that children think and communicate differently to adults (Piaget, 1932; Barker and Weller, 2003), and that it is up to us, as adults, to account for children's strengths in research.

In this current study methods typically reported as best practice with children were employed (Literat, 2013; Biggeri and Anich, 2009), these methods have been praised for enabling children to express their opinions and voices within research (Driessnack, 2005).

As a means of ensuring an awareness of the researcher's responsibilities and to ensure that legal requirements were adhered to, a DBS check was obtained, along with the NIHR Introduction to Good Clinical Practice (GCP) eLearning training and NIHR Informed Consent in Paediatric Research training.

4.3.1 Representation

Representations are central to the process by which cultural knowledge is produced, exchanged and circulated in every instance of personal and social interaction (Gall, 1997). The researcher was conscious that in order to effectively represent the children there would be required to account for the individual children and their experiences, age and gender.

Representing children is not regarded as a straightforward task, the concept of childhood is dependent on how people view it and childhood is often (re)produced in relation to those cultural perceptions of childhood prevalent in the surrounding society (Ariès, 1962; Corsaro, 1997). However, it is necessary to represent and include children in research if meaningful data is to be produced (UNCRC, 1989). Accessing and representing children within research is not only difficult because of the adult presuppositions that we are naturally inclined to, but also due to methodological challenges and expectations the researcher faces (Sharp, 2001). It is widely understood that children communicate differently to adults, and so it becomes difficult for the researcher to recognise children's views and voices when they are expected to provide adult typical data, such as long interview transcripts and detailed written accounts (Maconochie, 2008). The researcher wanted to avoid simply listening to or extracting the views and voices of children within research (Mand, 2012), and instead "hear, interpret and make meaning" (Ebrahim and Muthukrishna, 2004; 85) with the children in a way that they are familiar with (Cook and Hess, 2007).

Although using child-centred methods can overcome issues of misrepresentation, these methods can generate data that are complex in terms of 'capturing' meaning. It is becoming popular to employ visual and creative methods of data collection to identify and evaluate children's emotions, experiences and development (Burkitt, 2004), as well as explore their conceptions and meaning making of activities (Ring, 2006). These methods are also commended for their ability to maximise children's involvement in research (Pfister & Vindrola-Padros, 2012) and to address sensitive topics. Nevertheless, there is still some resistance to using these methods.

There are concerns that the authenticity of the children's voice and views are nullified when the researcher attempts to interpret and re-present this child focussed data. This 'crisis of representation' occurs when an adult researcher, who does not share the same views, experiences or ideas as the children, attempts to frame the child-made data within the study (Lincoln and Denzin, 2000). However, this crisis of representation is not unique to children, in fact, it is relevant across all qualitative research where an "other's" voice is represented. Whilst it may be the case that issues of representation are more obvious with children, it is not the case that this inherently any more problematic than with adults (Maconochie, 2008). Therefore, the question is not "Can I rely on the child's voice?" but instead, "Am I, as an adult researcher, presenting what the child has said, as expressed by *them*?".

It is not proposed that, because of the inclusion of children, this research resists adult interests or becomes child centred. However, by providing the children with tools and methods that are *typically* child-centred, the children and the researcher were able to co-construct and formulate ideas, views and understandings. It is also considered hat the co-constructed knowledge is not void of the researcher's own influences. However, the study was conducted mindful of the issues that can arise when including children in the research and aimed to collaboratively produce information about the acceptability of medicine. The researcher was also conscious that the methods that are used to evaluate the acceptability of medicine are used by <u>both</u> children and adults and, like Dahlberg et al (1999), it is therefore emphasised that meaning making, rather than seeking to capture direct voices, acknowledges the values of interpretation, contextuality, and subjectivity, especially in the context of acceptability assessment development.

4.3.2 Gaining access, consent and assent

One of the main challenges when conducting research with children is negotiating access at the varying levels with adults who have a responsibility for the child (Sime, 2008). The multiple settings in this study required consideration of each setting, and individuals that would be required to obtain consent from in order to undertake the study. In each setting, the first person that was typically met with was the gatekeeper, these included the head teacher at the schools, event organiser at the museum, group leader at the guides or research and ward managers at the hospital. Throughout the study, each gatekeeper was provided with an Information Summary Sheet (Appendix 35) and permission (along with any other necessary approvals) was granted by each adult gatekeeper to conduct the research at their organisations.

A further level of access from parents or guardians is required when conducting research with children. The children's well-being was of high importance throughout the study and consent and assent procedures followed current guidelines from the British Medical Association (BMA, 2016) which state that for under the age of 16, consent from a parent/legal guardian is first required.

Parent information sheets (Appendix 8) and two Child Information Sheets, one for each age group (5-7, 8-12 years) (see Appendix 10 and 11) were developed; these had full details about the research study, potential risks and benefits of participation, confidentiality, and their right to withdraw. These documents were produced and amended in consultation with the Liverpool YPAG at Alder Hey. The group is a community of members between the ages of 10-15 years old who meet up every six weeks to support the design and delivery of health research in children and young people. This ensured that the documentation was presented in an accessible, interesting and appropriate way for the age groups relevant to the study.

As all children in this study were under the age of 16, parents were asked to read through detailed parent information forms and consent sheets. Children were provided with child-friendly information forms and assent sheets and parents were asked to read

through these with their child/children to ensure that both parent and child were fully informed and in agreement to take part in the study.

In the clubs and schools, the children and their parents were provided with information and consent/assent sheets by either the researcher or gatekeeper in each group. They were given at least a week to read through information sheets and consider taking part in the study. In the hospital setting parents were required to provide verbal permission before I could talk to their child about taking part in the study. Once their permission was attained, the child was provided with a child-friendly information sheet.

In the museum setting the consent process was slightly different to the other settings. At the stall large information sheets were clearly displayed on boards and had a variety of parent and child information sheets on the tables. Before the children were given an activity sheet, parents were asked if they agreed to allowing their child to take part. Details about recruitment have been presented earlier in the chapter (section 4.1.5).

Apart from the children at the Museum, all of the children who participated in the study provided written assent. At the museum, notions of implied consent were relied on (Stephen et al, 2008). After they had finished their drawing or activity, the children were reminded that if they posted it into 'Dr Diamond's Letter Box' this meant that they were agreeing to be in the study. The physical act of posting the drawing was regarded as their assent.

Throughout the data collection assent was viewed as a "process" (Heath et al, 2007, 409), relying on the children's verbal and behavioural cues as their on-going willingness to participate (Flewitt, 2005). It was emphasised that their participation was voluntary by regularly reminding them that they could "play with something else" or "do a different activity" if they wanted to, highlighting their rights to withdraw at any time. This was particularly important when moving from one activity to another. The nature of the workshops allowed the children to participate when, and in what activities, they wanted to without them having to formally explain when they were leaving the activities. If the children re-joined the activities verbal assent was required to ensure they were happy to continue (Hall, 2009).

4.3.3 Confidentiality and anonymity

The confidentiality of all children in this study, and their data, is assured as far as possible by using pseudonyms and the confidential storing of all data on secure and password protected computers (Article 5, General Data Protection Regulation, 2016). Any identifiable data including paper copies of information data containing the names, age and ID number, such as consent or assent forms, were stored in a sealed envelope in a locked drawer in the researcher's office at the University. Any scanned documents were securely stored electronically on a password protected service at Edge Hill University. Physical copies of identifiable data that was collected at the Children's Hospital were stored securely in sealed envelopes and in a locked filing cabinet at the hospital whilst the researcher was on site. At the earliest possible convenience, the researcher transported documents from the hospital to the research office at the University. Any data that had identifying or potentially identifying data were stored separately from the anonymous data. The device(s) used to record the audio data was not left unattended from the researcher, unless stored in a secure drawer within the researcher's office. Audio files will be kept on a secure server until the thesis has been submitted and approved, in any case that the researcher may need to listen to the raw data. All personal data was anonymised at transcription, and all identifiable data was removed from the transcripts and observational data.

It was made clear to the children that if a situation arose in which there was a reasonable cause for concern that more harm would come from maintaining confidentiality (e.g., in a situation where a child is the victim of harm), this would need to be reported to an independent adult at the venue, and appropriate action would be taken in line with the organisation's and Edge Hill University's policies and procedures. Thankfully this was not a necessary procedure during the study.

Rather than assign a pseudonym to the children to provide anonymity, children were asked if they would like to pick their own. Many of the children opted for non-typical names such as "popcorn" or "doo-doo" and the use of names of superheroes and princesses such as "Superman" and "Belle" was also common. Some of the children seemed resistant or unsure about choosing their own names and would ask "if that [name] was okay". Following the example of previous work such as that by Moorefield-

Lang (2010), the children naming themselves was welcomes as it was believed this was a 'stamp' of their identity and afforded them more agency in meaning-making and ownership. The children wore name badges in the workshops which had their chosen names written on them, these names were also put on their worksheets and drawings so that when we were talking it was easy to match up conversations to workshop outputs. A few children put their actual names on drawings and activities, and so before the workshops ended, they were asked whether they meant to do this, or whether they mistakenly put their actual name rather than pseudonym. This was believed important to clarify in case the children wanted to take ownership of these pieces of work or take them home with them. In most cases this was simply a mistake, and so before using the images these named were removed/covered.

4.4 Data Analysis

There is no one method specified for analysing research conducted using a generic qualitative approach. The literature provides a variety of data analysis approaches employed to undertake generic qualitative analysis. Some studies have relied on thematic analysis (Bellamy et al, 2016; Carter-Greene, 2019), whereas others have made use of inductive analysis (Liu, 2016), and framework analysis (Pope et al, 2000; Cross et al, 2005). Despite the variety of data analysis methods used in generic qualitative research, Merriam (2002) stresses that the purpose of generic qualitative research is to seek to understand how people interpret, construct or make meaning from their world and experiences. Building on this, Lim (2011, p52) adds that the methods used within this research are "highly inductive", making use of open codes, categories and thematic analysis. Therefore, the use of thematic analysis in the current study aligns to the nature of generic qualitative research outlined above, accounting for the "rich description" (Lim, 2011, p52) and intentional flexibility of generic qualitative research (Thorne, Kirkham, & O'Flynn-Magee, 2004).

Thematic Analysis is a widely used generic method of analysis which involves "searching across a data set – be that a number of interviews or focus groups, or a range of texts – to find repeated patterns of meanings" (Braun & Clark, 2006, p. 86). A primary advantage of thematic analysis is that it is a method, rather than a methodology (Braun and Clark, 2006; 2013), and so is not bound to any one

epistemological or theoretical perspective (Maguire & Delahunt, 2017). This offers a process of data analysis which allows for flexibility and that is compatible with many research approaches, this is a significant advantage when considering its use with generic qualitative research (Percy et al, 2015). King (2004) argues that the use of Thematic Analysis is beneficial when examining a large qualitative data set. It allows for the examination and comparison of different participants' perspectives, and is useful in the subsequent synthesis, analysis and communication of results (Braun and Clark, 2006; Polit and Beck, 2008).

Whilst offering advantages in its flexibility and accessibility (Braun and Clark, 2006; King, 2004), there are also disadvantages associated with this method of analysis. A key disadvantage relates to the flexibility of the approach. The variety of ways to approach thematic analysis has caused confusion and its validity has been questioned (Braun and Clark, 2014). However, such criticisms are often related to a "lack of understanding about the potential of TA (Thematic Analysis)" (Braun and Clark, 2014, p2) and the 6-step framework recommended by Braun and Clark (2006) provides a systematic and robust method for coding and identifying patterns within a qualitative dataset. This framework is reported to be useful for those undertaking health research and is the approach adopted for analysis in this study.

The aim of thematic analysis is to identify themes. Braun and Clark (2006) distinguish between semantic and latent themes. The process for identifying semantic themes (i.e. the things a participant has written, drawn or said- nothing more than the explicit or surface meaning of the data) is presented in Table 4.4 The latent level themes aim to look beyond what has been said and "… starts to identify or examine the underlying ideas, assumptions, and conceptualisations- and ideologies- that are theorised as shaping or informing the semantic content of the data" (p84). To overcome the criticisms of inconsistency and lack of coherence when developing latent themes (Holloway and Todres, 2003), it is important that the researcher is explicit about their epistemological position and that this is applied to the study's analysis and is coherent with the study's empirical claims (Holloway and Todres, 2003; Lorelli et al, 2017).

The provision of structure and order that Thematic Analysis offers helps to guide the researcher through a well-structured approach to handling the data and therefore

allowing for greater transparency of the analysis (King, 2004). This focus on transparency is encouraged by Braun and Clarke (2006) to help the researcher understand and make clear their own theoretical position and how this might influence the analysis.

Thematic Analysis can be used in both an inductive (bottom-up) and deductive (top-down) way (Maguire and Delahunt, 2017). This study used an inductive approach as this made sense in terms of the focus on meaning-making, in-depth perspectives, views, feelings and the reality of children in respect to the acceptability of medicine. The semantic analysis therefore was not driven by the researcher or research questions, but by the data itself as its focus was on what each group of children had to say about the acceptability of medicine. However, it is not claimed that the research questions did not influence the data analysis at all, as the researcher was conscious that themes identified would be influenced by the research aims. The researcher worked hard to ensure that the analysis moved beyond simply describing what was said, and into latent analysis of the data by interpreting and explaining it.

Following Braun and Clarke's (2006) six phase framework of Thematic Analysis, themes were identified both within and across participant groups. This framework provided a systematic process of analysis which was followed closely throughout the data analysis in this study.

Table 4.5: Six phase framework of Thematic Analysis (Braun and Clarke, 2006)

Phase 1: Familiarisation	Is common to all forms of qualitative analysis – the researcher must immerse themselves in, and become intimately familiar with, their data; reading and re-reading the data (and listening to audio-recorded data at least once, if relevant) and noting any initial analytic observations.
Phase 2: Coding	Also a common element of many approaches to qualitative analysis (see Braun & Clarke, 2012a, for thorough comparison), this involves generating pithy labels for important features of the data of relevance to the (broad) research question guiding the analysis. Coding is not simply a method of data reduction, it is also an analytic process, so codes capture both a semantic and conceptual reading of the data. The researcher codes every data item and ends this phase by collating all their codes and relevant data extracts.

Phase 3: Searching for themes	A theme is a coherent and meaningful pattern in the data relevant to the research question. If codes are the bricks and tiles in a brick and tile house, then themes are the walls and roof panels. Searching for themes is a bit like coding your codes to identify similarity in the data. This 'searching' is an active process; themes are not hidden in the data waiting to be discovered by the intrepid researcher, rather the researcher constructs themes. The researcher ends this phase by collating all the coded data relevant to each theme.
Phase 4: Reviewing themes	Involves checking that the themes 'work' in relation to both the coded extracts and the full data-set. The researcher should reflect on whether the themes tell a convincing and compelling story about the data and begin to define the nature of each individual theme, and the relationship between the themes. It may be necessary to collapse two themes together or to split a theme into two or more themes, or to discard the candidate themes altogether and begin again the process of theme development.
Phase 5: Defining and naming themes	Requires the researcher to conduct and write a detailed analysis of each theme (the researcher should ask 'what story does this theme tell?' and 'how does this theme fit into the overall story about the data?'), identifying the 'essence' of each theme and constructing a concise, punchy and informative name for each theme.
Phase 6: Writing up	Writing is an integral element of the analytic process in TA (and most qualitative research). Writing-up involves weaving together the analytic narrative and (vivid) data extracts to tell the reader a coherent and persuasive story about the data and contextualising it in relation to existing literature.

The six stages in the table above were followed during the data analysis in this study. Some initial analysis of the data occurred during the data collection process during discussions with children about what they had drawn, their proposed rankings, their intended meanings and contextualisation of their data.

Familiarisation (Phase 1) occurred whilst the task of transcribing the audio recordings was carried out. Each workshop and interview was independently transcribed as soon as possible following its completion, in order to capture not only the spoken word but also any non-audio data such as: facial expressions, body language, movements and pauses that would otherwise be lost in the audio recording. This was completed through listening and re-listening to each recording, transcribing each time, and verifying the transcript whilst listening to the raw audio file a final time. In an attempt to maintain the authenticity of the children's voices as far as possible, their words were

transcribed verbatim in order to ‘capture’ the children as they are, and as they presented their ideas and thoughts.

After immersion in each individual data set through repeated reading of the transcripts and through line by line analysis, the data was preliminarily coded (Phase 2). Although there is an argument to use online software for this step in the analysis process (Smith, 2017), the researcher believed this process took away the authenticity and immersion that qualitative analysis calls for. Therefore, it was decided that analysis would be conducted using hard copies of the transcripts, as suggested by Smith, Flowers & Larkin (2009). This was an active process, facilitated by the notes made during and after each data collection session based on the discussions with children (Paton, 1990). Having these notes available helped to contextualise the children’s responses and highlight key concepts and ideas that they identified as important in each age and gender group. Transcripts were initially coded as individual documents, initial ideas, codes, and themes were identified and transferred into a table. Coding the interview and workshop transcripts individually allowed for the individual child’s or group’s perspectives to be identified without trying to fit each transcript into a set of codes or themes from other interviews. This meant that different codes were identified and complements the inductive approach of data analysis adopted in this study.

The process for coding was in depth and ongoing and began by identifying semantic codes. These codes were easily identified through the labelling of surface meanings of what the children did or said, for example in one interview a child explained that they liked Calpol, so a code for Calpol was created along with ‘like’ or ‘positive’. Following this, latent codes, which capture the interpretations, assumptions and underlying ideas of the data were identified. In this example, the child’s positive view of Calpol seemed to originate from past experiences of taking the medicine, referring specifically to a time they could recall when Calpol helped them to get better. These codes were then grouped into themes.

Once these codes had been identified on hard copies of the individual transcripts, word files on the computer were created for each emerging theme (Phase 3). These files acted as ‘master themes’ where the relevant participant quotations were copied and pasted along with which transcript they were originally from and line number in

order to make identification a more structured process, as suggested by Smith (2009). This enabled the collation of quotations, searching for commonalities and differences between different participants perceptions in each workshop and interview. It also allowed an overview of how big each proposed theme was, with the frequency of supporting statements easily observable.

After each transcript had been coded and organised into one of the theme files, sub-ordinate and super-ordinate themes were refined and re-organised into a table (Phase 4). This process began by grouping all similar themes together and condensing themes where there was overlap or repetition, however this was an iterative process and as the themes developed consideration was given to the richness of data and its relevance to the research questions. It was evident from the analysis that the findings would be split into two sections- the first focussing primarily on what children had to say about the acceptability of medicines, and the second focussed on children's drawings, re-development and new ideas for assessing the acceptability of medicines. Therefore, two separate 'master' tables were developed, and it was decided that it would be beneficial for the clarity of the findings to display these independently with the discussion chapter (Chapter 7) linking between the two.

Once the narrative of each theme began to take shape it was then evaluated how these themes fitted together into the overall story of the data. The theme tables were reviewed by the supervisory team to ensure that sub-ordinate and super-ordinate themes were understood and grounded in data (Phase 5).

Themes were condensed and organised further and pulled together into a more simplified table. A narrative was then formed around the themes to explain the story in more detail, using verbatim quotations from the participants as pillars for the story to build on (Phase 6).

To ensure the trustworthiness of the process of Thematic Analysis in this study, I followed Lincoln and Guba's (1985) criteria for evaluating trustworthiness, presented in Table 4.5.

Table 4.6: Lincoln and Guba's (1985) Criteria for Trustworthiness

Credibility	Confidence in the 'truth' of findings based on the research design, subjects/informants and context.
Transferability	Applicability of the findings in other contexts.
Dependability	Consistency and replicability of the findings with the same subjects or in a similar context.
Confirmability	Degree of neutrality or the extent to which the findings of a study are shaped by the respondents and not researcher bias, motivation or interests.

4.4.1 Image analysis

Drawings in this study were used primarily as a way to facilitate discussion (Gross & Hayne, 1998; Pipe et al. 2002). It is believed that children attribute meaning not necessarily to the picture that they draw, but the action of drawing (Praiser, 2017), therefore observations were made of the children drawing and notes were made to provide context for the drawings within the discussion. Therefore, drawing was used more as a projective measure of data collection. That being said, in line with the data analysis approach outlined above, drawings were broadly analysed based on what the children talked about. Kuhn (2003) provides a method of thematic analysis to analyse children's drawings. This method proposes a broad and interpretive model based on observations, focussing on 1) the descriptive evaluation of the drawing, 2) the evaluation of the image, and 3) the thematic evaluation of the drawing.

4.5 Overview

In this chapter the aspects related to the inclusion criteria, sample, recruitment and methods of data collection have been discussed, along with the conduct of the workshops, ethical considerations and data analysis. The aim of this chapter was to provide an open and structured explanation of the research process. However, this process was not linear, instead it was an ongoing iterative learning experience.

The generic qualitative approach and subsequent Thematic Analysis provided the data that underpinned the findings chapter. The development of the following chapter was

highly dependent on a sensitive and interpretative effort to present the co-constructed reality of the acceptability of medicine, whilst maintaining the authenticity of the children's voices.

Chapter 5
Findings 1: Exploring Children's Perspectives to Improve the Understanding of the Acceptability of Medicines

5 Exploring Children's Perspectives to Improve the Understanding of the Acceptability of Medicines

This chapter presents an overview of the demographic information of the children who participated in the study and the findings relating to children's perspectives of the acceptability of medicines. The findings are organised into three super-ordinate themes: *What Children Can Tell Us about the Acceptability of Medicines; What Helps Improve the Acceptability of Medicines to Children;* and *What Reduces the Acceptability of Medicines to Children.* These themes were formed following the data analysis process described in section 4.4 of the previous chapter.

5.1 Demographics: Participant Characteristics

In total 111 children participated in the study within three main settings: schools/clubs, hospital environment and museum.

Overall similar numbers of girls (n=66) and boys (n=45) were recruited into the study, and more children (66%) were in the younger age bracket (aged 5-7-years; n=73) than in the older age bracket (aged 8-12-years; n=38). In total, 27 children participated via either the two primary schools (n=8) or via two Rainbow and one Brownie groups (n=19). No boy scout groups gave access, so no boys were recruited from these groups. Within the hospital, children (n=3) were recruited from two wards and the museum setting accounted for the majority of children (n=81) recruited to the study. In Table 5.1 the participant recruitment settings are broken down into more detail to provide a more comprehensive overview of the recruitment process.

Table 5.1: Total number of children by setting, sub-group and participant characteristics.

	Schools			Clubs			Hospital	Museum	Total	%
Groups	School 1 Group 1	School 1 Group 2	School 1 Group 1	Rainbows 1	Rainbows 2	Brownies	Ward	Museum	Total	%
Total	3	3	2	7	4	8	3	81	111	
Age (years)										
5-7	3	0	0	7	4	0	0	59	73	66%
8-12	0	3	2	0	0	8	3	22	38	34%

Gender										
Girls	1	1	0	7	4	8	2	43	66	59%
Boys	2	2	2	0	0	0	1	38	45	41%
Children regularly taking prescribed medication										
Yes	1[a]	2 [a,b]	2[c]	Not known			3	not known	8	7%

[a]inhaler; [b]cetirizine, [c]medication for ADHD

In order to provide some context for the presentation of quotes and artwork, each quote or image is presented using the child's chosen pseudonym (if appropriate), their gender, age, and the setting (school/club, museum, hospital) they were recruited from, e.g., Alex, Boy, 8-12yrs, Hospital. If the child did not provide a name, or in group sessions where it was difficult to distinguish the individual contributions of specific children, then the information provided is less detailed, e.g., Girl, 8-12yrs, School 1. All of the quotes are presented verbatim using the spelling the children used in their written comments or reflecting the language and word usage in their verbal communications.

Three super-ordinate themes and six sub-ordinate themes were developed and are summarised in Figure 5.1. These themes are presented in the form of a narrative supported with the most pertinent quotes from the data.

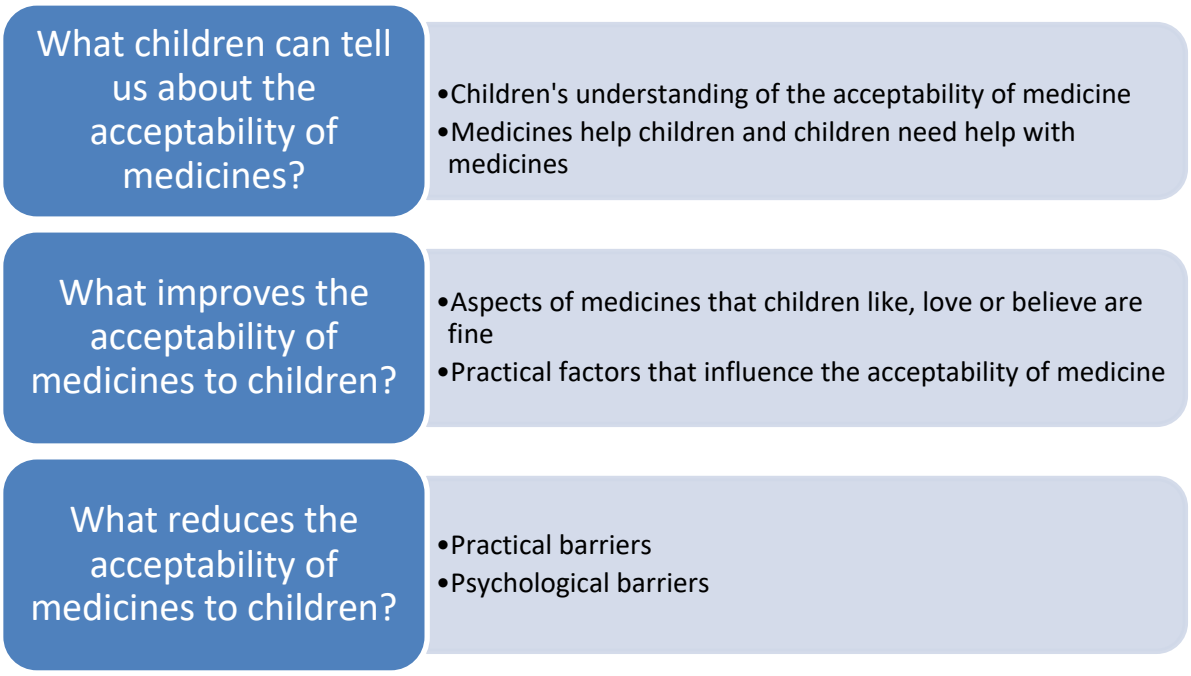


Figure 5.1: Summary of three superordinate (dark blue bubbles) and six subordinate (light blue bubbles) generated from the data collected from the children in the study.

5.2 What Children Can Tell Us About the Acceptability of Medicines

The first super-ordinate theme identified in the data was regarding what children know about the acceptability of medicine. This included how children defined acceptability, the factors they believe impacts the acceptability of medicines, and the belief that medicines help children. This was organised into two sub-ordinate themes *Children's Understanding of the Acceptability of Medicines,* and *Medicines Help.*

5.2.1 Children's understanding of the acceptability of medicines

During the initial discussions, and following prompts from the activity booklets, children talked about what they understood about the acceptability of medicines. Most children provided an explanation of acceptability that was broadly similar to definitions of acceptability used by clinicians and academics within current research work with Alex explaining:

> *'It means like if it's ok for you, like yes or no. If you're fine taking it" (Alex, Boy, 8-12yrs, Hospital).*

This broad understanding was evident across most children, including those who take medicine regularly, children who take medicine occasionally for minor health reasons (e.g. common cold) and those taking medicines such as daily vitamins. It was common for children to describe acceptability using words such as 'OK', 'accept' and 'agree' and whilst their descriptions were generally accurate they often framed them in a way that was seeking confirmation that this was the case: "*Does it mean like if it's ok for you?" (Belle, Girl, 8-12yrs, Hospital),* "*How you accept medicine?" (Anika, Girl, 8-12yrs, Brownies*), and *"I think it means when you accept something… it means when you agree with something" (Girl, 5-7yrs, Rainbows 1).*

Other children were less sure of their understanding, "*Acceptability means… no I don't get that" (Girl, 8-12yrs, Brownies)* or were clear that they did "*not know what acceptability means" (Girl, 5-7yrs, School 1).* However, some guessed what it meant, as demonstrated by one child who asked if acceptability "*is it like, what it does?" (Girl, 8-12yrs, Brownies).* A couple of children who had difficulty explaining what an

acceptable medicine was explained it as something "*that you're, erm, not allowed to take it on your own" (James, Boy, 8-12yrs, School 1),* or something "*that you can't use" (Joy, Girl, 8-12yrs, School 1).*

Children who did not seem to understand the concept of acceptability of medicines tended to think in terms of experiences and examples of where they had heard the words 'acceptable' or 'not acceptable' being used before, even if this was not necessarily related to medicine. For example, one child explained acceptable as "*if you are being bad or not" (Boy, 5-7yrs, School 1)*. A boy talked about past experience of their parents using the word and explained that "*Ex-cept-able* [spelling it out] *means if you are bad it says that's NOT acceptable, and that's what your mummy or daddy uses they say "that's NOT acceptable" if you hit or kick someone" (Boy, 5-7yrs, School 1)*. Millie talked about how their "*teacher said unacceptable to [child] because he always be's [sic] naughty" (Millie, Girl, 5-7yrs, Rainbows 1).*

There were variations in how the acceptability of medicines was interpreted by children. Whilst the majority of children had a good perception about the acceptability of medicines, relating it to either agreeing or accepting something, some children did not or could not provide a coherent explanation of acceptability.

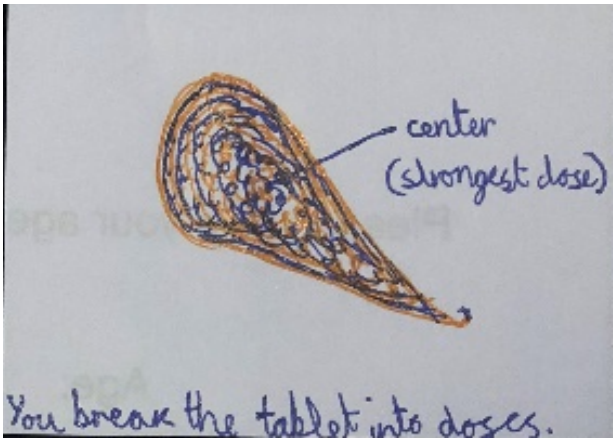
Expanding on their understanding, children talked about their thoughts and ideas of medicines and the acceptability of medicines. Many children explained the concept of acceptability as indicating practicalities of taking the medicine, and the idea that an acceptable medicine is something *"that someone is allowed to use it a bit" (G, Boy, 8-12yrs, School 2).* The idea of being allowed to take medicine was a recurring idea with Brooke explaining "*Does it mean if, if you're allowed to take it on your own?" (Brooke, Girl, 8-12yrs, School 1).*

The children also discussed whether a medicine's acceptability would relate to whether *"you're not allergic to it" (James, Boy, 8-12yrs, School 1),* "*…if you like it" (Joy, Girl, 8-12yrs, School 1)* and/or if you are "*old enough" (Brooke, Girl, 8-12yrs, School 1)* to take it. The fact that the children discussed the practical requirements for the person taking the medicine suggests that they think about the practicalities of taking medicines and the positive and negative effects that medicines can have (see Figure

5.2). Children also considered the difference between knowing what acceptable means and the limitations of being asked whether or not a medicine was acceptable, with one girl explaining that "I *wouldn't know if it was acceptable if I had never had it before" (Girl, 8-12yrs, School 1).*

Some children's ideas about acceptability addressed areas that are not typically seen as being part of conventional notions of evaluating the acceptability of medicine, such as bravery, "*Acceptable? Umm that means you have to be brave if you are having something that hurts" (Girl, 5-7yrs, Rainbows 1).* Others explained the acceptability of medicine as something that "*you really don't like, and you really don't want to have to do it again" (Girl, 5-7yrs, Rainbows 2).*

Whilst there were differences between children who had a good understanding of the acceptability of medicines and children who did not, it was clear that each child responded to the idea of the acceptability of medicine as something unique to them, whether accounting for appropriateness (age, allergies or usability), or whether it was an individual like or dislike. Acknowledging the tentative nature of providing numbers of children who could/could not provide a definition of acceptability, out of the thirty children who attended a workshop or interview in a school, club or hospital, over half (18 children) provided an understanding or discussion of acceptability broadly similar to how it is typically understood and used in medicine development.



Ingredients: penecilin, water, sugar, paracetamol (it cures stomachache)

Dear Dr. Diamond… my medicine is called yummious tabletious. I chose the colours because you don't want to put people off with strange colours or make people want to eat them all the time. I have chosen this shape because you can break parts off the medicine for different doses. This medicine would taste like strawberry so that people would like the taste but not like it so much that it will make you want to take the medicine all the time. I hope that you will try my medicine out.

From "SRLQ" [sic]

Figure 5.2: Image of medicine (Girl, 8-12yrs, Museum).

5.2.2 Medicines help children and children need help with medicines

One of the first topics children discussed during the workshops was that they "*know medicine helps lots of children"* (*Popcorn, Girl, 5-7yrs, Rainbows 1).* This idea was commonly held, and many children referred to how medicines "*help" (Girl, 8-12yrs, Brownies*). The topic of helping was initiated by the children when they were asked "has anyone had medicine before?".

The idea that medicines help was discussed by children whether they were taking medicines regularly or not, showing that they understood that medicines help children, with one girl explaining "*it helps us" (Girl, 8-12yrs, Brownies)*. A key idea was that "*medicine helps you to stop being poorly" (Katie, Girl, 5-7yrs, Rainbows 1)* with some children elaborating on how medicines help across a range of different conditions, for example:

> "*it [medicine] helps you get better if you're not well, if you've got chicken pox or spots or anything like that" (Girl, 5-7yrs, School 1).*

Building on this idea that medicines help improve your physical condition was the idea that medicines also "*make you feel [emotionally] better when you're poorly" (Girl, 8-12yrs, Brownies)* showing that they understood that medicines could help in two ways. The recognition that medicines make them feel better was also found in children's drawings from the museum group, in Figure 5.3 a boy wrote about and had drawn his medicine as a marshmallow because he thinks '*children will want to eat marshmells [sic]',* and that '*medisen [sic] will make children feel better'.*

Ingredients: marshmellow, medisen, medisen for tummy ache

"Dear Dr. Diamond… because I think children will want to eat marshmells [sic] and medisen [sic] will make children feel better"

Figure 5.3: Image of marshmallow medicine (Boy, 8-12yrs, museum).

Children also talked about the preventative role of medicines as they knew they were not only given when "*actually if you are poorly" (Girl, 8-12yrs, Brownies)* but also helped to *"make you not get really sick" (Girl, 8-12yrs, Brownies),* revealing insight into the consequences of not having medicine:

> *"Sometimes if you don't have it then you will get more poorly" (Girl, 8-12yrs, Brownies)*

Building on the idea that medicines can help to overcome or prevent illness, many children referred to their routine of having a "*vitamin every morning" (Pineapple, Girl, 5-7yrs, Rainbows 1)* and the association that "*medicine keeps you healthy" (Girl, 5-7yrs, Rainbows 1).* The link between children's experience and holding a particular viewpoint about medicines was common and, arguably, linked to how children knew that medicine would make you *feel* better as well as *knowing* that it was helpful. This link was observed in the following dialogue between Pineapple, who is allergic to cats and dogs, and the researcher:

> "Pineapple: *I know a medicine... Piriton*
> Beth: *do you know what that's for?*
> Pineapple: *stopping people from itching or getting itchy eyes*
> Beth: *do you like it?*
> Pineapple: *yeah because I'm allergic to cats and they make my eyes itchy" (Pineapple, Girl, 5-7yrs, Rainbows 1).*

Here, Pineapple explains how she knows a medicine, Piriton, and how this medicine helps by *"stopping people from itching or getting itchy eyes" (Pineapple, Girl, 5-7yrs, Rainbows 1).* She then goes on further to explain how *she "went to Mark's and they have a little dog and I'm allergic to dogs and my eyes went a little bit funny, and then I had Calpol*" *(Pineapple, Girl, 5-7yrs, Rainbows 1).* The belief she holds of medicines helping appeared to come from the association of her experiencing itching when she is around cats and dogs and how, in her experience, Piriton and Calpol has helped her eyes stop being itchy. Although she has made a link between Calpol and it helping her itchy eyes, Calpol's use is not intended to help itching. However, its pain relief characteristics and her perception that medicines help could have led to this link.

A similar view is also expressed by Alex, who explains why an "acceptable" medicine for him would be Calpol because *"it also helps me" (Alex, Boy, 8-12yrs, Hospital).* Alex explains that he would choose Calpol and, although many other children have explained that they like the "*strawberry Calpol" (Boy, 5-7yrs, School 1)* referring to its taste, Alex explains he would choose it because it helps him. Again, the view that 'medicine helps' was initiated by the child, and perhaps highlights that not only is the efficacy of the medicine a priority for the child, but also positive past experiences with medicine are key to facilitating a child's positive belief system and their constructed knowledge about medicines. Another child from the museum group also drew a medicine and explained that this would be the best medicine to create because it would be '*helpful*' (Figure 5.4).

Ingredients: Soothing smells, orange flavour, well serum, round, hard

"*Dear Dr. Diamond… I have chosen this meadeacene [sic] and its ingredience [sic] because it sounds helpful"*

Figure 5.4: Image of soothing, orange medicine (Boy, 8-12yrs, Museum)

Building on this, a distinguishing feature relating to the acceptability of medicines was that not only did children know that medicine helps them, but a number of children explained that they "*accept medicine because it helps me" (Girl, 8-12yrs, Brownies)* and therefore the driver for them accepting medicine was the knowledge that it helped them:

> *"I accept medicine because it helps you when you're poorly" (Girl, 8-12yrs, Brownies)*

The belief children hold that medicine helps was also used to explain how children can weigh up the advantages and disadvantages of taking medicine. Children are observed accepting the negative aspects of medicine, such as taste, in the belief that it will be beneficial for them. Alex talked of a medicine he was given when he was being put under general anaesthesia at the hospital, and although he mentioned that it didn't taste nice, he knew that it was given to him to help and therefore accepted it.

"even if it tastes horrible. Like when I went to sleep on the 23rd the taste in my mouth was horrible- but it helps" (Alex, Boy, 8-12yrs, Hospital).

5.2.2.1 Medicines help you join in

As well as medicine helping children to *get* better and *feel* better, they also talked about how medicine helps children to take part or join in. Some conditions make it difficult for children to take part in typical daily routines at school or with friends. This can lead to isolation for the child, being unable to do the same things that their friends do. In his interview, Alex explained that his medicine helps him by allowing him to take part in the daily mile, a school activity that he could not take part in without his medicines:

"Yeah and it also helps me. Usually I wouldn't be able to walk in the mile, but I can with it… in school. My friend, well best friend actually, he usually finishes it really quick cos he's one of the fastest in the class" (Alex, Boy, 8-12yrs, Hospital)

To provide context for the significance of this, the aim of the daily mile is to improve physical, social, emotional and mental health, and wellbeing of children. Alex explains how his ability to join in with the daily mile is because of his medicines, he explains that it helps him take part and be with friends. The notion that Alex attributes his ability to join in the daily mile to his medicines is crucial in understanding the extent of the *help* provided by his medicines.

5.2.2.2 Adults help children with medicines

Overall, aside from specifically talking about adults helping them with medicines, the children talked more generally about the ways in which adults help them when they are poorly or hurt:

"*do you know a doctor called Doctor [name]? He helps me… he always helps me!" (I, Boy, 8-12yrs, School 2).*

This was also reiterated in another workshop where the children talk about how Popcorn's mum helped another child when they hurt themselves:

Rosie: *isn't your mum a doctor Popcorn?"*

> Popcorn: *Yeah my mum's a doctor… a school nurse, my mum is a school nurse! How did you know?!*
> Rosie: *my brother broke him [sic] finger and your mum had a look at it… because I saw it!" (Rosie and Popcorn, Girls, 5-7yrs, Rainbows)*

Adults were also talked about as helping with the various processes associated with medicines administration. One boy describing how her mother used a syringe to get liquid medicine out of a bottle explained *"my mum put it on a um... a special thing, you can get orange or purple, and then you slide it into the bottle… yeah you slide it into the medicine and then you just slide it into your mouth" (Boy, 5-7yrs, School 1)*. Another boy explained that adults were helpful as children "*would have to have an adult to get the water for them" (G, Boy, 8-12yrs, School 2)* if they were taking a tablet. Another boy builds on this, stating that is "*because children aren't allowed to get them on their own they have to have an adult" (I, Boy, 8-12yrs, School 2).* However, a boy who frequently takes medicines for Attention Deficit Hyperactivity Disorder responds to this explaining that although at school he can use his medicine on his own, at home he needs help with his medicines from an adult:

> "*yeah, they are, I do. I do when I'm in school. Just at home I have no clue where it is, so nanny has to get it for me at home" (G, Boy, 8-12yrs, School 2).*

The idea that children need help from adults with their medicine administration depending on the environment they are in is one which was mentioned a number of times and is important to highlight. When asked if it would be better if a child could take their medicine on their own some agreed that this would vary with one boy explaining that they:

> "*would still need help, I need help but sometimes I don't because I can just puff it on my own without the inhaler thing (spacer) like I have to do… erm, like before I have my football match today. I have to do my own blue one because I play football" (Boy, 5-7yrs, School).*

5.3 What Helps Improve the Acceptability of Medicines to Children?

Throughout the interviews and workshops, children spoke positively about many factors relating to medicines. The factors found to facilitate acceptance fall into two sub-ordinate themes: *Aspects of Medicine that Children Like, Love or Believe are Fine,* or; *Practical Factors that Influence the Acceptability of Medicines.*

5.3.1 Aspects of medicines that children like, love or believe are fine

All children talked about things they liked, loved or believed were fine about medicines; typically, these aspects related to taste or smell, and/or the form of the medicine.

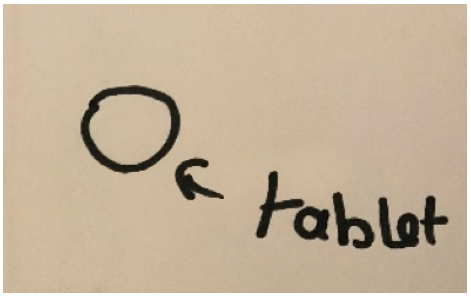
5.3.1.1 The taste and smell of medicines

The idea that the acceptability of a medicine "*depends on flavour" (James, Boy, 8-12yrs, School 1)* was common. Mainly for those children who did not take medicines as part of a daily routine "*what it tastes like is important" (Girl, 5-7yrs, School 1).* Interestingly, one of the main reasons for this importance was that "*it might be the wrong medicine, you need to check",* with the suggestion being that the taste of the medicine would enable the child to identify the 'right' medicine.

Some children thought that medicines with no taste would be a good idea and that an acceptable medicine would be one *"you wouldn't taste" (Girl, 8-12yrs, Brownies).* Inhalers were often talked about positively as they had '*no taste'*:

> "*If you swallowed it your tummy wouldn't feel any taste… I know because it's just only air that's going into your mouth. And cos in your tummy is like nothing. It just taste like air… it taste like anything but not taste. It tastes good, I like it" (Girl, 5-7yrs, School 1).*

However, children also talked about liking or loving the taste of some medicines, specific medicines such as Calpol were talked about as "*tasting nice" (Alex, Boy, 8-12yrs, Hospital).* When asked what would improve Calpol, children explained that "*nothing" (Girl, 5-7yrs, School 1)* would make Calpol better. A number of children referred to wanting the taste of Calpol specifically, one child from the Museum drew their medicine (Figure 5.5.) explaining that it would '*have the taste of strawberry calpol because I like the taste of calpol [sic].'*



Ingredients: (general helpful medicine stuff), strawberry flavour

Dear Dr. Diamond… I have chosen the shape and size as it would be easy to swallow. It would be wite and have the taste of strawberry calpol because I like the taste of calpol [sic].

Figure 5.5: Image of 'easy to swallow' tablet (Girl, 8-12yrs, museum)

Other children suggested that the flavour "*strawberry or any other flavour like that" (Girl, 5-7yrs, School 1)* would be good for other medicines; one boy explained that they:

> "*take two (medicines), one is a gummy bear and one is these (tablet)… it's like a peppa pig and it taste like strawberry! No, my peppa pig taste like raspberry… I like both of them" (I, Boy, 8-12yrs, School 2).*

"Strawberry" (Girl, 5-7yrs, Rainbows) was the taste that the children commonly talked about as one they loved: *"I love them ones because they taste like strawberries" (Boy, 5-7yrs, School 1).* When asked what would make medicines better, it was suggested that "*if you could make it like, make it, it would be like… the ingredients would be strawberries!" (I, Boy, 8-12yrs, School 2).* This was common in all groups, particularly within the pictures from the museum, with most of the children explaining that they would choose a strawberry flavour for their medicines (Figure 5.6).

Ingredients: lemon and lime flavouring, strawberry dust, rainbow, red water, ruby liquid, snow, ice, sweet orange and mango scent

Dear Dr. Diamond… I chose these ingredient because lemon and lime taste great. Strawberry also tastes delisios [sic].

Figure 5.6: Image of rainbow medicine (Girl, 5-7yrs, museum)

Children also talked about liking orange tasting medicines "*I take it orange and I did actually like it" (Girl, 5-7yrs, School 1).* However, a couple of children associated the taste of strawberry medicines to spice, which negatively affected their opinions as can be seen in the following conversation between three children:

> *"*Boy: *it wasn't like normal strawberry; it was like it was spicy*
> Girl: *that's why I didn't like it*
> Boy: *too spicy" (Boy and Girl, 5-7yrs, School 1)*

The perception that medicine was *"a bit spicy" (Boy, 8-12yrs, School 1)* originated from children's experience with medicine, whether it was through their own experience with taking medicines, or whether they observed someone else taking medicines and drew

conclusions that because their *"mum takes one and drinks water because it's like, spicy"* (Girl, 5-7yrs, School 1*).*

Apart from taste, children talked about the impact of smell and this was often linked to the flavour such as "*mine smells like… strawberry" (Boy, 5-7yrs, School 1)*. Explaining that "*sometimes they [medicine] can be smelly… they can smell nice and not nice" (Girl, 5-7yrs, School 1).* The smell of strawberry was generally talked about positively, one girl explained that they "*have a medicine at home and it smells like strawberries and I love it" (Girl, 5-7yrs, Rainbows 1).*

5.3.1.2 The feel of the medicine

Children also talked about the feel of medicines and explained that if they were designing an acceptable medicine "*it would not be bumpy" (Girl, 8-12yrs, Brownies)* and that "*it would be smooth" (Girl, 8-12yrs, Brownies).* Another child reiterated this idea and explained that an acceptable medicine "*wouldn't have like bits in it" (Girl, 8-12yrs, Brownies).* Mouthfeel was thought to be important to some children at the museum who drew a picture of a medicine with a spoon (Figure 5.7). She explained that the most important thing was that it was "*esy to swally [sic]".* The idea that a medicine should be easy to swallow was also reiterated by another child from the museum who explained that they '*have chosen the shape and size as it would be easy to swallow'* (see Image 5.8). However, other children did not think that it being easy to swallow was as important as the imperative was just to take the medicine: "*because you need to swallow it, so that doesn't matter because you just swallow it without feeling. You just have to…" (Girl, 5-7yrs, School 1).*

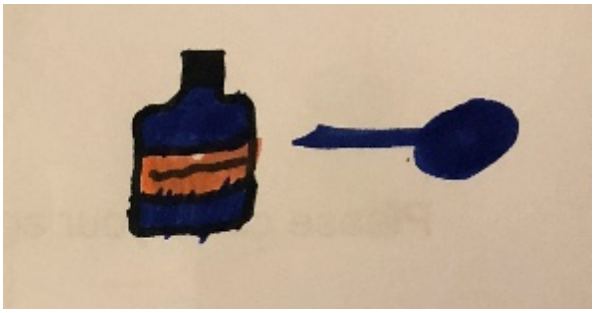
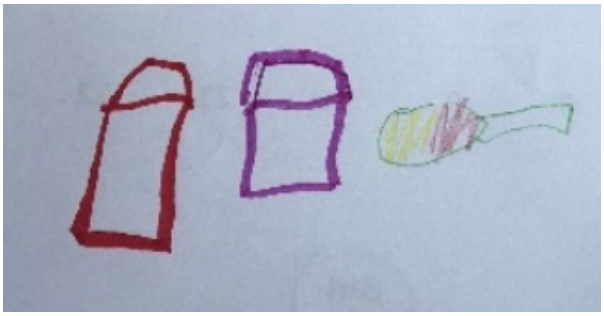


Figure 5.7: Image of medicine with a spoon (Girl, 8-12yrs, Museum)



"I have chosen the shape and size as it would be easy to swallow"

Figure 5.8: Image of 'easy to swallow' medicine (Girl, 5-7yrs, museum)

5.3.1.3 Real, normal or adult medicines

Children's perception of the medicines also seemed to be a factor influencing how acceptable they found them. A lot of children expressed positive views about taking 'real' tablets, Bella explained *"I love them... I love real tablets!" (Bella, Girl, 5-7yrs, Rainbows 1)*. Real tablets were talked about in a number of different ways; some children talked about real tablets as those which they had observed adults taking, others referred to the form and colour of real medicines in comparison to a typical children's medicine (e.g. a white tablet compared to a chewy orange or purple medicine).

Although Bella did not expand on what she meant by 'real tablets' when prompted, the idea that children liked medicines because they were *real* was common. Some children perceived real tablets as being like those they had observed their parents and other adults taking:

> "*what my mum does, she takes two tablets when she's poorly" (Girl, 5-7yrs, School 1)*

Other children in the same workshop added *"that's what my mum does" (Girl, 5-7yrs, School 1) … "my dad and my mum do that too" (Boy, 5-7yrs, School 1).* Additionally, children explained that they "*saw my grandad and my nan take them (tablets). I've saw my mum and my dad take them" (Girl, 5-7yrs, Rainbows 2).* Children's perceptions of these 'real' medicines were generally positive, with one boy explaining that he wished he *"could taste them (capsules) one day" (Boy, 5-7yrs, School 1).*

Children associated the idea of 'adult medicines' with the colour and form of a 'normal' medicine:

> "*I think… tablets? Um... look like white like normal tablets" (Boy, 5-7yrs, School 1).*

In contrast to these 'real medicines', children distinguished between medicines made for adults and medicines made specifically for children: "*it was like a kid's one… but not like the orange one, like a purple" (Girl, 5-7yrs, Rainbows 2).*

As well as distinguishing certain features such as colour and form, children also distinguished between adult and child medicines by the mode of delivery (whether the tablet was to be swallowed whole or chewed). When showed a picture of a white round tablet, one child explained:

> "*you know like you showed the tablet you showed, you don't chew it do you? You just swallow it… but my peppa pig gummy bear you can't swallow it you have to chew it" (I, Boy, 8-12yrs, School 2).*

However, when asked if they had ever taken a tablet, one child explained "*no because sometimes they're… because some are for adults…" (Girl, 5-7yrs, Rainbows 2).*

5.3.1.4 Not really like medicine, sometimes like sweets

In contrast to the perceptions of 'adult' or 'real' tablets, chewable tablets were mentioned frequently as a 'child's medicine', and were also talked about positively across the workshops:

> "*I have one for health like, it has um vitamins in them, and they are quite nice" (James, Boy, 8-12yrs, School 1).*

Talking about chewable tablets some children explained that they "*love them ones" (Girl, 5-7yrs, School 1)*, explaining that they "*like them… I think I have vitamin D and vitamin C" (Girl, 5-7yrs, School 1).* The way that children's perception of medicines can improve acceptability can be noted where children believe that some medicine is "*not really like medicine" (Boy, 5-7yrs, School 1).* This was explained by one child where she did not "*even realise they're vitamins, you can only tell on the box" (Girl, 5-7yrs, Rainbows 1).* Other descriptions of chewable tablets included being "*kind of like gummy bear things but they're like jelly babies" (Girl, 5-7yrs, Rainbows 1),* like "*chocolate" (James, Boy, 8-12yrs, School 1),* or "*like chewing gum" (Joy, Girl, 8-12yrs, School 1).* When asked to create their own medicines, at the museum, children continued the sweet tasting theme often drawing something that "*makes me happy"*

for example, a cheerful unicorn, a smiling gingerbread person or a dinosaur in the images (Figures 5.9-5.11) and linked these to sweet tastes and treats such as cupcakes, sweets , chocolate and gingerbread. Whilst these sweet-like perceptions are different for most children e.g. a jelly baby compared to a gingerbread man; the children's associations were generally positive.

"Cupcakes because it tastes nice and makes people better"

Figure 5.11: Image of unicorn medicine (Girl, 8-12yrs, Museum

The dinablet- because I like dinosaurs and sweets"

Figure 5.10: Image of dinosaur medicine (Boy, 5-7yrs, museum)

"*I love chocolate gingerbread men. Chocolate is easy to eat and tastes nice"*

Figure 5.9: Image of gingerbread-man medicine (Boy, 8-12yrs, museum)

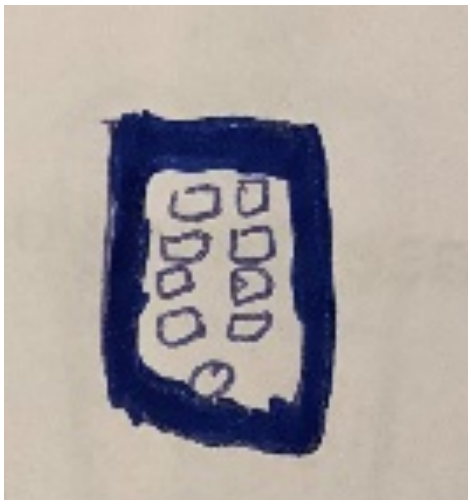
The children made associations between some medicines and sweets and many medicines were described as looking "*like sweets" (Girl, 5-7yrs, Rainbows 1)* or described as specific sweets such as "*like little gummy bears" (Boy, 5-7yrs, School 1)* or "*like a peppa pig gummy bear" (I, Boy, 8-12yrs, School 2)*. Some children explained that they "*pretend they [medicines] are like sweets" (Girl, 5-7yrs, Rainbows 1).* The idea that medicines were like sweets was also talked about in relation to the efficacy of the medicine in that efficacious medicine would not be horrible to take:

> *"It would make you better when you are poorly, and it would be like a sweet so that it's not horrible, it wouldn't be horrible" (Anika, Girl, 8-12yrs, Brownies).*

The idea that sweet-like medicines would improve the acceptability of medicine was also talked about when children were asked to use their imaginations to develop their very own medicine. One child explained that:

> "*one thing that would make medicine better and make younger children like it is if it was a bit more nicer and not yucky" (Anna, Girl, 8-12yrs, W6, Line 23).*

Figure 5.12 shows an "*iTablet"* designed to taste like a gummy bear and "*phone shaped because everyone is always on their phone".*



Ingredients: a gummy phone

Dear Dr. Diamond… my medicine is phone shaped because everyone is always on there phone. It will taste like gummy bears. It feels soft and squishy and will smell really fruity. The size would be about the size of a playing card and it will be called the iTablet. [sic]

Figure 5.12: Image of iTablet (Boy, 8-12yrs, museum).

Other children talked about the 'sweetie' flavour being important and Jo-jo talked specifically about how having "*a lolly-pop flavour" (Jo-jo, Girl, 5-7yrs, Rainbows 1)* would be the best for her medicine. The sweets idea was continued with Katie describing an ideal medicine with "*sweeties inside it… the sweets are inside the medicine… and at the bottom there's a lolly pop and you get to eat the lolly pop! (Katie, Girl, 5-7yrs, Rainbows 2).* Children at the museum frequently drew sweet-like medicines, one child explained they created the *'roll on bubble-gum to fool kids so they would take it' (Girl, 8-12yrs, Museum*) (see Figure 5.13 for Roll on Bubble-gum).

Despite the idea that "*you can pretend they are like sweets" (Girl, 5-7yrs, Rainbows 1),* the children knew "*they are not actually" (Girl, 5-7yrs, Rainbows 1)* sweets. A couple of children explained that even though "*they look like sweets… they're not" (Girl, 5-7yrs, Rainbows 1).* Another explained:

> "*Also, my mum said don't take them from strangers because you think they're sweets but they're really not" (Girl, 5-7yrs, Rainbows 2).*

Children also had an awareness of the safety around medicines and accepting medicines from strangers.

5.3.2 Practical factors that influence the acceptability of medicines

Children also talked about the practical aspects of medicines that they believe are important to medicine acceptance. When asked which aspects of medicines were important, the children talked about ease of use and appearance as key factors. Alex summed things up explaining:

> "*umm mainly how easy the medicine is to use, the size of the medicine, it's just really them three… actually it might be how it feels in my mouth as well" (Alex, Boy, 8-12yrs, Hospital)*

Alex also thought of an additional factor, that he did not say out loud, which was 'how often you have to take the medicine'. These factors were reported by other children across the workshop groups and interviews and will be discussed below.

5.3.2.1 How easy medicines are for children to use

The idea that it is important that medicine is easy to use was a common finding. When asked to rank the factors from most important to least important, children across all age groups and settings, explained that they "*would put it that's how easy it is to use" (Boy, 5-7yrs, School 1)* as the most important or *"that's the second importance" (Girl, 5-7yrs, School 1).*

Whether medicine was easy to use depended on whether the medicine required any other aid to take it (e.g. a glass of water or a spoon) and whether the child could take the medicine on their own or if they needed help from someone else such as parents and grandparents (section *5.2.2.2*). When children discussed whether a medicine would be easier to use if taken on a spoon or a syringe most children explained that a syringe was *"better than a spoon because then you just don't have to like pour it into the spoon and you can just suck it out of the syringe" (Boy, 5-7yrs, School 1).* Having the appropriate tools such as their preferred tool to dispense the medicine (e.g. a syringe) increased the acceptability of the medicine as it prevented issues such as

spilling the medicine and ensured you got the *"right amount"* of medicine as James clearly explained:

> *"Syringe because, cos with a spoon it's quite easy to spill. And if you spill some you might not get the right amount" (James, 8-12yrs, School 1).*

However, although using the syringe was generally the preferred method, children also considered that taking medicine from a syringe could cause issues, as it could be difficult to "*fit the syringe in it [bottle]" (Girl, 5-7yrs, School 1).* James, who noted the potential problem with fitting the syringe, also noted that both spoons and syringes had their own challenges:

> *"Umm if it was a syringe it's quite hard and if it's a spoon it's hard. Because you might spill the spoon and you might not get the syringe in right" (James, Boy, 8-12yrs, School 1).*

Children at the museum who were asked to create a new medicine also considered how easy the medicine would be to use, often drawing their liquid medicines along with a spoon. However, some children created new forms of dispensing medicine that they believe would be easier or more appropriate to use, such as Roll-on Bubblegum medicine (Figure 5.13)

Ingredients: strawberry, bubblegum flavouring, normal medicine stuff

Dear Dr. Diamond… Its roll on because it's easier than putting it on a spoon. The bottle is a large size so it will last long."

Figure 5.13: Image of Roll-on Bubblegum medicine (Girl, 8-12yrs, museum).

The idea that adult help could improve acceptability by making the medicine easier to use was discussed by many of the children. Although this has been explored in section 5.2.2.2, it is important to bring attention to it here to show how not only can *adults help,* but also that this help is pivotal for a lot of children feeling competent or comfortable taking their medicines.

Boy: *Maybe that one's it, how easy is the medicine maybe, that one is number 1 too*
Beth: *How easy it is to use? So, is it important that you can take your inhaler on your own?*
Boy: Not for me because I can't do it
Beth: Would it be better if you could use it on your own?
Boy: I would still need help, I need help… (Boy, 5-7yrs, School 1)

For children who take medicines as part of a regular routine, it was common to see that the perceived acceptability and influence of ease-of-use were dependent on the particular context or situation. Typically, at school they have to take more responsibility for their own medicine administration whereas at home their parents take on the responsibility.

5.3.2.2 What the medicines look like

There was an overall agreement across the workshops and interviews that "*the colour… and what it looks like" (Girl, 5-7yrs, School 1*) were the least important factors influencing the acceptability of a medicine. This is highlighted in a conversation between two children in one of the age 5-7-year group workshops:

Boy: *that one's deffo got to be number 6*
Beth: *which one?*
Boy: *that one, what it looks like that doesn't even occur*
Girl: *colour?? colour??! That's not important that, that's number 6 that, colour (Girl and Boy, 5-7yrs, School 1)*

Some of the older children from other workshop groups further reiterated that the colour of medicine was not important, and this was summed up by Brooke who said "*mm nope not important" (Brooke, Girl, 8-12yrs, School 1).* The idea that colour was *"not really" (Alex, Boy, 8-12yrs, Hospital)* important was observed both in children taking medicines more frequently and those inexperienced in taking medicines, with it being described as "*not even a little tiny bit important" (Boy, 5-7yrs, School 1).*

However, the images that children drew were almost all colourful, or presented in colourful packaging. Within the museum images, children explained they had designed their medicines with certain colours because they like it, or because it was their favourite colour. Children associated certain colours with medicines they had

experience with such as “medicine is green” (*Boy, 8yrs, Museum)* and “*purple because this is the colour of the medicine at home” (Boy, 5yrs, Museum).* Additionally, children associated colours with certain tastes and smells, one child explained they would choose an orange colour because “*it looks like honey” (Boy, 6yrs, Museum)*, or yellow because “*it like banana [sic]” (Girl, 7yrs, Museum).*

Similarly, there were some conflicting ideas about the importance of what the medicines look like. Despite most children believing that appearance was not of high importance to acceptability, some children considered that appearance might be important if that is how you identify your medicine. When asked whether how the medicine looked like was important, one child explained:

> “*maybe if you buy the wrong kind of medicine and you eat it without realising you might not be well and you might need a different kind of medicine” (Girl, 5-7yrs, School 1).*

It is interesting to note that this comment did not concern the influence of appearance on perceived acceptability, but rather the appropriateness of the medicine to treat the health issue. The child had considered that if the medicine did not look a certain way, there was a chance of getting confused and becoming sick if they took the wrong medicine by mistake.

However, some children associated the look of a medicine with what they thought it might taste like. Capsules were described as looking “*even nicer than ice cream because they look, they don’t even look spicy” (Girl, 5-7yrs, School 1),* another child continued explaining that:

> “*It looks like they don’t have spice in them because the tablets look like they have teeny weeny bits of sugar on them, and it [capsule] doesn’t look like that!” (Boy, 5-7yrs, School 1).*

Therefore, the perception of medicine appearance could improve acceptability, with one child explaining that they “*wish they could taste them one day” (Boy, 5-7yrs, School 1).* The idea of certain medicines appearing more acceptable than others was also identified in the pictures drawn by the children at the Museum. In Figure 5.14 a girl has drawn two, small capsule-like medicines and she explained that they were “*to*

swallow, they would taste like bubble-gum because it's so tasty. Red to match bubble-gum" (Girl, 8-12yrs museum).

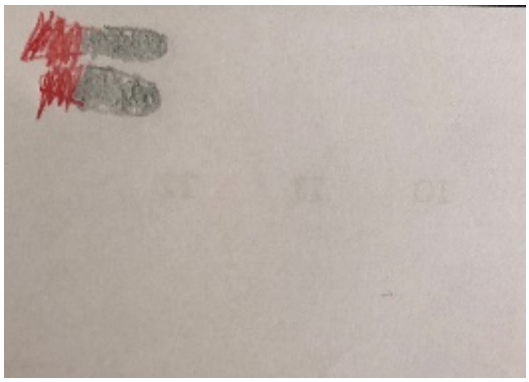


Figure 5.14: Image of bubble-gum capsules (Girl, 8-12yrs, museum).

As seen in other sections, children's perception seems to be a strong indicator of how acceptable a child considers medicines.

5.4 What Reduces the Acceptability of Medicines to Children?

Children generally used "*hate" (Alex, Boy, 8-12yrs, Hospital)* or "*dislike" (James, Boy, 8-12yrs, School 1)* to describe certain unpleasant or difficult characteristics of medicines such as size, horrible taste or its disruption to daily routine. These created both practical and/or psychological barriers influencing the acceptability of medicines. Practical barriers included disruption to routine, side effects and some of the physical characteristics of the medicines such as mouth feel or tendency to disintegrate as well as a nasty taste. Medicines were often described as being "*horrible"* (Popcorn, Girl, 5-7yrs, Rainbows 1*)* and "*disgusting" (Pineapple, Girl, 5-7yrs, Rainbows 1)* and children explained that they "*didn't like medicine"* (Lex, Girl, 5-7yrs, Rainbows 1) because it "*tasted so horrible" (Popcorn, Girl, 5-7yrs, Rainbows 1)* or it *"turns into little bits" (G, Boy, 8-12yrs, School 2) or was "oversized" " (Alex, Boy, 8-12yrs, Hospital).*

Psychological barriers related to worries and fears around taking medicines, sometimes these two factors were independent and other times physical barriers created psychological barriers, and vice versa.

5.4.1 Practical barriers

5.4.1.1 How many times and where you have to take your medicine

The disruption caused by some medicines was an important barrier for some children who thought that "*how many times you have to take medicine that's important" (Girl, 5-7yrs, School 1)*. Children at the hospital were most likely to talk about how frequency and location was important, both Belle and Alex, despite knowing that their medicine was necessary, did not like that they had to go into hospital to have it and *"basically miss school or weekends" (Alex, Boy, 8-12yrs, Hospital).*

> *"umm because I have to take megatrexate [sic] every week I don't really like it, 'cos that means I'd have to come into here [hospital]" (Alex, Boy, 8-12yrs, Hospital)*

5.4.1.2 The feel of the medicine in your mouth

A frequently mentioned reason was the feel of the medicine in the child's mouth, a factor addressed in research as mouthfeel. This aspect of acceptability focussed on liquid and tablets (including chewable tablets). The idea that the way medicine feels can influence the acceptability of medicine was mentioned by some of the children. Alex explained how *"…actually, it might be how it feels in my mouth as well cus I don't want it feeling all rough and not able to swallow" (Alex, Boy, 5-7yrs, Hospital).*

The disintegration of tablets could reduce their acceptability, with 'G' (pseudonym) noting "*when the tablet melts it turns into all little bits and it's horrible" (G, Boy, 8-12yrs, School 2).* The idea that the medicine breaking down into *"little bits"* was a prominent issue, as 'G' explained:

> *"…but when my medicine that I take melts in my mouth it tastes like, it just taste like someone's pooed in it ……. Yeah it taste horrible, so you have to have water and make sure it doesn't start to melt" (G, Boy, 8-12yrs, School 2).*

The theme of disruption was again present, with the same child explaining that his medicines needed to be taken with a drink to help him swallow it or protect him from the bad taste when the tablet started to disintegrate. He explained that even though his tablet is *"made out of strawberries, when my medicine that I take melts in my mouth it taste… horrible" (G, Boy, 8-12yrs, School 2)* which means "*you have to have water and make sure it doesn't start to melt".* The inconvenience for 'G' is to remember his medicines three times a day as well as "*my water"* (G, Boy, 8-12yrs, School 2*),* and

that he has to *"have an adult to get the water" (G, Boy, 8-12yrs, School 2)* for example, "*nanny has to get it for me at home" (G, Boy, 8-12yrs, School 2).* As well as causing an additional disruption that he needs to remember his medicine and his water, having to rely on an adult's help also reduces his self-efficacy and ability to use his medicines on his own.

Interestingly, one girl who only took medicines for minor coughs/cold and allergies, explained that mouthfeel was not important as the imperative was to take the medicine "*because you need to swallow it, so that doesn't matter because you just swallow it without feeling. You just have to…" (Girl, 5-7yrs, School 1)*. She views taking medicine as something you *just have to do* and therefore does not believe that the feel of medicine is important. Whilst this is interesting, her belief that "*you just have to"* perhaps reflects her experience with medicine, and with what she has been told when she has needed to take medicines.

5.4.1.3 Size or amount

Children talked about how the amount or "*the size of the medicine is important" (Girl, 5-7yrs, School 1)* to acceptability. Many children talked about their previous experiences with medicines and how these experiences have led to their beliefs about what makes a medicine an acceptable size. Typically, children disliked medicine being too big or having to take too much/many and both aspects were seen as a negative factor in terms of acceptability. James summed up his dislike of tablets by mentioning both the size and number of tablets they had once taken which has led him to having an aversion for tablets:

> "*I don't really like getting the tablets to swallow because once, I think, once I had this really bad cold and they* [*the tablets] were like that big [showing me with his finger] and I had to take eight at a time" (James, Boy, 8-12yrs, School 1)*

The idea that the size or amount of the medicine can cause an issue for children was reiterated by another child who explained that "*if you have it oversized it can make you feel ill if you have too much medicine" (Alex, Boy, 8-12yrs, Hospital).*

Although 'volume issues' such as the size or amount of the medicine were seen as problematic by some children, emotional and psychological responses such as worries and fears, were also important to the overall acceptability. These feelings were often coupled with a physical and/or behavioural response when taking medicines such as "*I choke a lot… because I don't like it" (Girl, 5-7yrs, School 1)* or kicking off when taking medicines too frequently, as Alex explained:

> "S*ometimes you can start to kick off…I usually do that because I haaate megatrexate (sic) and taking it" (Alex, Boy, 8-12yrs, Hospital).*

Alex's behavioural response of kicking off is in retaliation to having to take that specific medicine, because of the frequency of having to take it, and the fact that he has to go into hospital to take it which in effect means he has to miss school or his weekends to have the medicine. His kicking off would suggest that this disruption to his daily life causes an issue in the acceptability of this medicine for him. Although volume factors and affective (emotional and psychological) responses overlap, the emotional and psychological responses are addressed discretely in the following sub-theme.

5.4.2 Psychological barriers

5.4.2.1 Worry

Children talked about worry in relation to taking medicines. These worries related to the incorrect administration of medicines, negative side effects of taking medicines (such as being sick and choking or the pain associated with injections), and the appearance or perception of the medicines. In one workshop where some of the children were talking positively about tablets and how they enjoy taking their vitamins, Doo-doo who had previously talked about how taking medicines was *"scary"* exclaimed "*Why does everyone love taking tablets?! I hate them!!" (Doo-doo, Girl, 5-7yrs, Rainbows 1).*

Common worries were related to side effects, including coughs, vomiting and that "*you might even be sick" (Girl, 5-7yrs, School 1).* James explained a physical side effect that "*some of my inhalers after I've had them I come up with a cough" (James, Boy, 8-12yrs, School 1).* Whilst the inhaler is used to help his health condition it appears that an issue for this child is that he *"stops wheezing and starts coughing" (James, Boy, 8-*

12yrs, School 1). This worry or apprehension was typically related to what the child already knew about medicines, their actual experience with medicines or their experience of being told about medicines. Children expressed various worries about swallowing a tablet whole. One worry was that doing this would make them vomit:

> "*if you swallow it and then if you like swallow it whole, you might be sick in case it gets stuck in your bones" (Boy, 5-7yrs, School 1).*

Other worries included the danger of having a tablet stuck or choking on a tablet, and another child explained it was "*because you might choke, if you don't chew it you might choke" (Girl, 5-7yrs, School 1).* Their response to this danger was to chew the tablet. However, this belief might cause problems if there was a time where they were asked to swallow a tablet whole.

The fear of feeling unwell was also associated with taking too much medicine:

> "*yeah cos if you have oversized… it can make you feel ill if you have too much medicine" (Alex, Boy, 8-12yrs, Hospital).*

Children also expressed the worry that "*if you buy the wrong kind of medicine and you eat it without realising you might not be well" (Girl, 5-7yrs, School 1) or* "*if you pick the wrong medicine… and you have it you might be sick" (Girl, 5-7yrs, School 1)*, this is an important consideration in understanding why children might be opposed to taking medicines. Children believing that their medicine is the *right* medicine for them seems an important consideration in making a medicine acceptable. The potential influence of past experiences is important to understand as it may explain why some children might have worries about certain medicines being associated with being sick or unwell:

> "*sometimes actually, when you have medicine it might actually make you sick, I can remember that from in an assembly a long time ago…" (Boy, 5-7yrs, School 1).*

Another worry that was mentioned by children was about having an overdose. This was mentioned by James who did not have a lot of experience with medicines, and so it is perhaps indicative that their lack of experience with medicines leads to them becoming worried when they do take it:

"*I just get worried about having an overdose every time I use it…*" *(James, Boy, 8-12yrs, School 1).*

Some of their worries were associated with administration or use of medicines and this worry has an impact on the factors the children believed to be important in the development of medicines. James explained that liquid medicines are "*quite hard. Because you might spill the spoon and you might not get the syringe in right.. and it might spill everywhere*" *(James, Boy, 8-12yrs, School 1)*. These worries reflect the child's altering belief in their own abilities to perform the task of administering medicines on their own, some children are required to take responsibility for their own medicines at school or where their primary caregiver cannot help. This is therefore something to consider when evaluating the factors that influence the acceptability of medicine.

In contrast to the beliefs that children hold (Section 5.3.2) that medicines "*makes you not get really sick" (Girl, 8-12yrs, Brownies)* the worries expressed about overdose, choking and oversized medicines highlight an alternate view to consider when evaluating the acceptability of medicines.

5.4.2.2 Fear

The main cause of fear in children in the study was medication given by "needle", although, some children expressed fear about taking tablets with Pineapple explaining that taking tablets was "*scary" (Pineapple, Girl, 5-7yrs, Rainbows 1)*. Fear of a medicine influenced the acceptability of a medicine.

The majority of children showed an aversion to needles, saying things such as "*don't even show me that"* [picture of a needle] *(Lex, Girl, 5-7yrs, Rainbows 2),* "*definitely not, no way hosay a needle!" (Boy, 5-7yrs, School 1)* and "*I do not want an injection" (Girl, 5-7yrs, School 1).* The main reason for children finding needles scary related to their appearance, with children explaining that they "*don't like the pointy bits" (Doo-doo, Girl, 5-7yrs, Rainbows 1)* and that the reason they did not like them was because they were "*sharp" (Popcorn, Girl, 5-7yrs, Rainbows 1).* In order to explain how sharp needles were, a few children used figurative speech to describe how they viewed them. One child explained it by showing me a small space between her thumb and

pointing finger, "*if it was likeee… that… it wouldn't really hurt would it?... like that wouldn't hurt" (Girl, 5-7yrs, School 1).* She continued and showed me two pencils, one with a sharp point and the other blunt (Figure 5.15) "*if it was like that (*the blunt pencil) *it wouldn't really hurt you, it would be really really fine wouldn't it? Because it wouldn't be sharp" (Girl, 5-7yrs, School 1).*

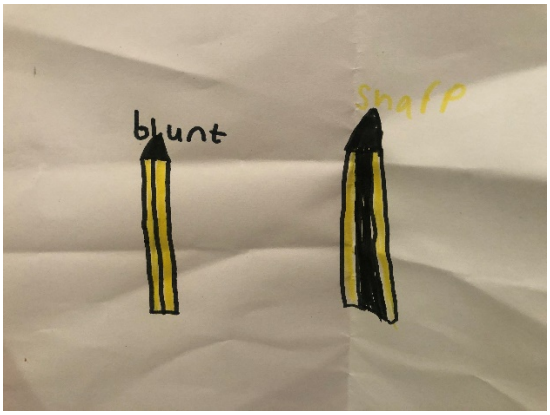


Figure 5.15: Image of blunt pencil and sharp pencil (Girl, 5-7yrs, School 1)

The pencil analogy was also used in another workshop where 'EV' explained that "*it's like a sharpened pencil… it's pointy" (EV, Girl, 5-7yrs, Rainbows 1).* Needles were also described as scary "*because it like, looks like a mountain top but smaller" (Boy, 5-7yrs, School 1)* and "*yeah it looked spikey like that" (Girl, 5-7yrs, School 1).* The way that needles look seems to be the main cause of fear in children in this study, with the belief that if you "*have to have a needle… it really hurts" (Girl, 5-7yrs, School 1).* Most children talked about how needles are "*painful" (Girl, 5-7yrs, Rainbows 1),* and Pineapple explained the cause of this pain is "*because of the needle thing" (Pineapple, Girl, 5-7yrs, Rainbows 1).*

Some children had personal experience with needles and vividly recalled this:

> *"one day I had an injection when I was about 2 or 3 and it was right there [pointing to his arm] and I screamed like this [child demonstrated by 'screaming', showing his mouth wide open and eyes tightly shut but with no noise]" (Boy, 5-7yrs, School 1).*

Other children, like Millie, had experience of a family member with a needle "*my mum had to have one on her arm" (Millie, Girl, 5-7yrs, Rainbows 2).* Depending on whether their experience of injections was positive or negative, seemed to influence children's

opinions about whether the medicines given by injection were positive or negative. Pineapple explained that she was "*going to get one of them [needle] done anyway, for when I get my ears pierced" (Pineapple, Girl, 5-7yrs, Rainbows 1),* and when another child replied that they "*didn't want one" (Girl, 5-7yrs, Rainbows 1),* Pineapple told her that her "*nan said it only stings for a minute" (Pineapple, Girl, 5-7yrs, Rainbows 1).* Jo-jo explained that when she was much younger her "*hip wasn't in the right order and I had to have a needle… I was only one" (Jo-jo, Girl, 5-7yrs, Rainbows 1)* and although she said she could not "*remember",* she said that needles "*only hurt when you have it on your hip"* reflecting a belief based on her own experience.

Experiences that children had observed had a similar effect to ones they had personally and directly experienced. Some children had seen younger siblings have an injection "*that's what my brother was like, [brother's name] was like screaming and screaming" (Girl, 5-7yrs, School 1)*, which led to the belief that "*if you're little and you have something sharp in your arms or legs and you're only like little you would like scream" (Girl, 5-7yrs, School 1).* However, children noted a distinguishing line for screaming as a response, explaining that "*when you are only three or two" (Boy, 5-7yrs, School 1)* it would be okay to "*scream like this" (Boy, 5-7yrs, School 1)* whereas it would not be okay when older.

Some of the older children associated having a needle with needing to be "*brave" (Girl, 5-7yrs, School 1).* Most of the children who talked about needles, talked of bravery explaining that "*I had a needle because I was so brave"* (Girl, 5-7yrs, School 1), "*you have to be brave" (Girl, 5-7yrs, Rainbows 1)* or associated bravery with rewards "*I was brave and then I had chocolate buttons" (Boy, 5-7yrs, School 1).* Even children, like Katie, who had not had an injection thought that it would be painful and experienced a sense of dread with children explaining that "*I would dislike a needle a lot"* and the expectation of a negative behavioural response *"so I would cry" (Katie, Girl, 5-7yrs, Rainbows 1).* This is clearly evident in the following conversation between Popcorn and Lex in a workshop:

> Beth: *so why don't you like needles then?*
> L: *Because they painful and I scream*
> Beth: *How do you know they are painful if you've never had one?*
> L: *Errr I don't know*

P: *because I told L, because I had one and they are painful"*
L: *you scream, and it hurts! (Popcorn and Lex, Girls, 5-7yrs, Rainbows 1)*

The fear and negative experiences of others having needles or medicines can lead to a sense of dread for children who have not yet experienced the treatment. Children like Lex clearly projected this fear saying, "*I would dislike a needle a lot"* and the expectation of a negative behavioural response *"so I would cry" (Lex, Girl, 5-7yrs, Rainbows 1).*

In order to understand how to overcome some of these psychological barriers to acceptability of injections, children were asked what would make needles better. The response from each workshop was that "*if they weren't sharp and they were just like plastic" (Doo-doo, Girl, 5-7years, Rainbows 1),* the belief was that "*if it wasn't that sharp… then it wouldn't actually really hurt you" (Boy, 5-7yrs, School 1).* However, in contrast to the majority of children who had infrequent experience of needles, Alex, a child who had injections frequently, explained that *"umm the injections… basically the* (medicines) *I've had"* are okay. Similarly, one child in a workshop responded to a comment that needles "*really hurt" (Girl, 5-7yrs, School 1)* with a defensive tone "*EY, I have them!" (Boy, 5-7yrs, School 1).* The children, like James, who had needles regularly tended to say that they were OK:

> "*yep I have… I had an injection and I didn't cry… my most recent one was two or three months ago" (James, Boy, 8-12yrs, School 1).*

5.5 Conclusion

In this chapter findings generated from the first activities from the interviews and workshops which focussed on generating insight and knowledge of children's understanding of the acceptability of medicines have been described. These findings have been grouped into three sub-ordinate themes 1) *What Children Can Tell Us About the Acceptability of Medicines; 2) What Helps Improve the Acceptability of Medicines to Children;* and 3) *What Reduces the Acceptability of Medicines to Children.*

The following chapter will discuss the findings generated from the activities relating to re-designing and development the methods used to assess the acceptability of medicines with children.

Chapter 6
Findings 2: Exploring Children's Perspectives on Improving the Methods Used to Assess the Acceptability of Medicines

6 Exploring Children's Perspectives on Improving the Methods Used to Assess the Acceptability of Medicines

6.1 Introduction

This chapter will present the findings from the activities and discussions related to the re-development and design of the methods that are used to assess the acceptability of medicines. As described in the methods chapter, during the activities and discussions children were shown a range of the most commonly used scales from the literature (n=14); these scales included 11 faces scales, one numerical scale and two scales with both images and numbers on. As in the previous Findings chapter (Chapter 5), the demographics, participants, and analysis all remain the same. This chapter is organised into three key themes, the first two focus on children's responses to the scales and the final theme focuses on their ideas for improving the methods for acceptability testing: *Children's Experience and Understanding of Scales, Children's Preferences for Scales* and *Improving Acceptability Testing.*

In total, three superordinate themes and eight subordinate themes were developed and are summarised in Figure 6.1 below. These themes are displayed as a narrative supported with the most pertinent quotes from the data.

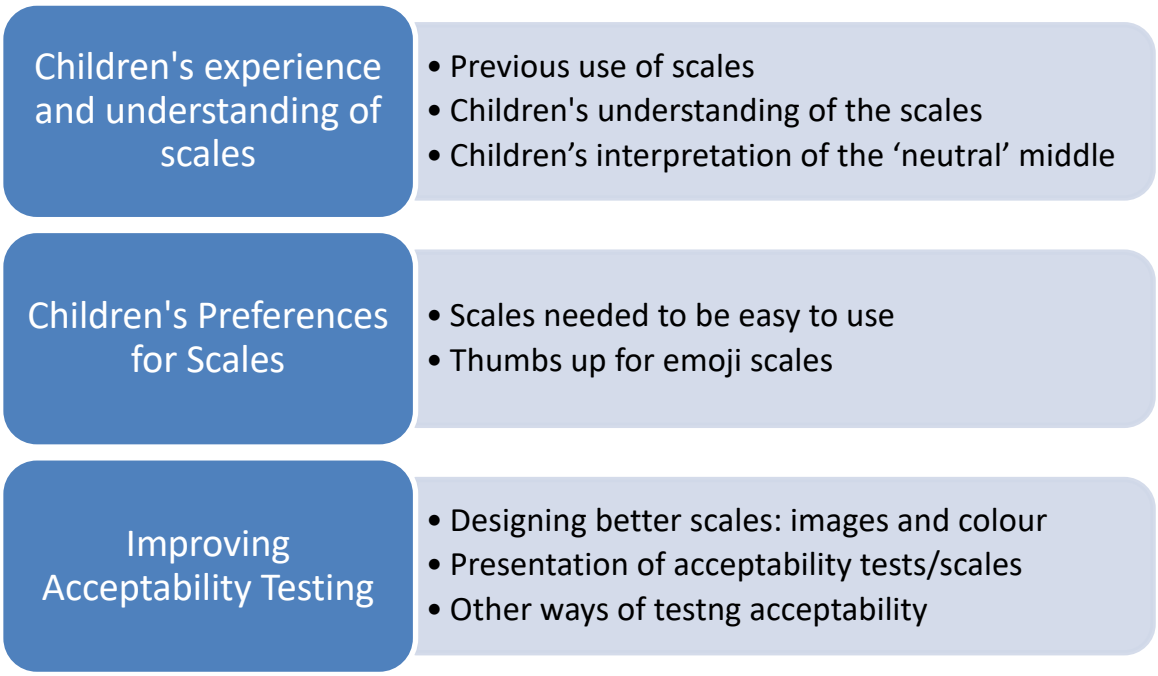


Figure 6.1: Summary of the superordinate and subordinate themes related to improving acceptability assessment.

6.2 Children's Experience and Understanding of Scales

The first super-ordinate theme developed from the data related to children's understanding of the current scales that are used in assessing the acceptability of medicines. This included whether or not children had used scales before and the implications of this, what children understood about the scales and about using the scales to evaluate medicines, and finally how children interpreted current scales and whether this was aligned to the purpose of the scale. This is organised into three sub-ordinate themes *Previous Experience of Using Scales*, *Children's Understanding of the Scales*, and *Children's Interpretation of Response Categories.*

6.2.1 Children's previous experience of using scales

Following initial discussions with each group and individual child it became clear that children had differing levels of knowledge and information about assessment scales used to evaluate medicines. It generally seemed that children's previous use of an assessment scale influenced their ability to use and understand the scales provided. Typically, children who had previously used or seen assessment scales before were more easily able to identify scales, with Lexi explaining *'I recognise that one' (Lexi, Girl, 5-7yrs, Rainbows)*. This was common both in children at the hospital '*I think it was this one [that he had used before], it's either that one or that one… 9 or 10' (Alex, Boy, 8-12yrs, Hospital),* and also those children from other settings who had either been in hospital or had some experience of hospitals:

> "*I've used that! I've used the happy face one because Dr.*Name* gave me a sheet and on the 29th October, I'm going to have an operation!" (I, Boy, 8-12yrs, School).*

As well as demonstrating an awareness of being able to identify scales and know what they were used for, these children also showed that they had a good understanding about how the scales were to be completed:

> "*Oh I know what these are, they tell you from 1-10 and then you put a dot where they ask you if it's nice" (G, Boy, 8-12yrs, School)*.

However, children who had not previously used them or had any experience with paper scales struggled to understand what they were. In one group, after being shown the scales to evaluate, Katie explained that '*they don't look like scales' (Katie, Girl, 5-*

7yrs, Rainbows 2) and the other children in this group agreed, explaining that they had never seen one before. This meant that children sometimes got confused or did not properly understand what the scales were asking them. This therefore led to differing understandings of the scales and the meaning of the categories used on each of the scales (explored in 6.2.2 and 6.2.3).

6.2.2 Children's understanding of scales

When looking at and evaluating the scales, most children explained that they understood what the two end anchors of the scales (0 and 10, or Very Happy and Very Unhappy) meant, *'One means bad and ten means great' (G, Boy, 8-12yrs, School 2).* Most children used their own faces and expressions to display their interpretation of 'I like it' or 'I dislike it' or drew what they thought the face would look like '*Like this! Like this!' (Girl, 5-7yrs, Rainbows).*

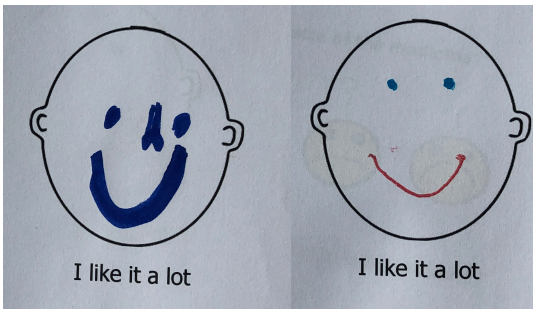


Figure 6.2: "I like it a lot"

Starting with 'I like it a lot', (Figure 6.2) the children explained that this anchor would be '*a big smiley face' (Girl, 5-7yrs, Rainbows)* and when asked what they thought it meant, most of the children agreed that it meant something like '*they really enjoyed it' (Girl, 8-12yrs, Brownies).* A lot of the children displayed an awareness between the end anchors and the category options, explaining that '*that one's a big smiley face and that one is just a little smiley face' (Katie, Girl, 5-7yrs, Rainbows).* The '*little smiley face'* was attributed to the 'I like it' response category, and it was agreed that this category would be *'a smiley face' (Millie, Girl, 5-7yrs, Rainbows 2),* it would look '*smiley'* and '*happy' (Figure 6.3) (Girls, 5-7yrs, Rainbows).*

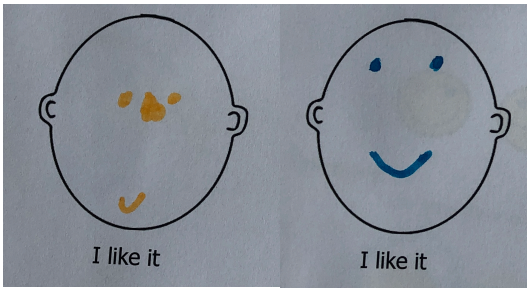


Figure 6.3: "I like it"

When explaining the 'I don't like it' (Figure 6.4) categories there was more of a variety in responses, however each had negative connotations. With some children explaining that it was a '*sad face, that would look sad' (Girl, 5-7yrs, Rainbows),* and *'that's a sad' (Millie, Girl, 5-7yrs, Rainbows 2).* When asked what they thought it meant, this face was described as being '*unhappy' (Girl, 5-7yrs, Rainbows).* However, other children thought that this face meant '*dislike it' (Girl, 5-7yrs, Rainbows)* and expressed this dislike using '*ewwww' (Girl, 5-7yrs, Rainbows).*

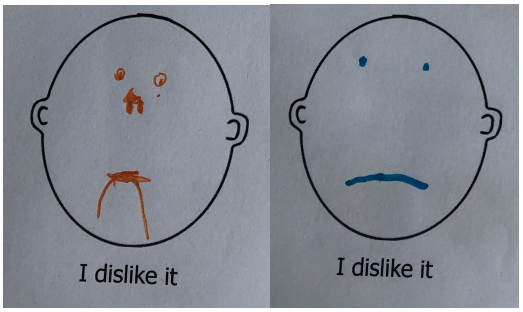


Figure 6.4: "I dislike it"

However, this was not always the case, and some categories on particular scales (see figure 6.5) caused some confusion. Typically, children were confused about distinguishing between some negative categories, seeing little difference between the categories. This was apparent in both the younger children '*I dislike it and I dislike it a lot are the same' (Girl 5-7yrs, Rainbows)* and the older children (8-12yrs) and in children who had and had not used the scales before. Alex, summed up the difficulties that some of the other children experienced:

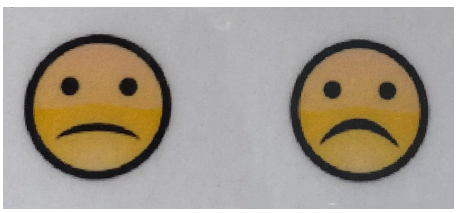


Figure 6.5: Dislike faces

Alex*: "I don't really get what's different… oh yeah now I see*
Beth*: The difference between the two sad faces? Wouldn't you be able to tell?*
Alex*: I didn't see cos the smiles are like each other" (Alex, Boy, 8-12yrs, Hospital)*

Other aspects of scales caused confusion, for example, when looking at a numerical scale that displayed zero as the most positive answer and ten as the most negative answer, children were quick to think it was the other way around. This is really clear in my conversation with Jo-jo:

Beth: What do you think zero means?
Jo-jo: Not very good
Beth: And what do you think ten means?
Jo-jo: AMAZING
Beth: Well…
Jo-jo: You know, really liked it?
Beth: So this one is a little bit different. So this one says that zero is…
Jo-jo: Reallllly good and ten is really bad?? (Jo-jo, Girl, 5-7yrs, Rainbows 2)

Whilst Jo-jo understood that the numbers on the scale related to the acceptability of the medicine being evaluated, the order of the scale did not initially make sense to her. Similarly, in another workshop children were confused about whether the zero meant that the medicine tasted horrible or that the medicine did not taste of anything- interpreting the '0' as a neutral response:

*"*I: *zero means urr disgraceful*
G: *yeah, zero means it doesn't taste of anything*
I: *yeah doesn't taste of anything, taste disgraceful*
Beth: *Oh. So does zero mean it doesn't taste of anything or that it's not very nice?*
I: *ummmm*
G: *just that it doesn't taste of anything" (G and I, Boys, 8-12yrs, School 2)*

Whilst G, one of the boys in this conversation, had earlier explained that *'one means bad and ten means great',* here he seems to interpret this scale differently. This could reflect a struggle to understand the scale without other descriptors such as images, or words he understands. Additionally, although G had previously demonstrated an awareness of how to complete numerical scales, when he used a facial scale, he interpreted the meaning of a scale anchor to relate to the size of the medicine rather than its acceptability.

"G: **circles a big smiley face* this is a big medicine*

Beth: *so is the smiley face because it's good that it's big or is the smiley face telling us that it's big?*
G: *yeah because it's big" (G, Boy, 8-12yrs, School 2).*

Referring back to the section *Adults Help* in the previous findings chapter *(Section 5.2.2.2),* at another point in the interview G explains that the scales would be easier to understand with somebody else helping the child to use it. He drew the picture below (Figure 6.6) and explained it:

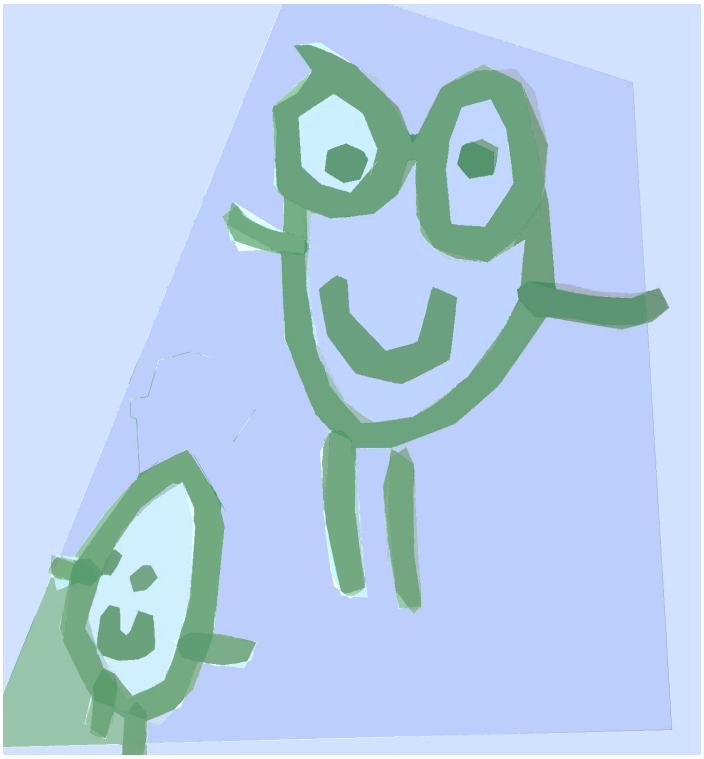


Figure 6.6: Adults help

"see look, look, I've drawn glasses so it shows that somebody else is helping them and here's the person that can't see or understand. See that person helped them read it" (G, Boy, 8-12yrs, School 2)

So, whilst G earlier displays an awareness of how to complete these scales, it may be that the scales he is evaluating are different to one he has previously used. This suggests that children would benefit from the current scale being used being explained to them, to ensure their comprehension of the scale is in line with the meaning of the scale. This also links to section 6.2.1, where children who have previously used a scale and have already had information about particular scales, are more likely to understand the scales and categories.

6.2.3 Children's interpretation of the 'neutral' middle

When evaluating the scales, the 'extremes' i.e. very happy or very unhappy, were talked about first and it seemed that most children had a good idea about what they meant. However, although generally the children had a good understanding of what the categories in the middle of the scales meant, they tended not to spontaneously talk about the middle categories, and so these answers were typically prompted by me asking the initial question '*what about these, the middle ones? What do you think they mean?' (Beth, Interview 7, Alex, Hospital).*

Children from four of the workshops and interviews described the middle face as being *'just okay' (Girl, 8-12yrs, Brownies),* '*not bad'* or *'in the middle' (Girl, 5-7yrs, Rainbows), 'the middle face means it's just okay' (G, Boy, 8-12yrs, School 2), 'yeah okaaay' (I, Boy, 8-12yrs, School 2),* and *'just like, good and bad' (Alex, Boy, 8-12yrs, Hospital).* When drawing what they thought this middle face would look like, one child explained that they were '*doing a straight one' (Girl, 5-7yrs, Rainbows)* (Figure 6.7).

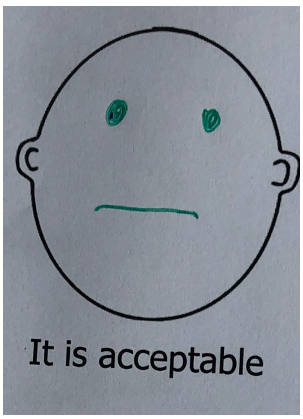


Figure 6.7: Straight face

However, the middle category caused confusion for some of the other children, and there was a greater variety in what the children interpreted the middle face to mean. When asked to draw a picture of a face that they thought would be in the middle, labelled 'okay', Jo-jo decided on a squiggly face (Figure 6.8) and asked '*what about that one?' (Girl, 5-7yrs, Rainbows).* When she was asked to draw a picture of a face that looked 'acceptable', she drew '*a tiny smiley face for it' (Jo-jo, Girl, 5-7yrs, Rainbows)* (Figure 6.9). Interestingly, acceptable and ok are often used interchangeably to talk about the middle categories on acceptability scales. However, this could imply that the language used has a greater effect on how children interpret

and respond to acceptability scales, and therefore an effect on which category represents the level to which children find a medicine acceptable.

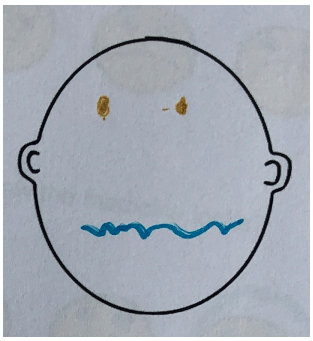


Figure 6.8: Squiggle face

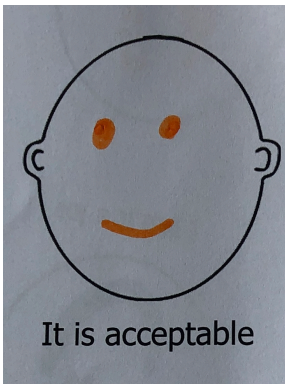


Figure 6.9: Small smile

In one workshop, children had differing opinions on what the middle face meant, with one child explaining '*that is like confused' (Girl, 5-7yrs, School 1),* and another saying that they '*would choose that one if I didn't like it, because I would go like [shows a facial expression matching the middle face]' (James, Boy, 5-7yrs, School 1).* Another child from a different workshop explained they were '*doing a thinking face' (Girl, 5-7yrs, Rainbows)* for the middle category. It is clear that different children attribute different meanings to the categories when they are not clearly explicit in their meaning i.e. 'very happy'.

6.3 Children's Perceptions on, and Preferences for Scales

The second superordinate theme relates to children's preferences for scales and the aspects that influence this preference. One of the key things that children talked about was how the scale needed to be easy to use, and those scales deemed as 'easier' to use were preferred over other scales. Similarly, children had preferences for specific types of scales, including what type of response category was used, whether this was displayed with or without words, and the number of response categories on the scale.

6.3.1 Scales needed to be easy to use and age-appropriate

One of the first reasons children gave for choosing a scale was that '*it's easier to use' (G, Boy, 8-12yrs, School 2)* (scale 11). Children explained how different scales would be the easiest to use for them, giving reasons for their choices. Most children talked about how the response categories on each scale would improve a scale's usability. In particular face scales were deemed as easier to use:

> *"G: it's easier! So so I know what that means, so if it's sad it means it tastes rubbish and if it's that one [points to small smile] it means it tastes a little bit good…"*
> *"I: and that's just great [big smiley face]" (I and G, Boys, 8-12yrs, School 2).*

Other children chose different scales for other reasons. In particular, when asked which scale would be best for him to use, James explained he '*thinks that one [Likert scale], because I find it a bit more exact'* (James, Boy, 8-12yrs, School 1). Similarly, another child from a different workshop asked if the Likert scale was *'maths? Can we do more maths?' (Anika, Girl, 8-12yrs, Brownies).* The Likert scale was deemed preferable for the children in the older age group (8-12yrs), and for those children who chose it, it was because they liked numbers and maths, or found the numbers more exact than the images on the facial scales. However, not all children agreed with this, and Joy explained that she thought the Likert scale '*was too difficult, I think that one [with faces] is easier' (Joy, Girl, 8-12yrs, School 1).*

Despite this, Joy was conscious that older children '*might be ten or something, so they might be able to use it [Likert scale]'* (Joy, Girl, 8-12yrs, School 1). Most of the children in the study were conscious that no one scale would be the best fit for every child, and age and ability were factors that children considered would change the appropriateness of a scale. When evaluating the emoji scales, despite already explaining which scale would be the best for him, Alex talked about how:

> '*the emojis kinda help the small ones [children] and they might just get confused [with stars], they might just think you're putting bigger stars on' (Alex, Boy, 8-12yrs, Hospital).*

Emojis were talked about being the easiest of the response categories to understand, G explained how '*emojis are actually the easiest to use, cos cos you can tell if it's*

angry easier, this one is number 12. You can tell what they mean easier' (G, Boy, 8-12yrs, School 2) (see Figure 6.11: Scale 12).

Similarly, a number of children talked about how words would either help or hinder the appropriateness of a scale. Alex explained how the words '*helped a bit, but say my 8-year-old sister is still reading year two books',* he chose three scales which he thought '*would be good*'…

> *"I think I would prefer mainly the ones without the words… because if little ones ever did that test and they didn't really know how to read them I think that one would be best because it has no words and it has clear expressions" (Alex, Boy, 8-12yrs, Hospital).*

However, G explained that he would not like a scale without words because if it has '*got no words, what if you don't know what the faces mean?'.* Both children show an awareness of considering other children and whether or not the response categories would be understandable. Whilst G explains he would prefer both words and images, he also goes on to offer a solution to what Alex describes as an issue if the person completing the scale could not read, '*if it's got words then an adult could read the words, somebody else could come and read the words' (G, Boy, 8-12yrs, School 2).* This idea that words would help children to understand was also reiterated by a girl in a different workshop group, she explains that the scale is '*really clear and has words so you know just what they all mean' (Girl, 8-12yrs, Brownies).*

6.3.2 Thumbs up to emoji scales

As well as emojis being talked about as making the scales easier to understand and use, overall, they were the preferred option for response categories on the facial scales. Children gave a number of reasons for this, including the additional expressions and hand gestures, the clarity of the scales and how well children believed the emojis reflected their own responses. When presented to the children, the scales were labelled 1-12 (full list of scales can be found in the methods section), these numbers will be referred to in the following section to distinguish which scales are being talked about.

Of all the scales, the scales referred to as the ones with '*the emojis' (Girl, 8-12yrs, Brownies) (Scales 9, 10, 11, 12)* were mentioned most often as being preferred. Key

reasons for these scales being chosen was '*because I like the emojis on it' (I, Boy, 8-12yrs, School 2) (Figure 6.10: Scale 11),* and *'that's like maybe they're emojis' (Boy, 5-7yrs, School 1) (Scales 9,10,11).*

Each of the scales had emoji-type faces on them, some in colour and some without. So, whilst there were other options of 'emoji' faces, children showed preference to a select few. One child preferred scale 12 (Figure 6.11) because of the colour of the images specifically, and whilst this was the only time colour was mentioned as a reason for choosing an existing scale, colour was mentioned in each workshop when re-designing scales (See section 6.4).

> *"There's more like colour and dislike is like an angry face' (Joy, Girl, 8-12yrs, School 1)".*

6.3.2.1 Happy and smiley

As well as colour, other reasons children liked scales related to the emojis used, in one workshop the children talked about how they liked Scales 9, 10 and 11 because *'they are all happy and smiley… AND that one is putting a thumbs up!!' (Boy, 5-7yrs, School 1)* (Figure 6.10). The fact that children chose these scales because they '*like this faces' [sic] (Girl, 5-7yrs, Rainbows),* and one of the key reasons given for this choice was because of the '*smiley face' (image 6.13: scale 8) (Girl, 8-12yrs, Brownies). 'I like 11 because I like the faces' (Girl. 8-12yrs, Brownies).*

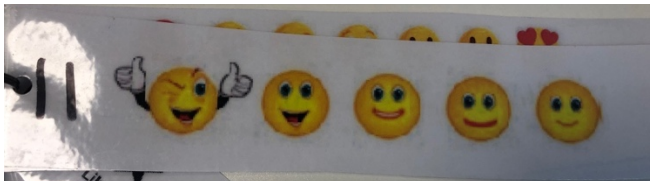


Figure 6.10 Scale 11

6.3.2.2 Children like emojis because they are clear

Another child added that she liked scales 10 and 11 '*because there's all sorts of different things on them' (Girl, 5-7yrs, School 1),* and the children generally agreed that they *'like the scale, I can do that' (James, Boy, 8-12yrs, School 1).* The idea that the children liked a scale because they could 'do' it, links to how easy they found it to use, and Anika explained why she decided on scale 12 (Figure 6.11):

"Cos it's got like just like really just like very clear, really dislike and like and I like that it's got different things like if you dislike it but didn't dislike extremely you could go for that one and if you liked it but didn't like it extremely you could go for that one and then if you if you erm, it was not good but not bad just in the middle you'd go for this one" (Anika, Girl, 8-12yrs, Brownies).

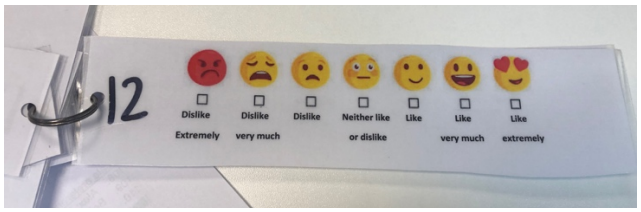


Figure 6.11: Scale 12

Being able to differentiate between the faces seemed like an important factor of the scales, one child explained that the emojis would be a good scale to use '*because they'll know that's happy and that one is less happy' (Girl, 8-12yrs, Brownies).* Similarly, in another workshop one of the children explained that he would chose number 5 (see Figure 6.12: Scale 5) '*because it's quite clear and bold, and things like this [scales 6,7,8] aren't very clear to see' (James, Boy, 8-12yrs, School 1).*

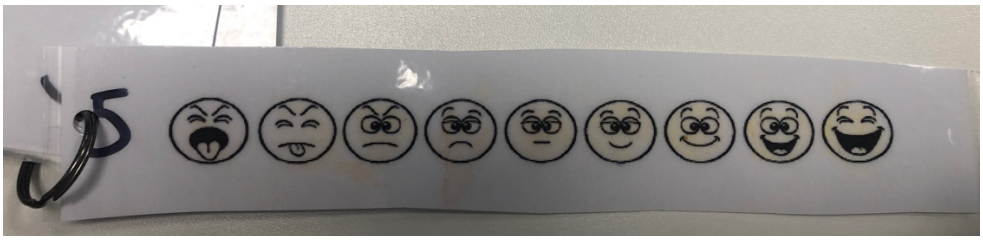


Figure 6.12: Scale 5

6.3.2.3 Other factors

Two children in one of the workshops chose scale 8 as their preferred scale to use when assessing acceptability because they thought that it was '*good that they have done a girl and a boy' (Anna, Girl, 8-12yrs, Brownies).* These children explained that they would choose this scale because:

"Anna: girls might understand the girl one and boys might understand the boy one…
Anika: because little girls might think, if they aren't a boy they might not understand that one but if they are a girl they might understand that one. So it's better." (Anna and Anika, Girls, 8-12yrs, Brownies)

However, two other children in this group disagreed, explaining that they '*don't think it matters… it doesn't actually matter' (Girls, 8-12yrs, Brownies).*

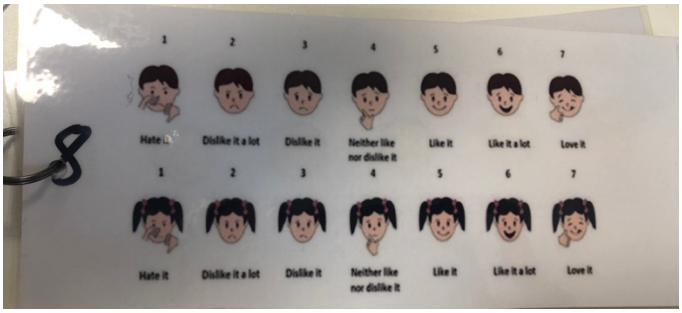


Figure 6.13: Scale 8

Scale 8 was also specifically highlighted as inappropriate for some children and other scales 6 and 7, were described as being unclear by some children. Alex thought scale 8 (Figure 6.13) was particularly unclear:

> *"But I wouldn't really suggest this one (pointing to number 8) because, that one [middle faces] it looks like they're just thinking and they're not saying good or bad. It just looks like they are thinking about what they are going to answer" (Alex, Boy, 8-12yrs, Hospital).*

The children also considered other factors, such as how accessible the scales were to other children, and Alex explained that he would pick the emoji scale 10 (Figure 6.14) in case a child could not talk:

> *"I mean like, say if someone couldn't talk and they didn't know how to, they could only do sign language and they didn't know how to say it they could just point or tick it" (Alex, Boy, 8-12yrs, Hospital).*

Figure 6.14 Scale 10

Systematic data were not collected regarding children's preferences for specific scales. However, some children commented that scale number 12 (Figure 6.11) was the most common scale chosen by children, the main reason for this being that children both liked and understood the emojis. Children also acknowledged that having

both pictures and words would be useful and helpful, as discussed in section 6.3.2.2. The second most common scale preferred by children was scale 8 (Figure 6.13). This was mainly chosen by younger children who expressed that they liked that the male and female options. However, this scale was not as popular with older children and, earlier in this chapter (Section 6.3.2.3), a discussion of the advantages and disadvantages of this scale was presented.

6.4 Improving Acceptability Assessment

The final super-ordinate theme was developed from what the children talked about regarding their thoughts and opinions of improving acceptability assessment. The children evaluated the currently existing methods of assessing acceptability and talked about their ideas to improve these for children. They also discussed ways that acceptability assessment could be improved, and this is explored in the following sections.

6.4.1 Designing better scales: images and colour

Firstly, children explained the different ways that they believed the assessment scales could be improved, these were organised into two key sections: *Improving the images used on the response categories* and *Using colour to improve the scales*.

6.4.1.1 Improving response category images

When looking at the scales almost all children redesigned or developed new faces and emotions for the response categories on the scales. These typically included additional behaviours or facial expressions that they believed would be easier to understand and use, which were generally more emotive.

Children mainly added to the negative end of the scales 'dislike it' or 'dislike it a lot' with the inclusion of tears and crying as can be seen from Jo-jo and Katie's discussion:

> *"Katie: No I dislike it a lot- So that's reaaaally bad*
> *Jo-jo: Waaah im crying [facial expressions to match the face she is drawing]*
> *Katie: I want him to cry*
> *Beth: Oh did you put him crying?*
> *Katie: If I dislike it a lot, I would dislikeeee a needle a lot so I would cry*
> *Jo-jo: Don't talk about them" (Katie and Jo-jo, Girls, 5-7yrs, Rainbows)*

In this exchange Jo-jo explains that *she* is crying as she draws the face, saying that if she disliked something a lot she would cry. Conversely, Katie explains that she wants *him* to cry, referring to the face she is drawing. Interestingly both children were given the same task and yet have interpreted it differently, with one of them drawing themselves on the scale, and the other drawing how they would expect someone else to react if they disliked something a lot. Katie then continues and uses her own experience, e.g. if she disliked a medicine she would cry, as a justification for why she had drawn the face crying. Similarly, in other workshops when asked what a face would look like if it was 'I dislike it a lot', the children showed me with their own expressions and body language, this included children crossing their arms, pursing their lips and frowning. The children then continued drawing the faces on the scale asking '*crossed arms? They might be crying… that's what my friend does' (Girl, 5-7yrs, Rainbow 2).* Similarly, in another workshop one of the children explained that '*my face would like when it was not acceptable for needles, I would go [demonstrates]' (Girl, 8-12yrs, School 1).* In each of these examples, the children use their own experiences, or their experience of another child taking medicine to base their belief of how they would look or act when they 'dislike it a lot' (See Figure 6.15).

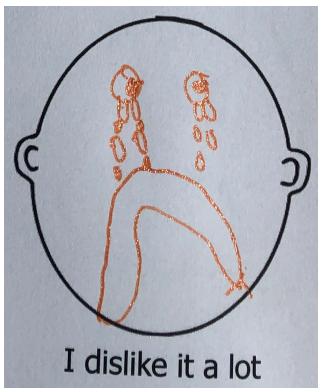


Figure 6.15: I dislike it a lot

As well as physical actions such as crossing arms and crying, children in this workshop also talked about specific facial expressions such as '*I'm doing a shocked face', 'I'm doing a straight face', 'I did a frown' and 'I'm going to do this one a frown' (Girls, 5-7yrs, Rainbows 2).* Each of these ideas are different and perhaps display children's differences depending on their experiences and how they believe they would act. Additionally, some of the faces that the children decided on such as *'a straight face'* are used in pre-existing scales as indicating acceptability or the middle response. This

has implications for the validity of the results of these scales when there is so much variance in children's interpretations.

Reiterating the earlier point that some children found it difficult to distinguish between the response categories, a number of children explained that they '*don't know what I dislike it'* would be (Millie, Girl, 5-7yrs, Rainbows). One of the children explained that for '*I don't like it… [they would be] sad and grumpy' (Girl, 5-7yrs, Rainbows 2).* In a different workshop, Jo-jo thought that it would be '*a sad face but like a lighter one, look like that [points to a face]' (see Image 6.16) (Jo-jo, Girl, 5-7yrs, Rainbows).*

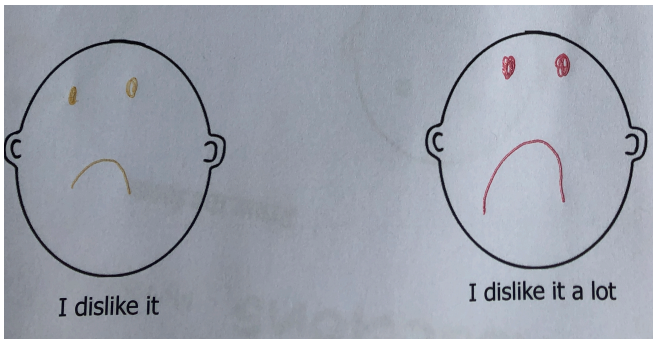


Figure 6.16: I dislike it

Katie, from the same workshop. explained that she would '*put it with tears in my eyes but I'm not crying yet' (Katie, Girl, 5-7yrs, Rainbows)* for 'I don't like it', in comparison to crying in 'I don't like it a lot'.

For the middle response category 'acceptable', children talked about a range of emotions and behaviours that they believed would represent acceptable. A number of children, like Alex, used a '*thumbs up for acceptable' (Alex, Boy, 8-12yrs, Hospital),* adding the thumbs up hand gesture to their drawings.

Additionally, children also included a smile on their 'acceptable' faces or picked '*the cool one with sunglasses' (Boy, 8-12yrs, School 1)* from the emoji sticker sheet. Whilst the child did not explain why he had picked the one with sunglasses, he explained that he '*likes that one… it actually looks like superman a bit because of the goggles glasses' (Boy, 8-12yrs, School 1).* In this workshop it became apparent that the child chose that specific face because he thought it was '*the coolest there' (Boy, 8-12yrs, School 1).*

6.4.1.2 Impact of colour

Whilst the colour of scales was only mentioned as a reason for one child choosing a scale (section 6.3.2.1) a majority of children incorporated colours into their re-designed scales and explained that different colours meant different things. In one workshop, Katie explained that she was using different colours for the faces '*because it shows how they actually feel' (Katie, Girl, 5-7yrs, Rainbows).* However, when asked why she had picked the colours she said that she did not know. Despite this, the concept that colours could display how a person, or face, 'felt' continued in another workshop where Ruby told me that she was '*going to choose yellow for happy face and red for sad'* and when asked why, she explained '*cos red is for angry and yellow is for happy' (Ruby, Girl, 5-7yrs, Rainbows 2).*

There was a recurrent theme around why children chose red or yellow to display their unhappiness or happiness with a medicine. One child explained that she '*is the confused one'* and asked if there was a red pen anywhere, when asked why she coloured it in red, she explained '*oh, because it's like your lips for red isn't it?' (Girl, 5-7yrs, School 1).* It is clear that the colour red had different meanings for each child, one using it to display unhappiness and the other using it to indicate that their face had red lips. The colour yellow was sometimes used '*for happy'*, and other times children used it for all of the response images, rather than having the scale without colour or a skin tone. Children talked about how they '*like the colours' (Jo-jo, Girl, 5-7yrs, Rainbows)* of certain scales, and scales without colours were described as '*stinky, it doesn't have any colours on' (Katie, Girl, 5-7yrs, Rainbows).* One child explained that they would '*want to change the colour of this one (scale)'* and when asked to which colour, she said *'yellow' (Girl, 5-7yrs, Rainbows 2).* Only one child explained that the colour would not make a difference, when drawing his face he used the orange pen and without prompting said '*I'm not saying it has to be orange'* (Alex, Boy, 8-12ys, Hospital), and continued saying it could be any colour.

6.4.2 Presentation of acceptability tests/scales

When re-designing and developing the existing scales, the children thought that the presentation of the scales could improve how appropriate the scales were to children. The typical format of an acceptability assessment page (Figure 6.17), was described by one of the children as '*boring'* (Girl, 5-7yrs, Rainbows).

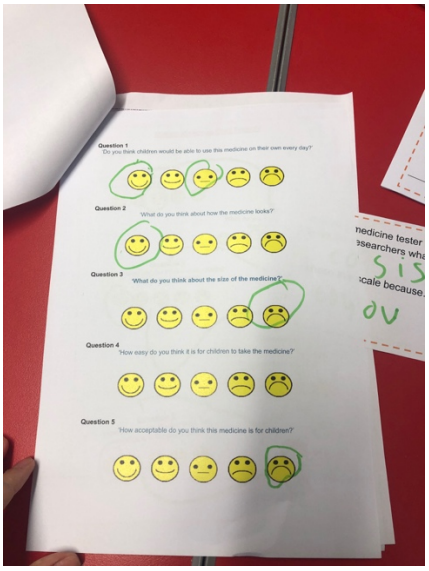


Figure 6.17: Typical scale used in acceptability assessment deemed to be "boring"

Most of the children expressed a preference for the scale which had been designed to look like an activity map (Figure 6.18); the individual scales remained the same but were displayed across the page, with a dotted line for the children to follow from one question to another.

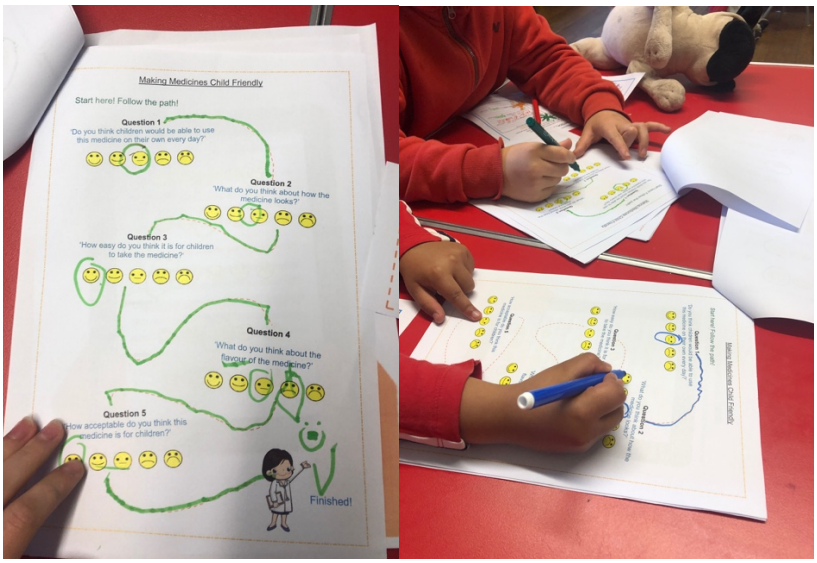


Figure 6.18: Acceptability assessment with activity map design

The children engaged well with this scale, most children expressed positive opinions on this presentation such as '*I love this one' (Girl, 8-12yrs, School 1),* and *'I like it this one' (G, Boy, 8-12yrs, School 2),* following the line and answering the questions by

circling the face that they thought best represented their feelings. In workshop 2, all of the children explained that they:

> "*would choose this one, I would choose this one… because there's loads of activities to do and you get your hands working and that one (original presentation) you have to think about a lot of it but this one you can play along" (Katie, Girl, 5-7yrs, Rainbows).*

The idea that this presentation was 'fun' was reiterated by another child who described it as being '*like a game' (Girl, 5-7yrs, Rainbows).* Building on this, Joy and other children explained that this presentation was '*just more fun and it's good for like little kids to do' (Joy, Girl, 8-12yrs, School 1).* There was a recurring idea that presenting the scales this way was '*easy' (Girl, 5-7yrs, School 1)* and more appropriate for all ages of children, with other children explaining the reason they liked it was because they could '*draw on it… I like following the map with felt tips'* and *'because we get to draw on it… children like to draw' (Girl, 5-7yrs, Rainbows 2).*

James said that he would be 'in the middle' with this option, and when asked why he explained that '*it would be better if it was like a map but with the number scale on it' (James, Boy, 8-12yrs, School 1).* This is an important consideration, as James has separated his thoughts on the presentation of the scale and the individual scales themselves.

Continuing with the game theme, some children explained that the scale designed to look like a children's game 'Top Trumps' (Figure 6.19) would be the best for them:

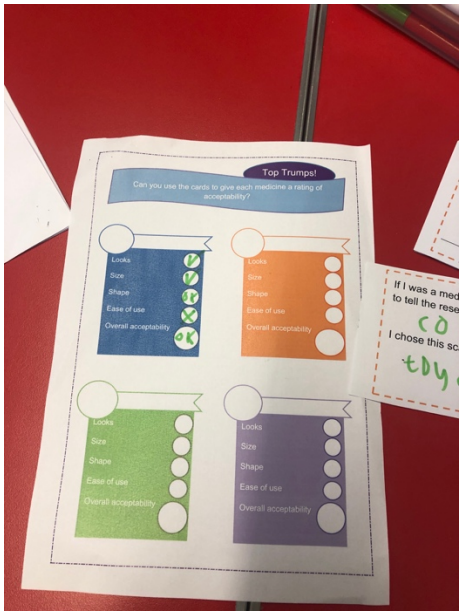


Figure 6.19: Game scale

James and Brooke gave this presentation a '*thumbs up' (James and Brooke, Boy and Girl, 8-12yrs, School 1),* and Joy said it was a *'winner winner' (Joy, Girl, 8-12yrs, School 1). James explained his* reasoning for Top Trumps being good was:

> *"Um because Top Trumps is quite fun and lots of kids play it and they find it quite easy to read" (James, Boy, 8-12yrs, School 1)*

Children from other workshops agreed that they would '*like the Top Trumps one' (Girl, 5-7yrs, Rainbows)*, and Anika explained it was '*because children like to play games and Top Trumps they all play and I think they would understand it' (Anika, Girl, 8-12yrs, Brownies).* However, although children explained that they liked this style, not all children knew about Top Trumps and some children did not complete the scale correctly (i.e. with numbers), instead writing in the space that the medicine was 'OK', as can be seen in Figure 6.19.

A couple of children preferred the 'iPad' design (Figure 6.20), and Joy explained this was because '*loads of kids go on their iPads so if they saw this they might think it's okay' (Joy, Girl, 8-12yrs, School 1).* This was reiterated in the Brownies group, where two children said that they would choose '*the iPad one because children use iPads a lot' (Girls, 8-12yrs, Brownies).* James, who previously expressed a liking for numbers, explained that although he liked the presentation, he '*just finds it easier with the numbers (scale)' (James, Boy, 8-12yrs, School 1).*

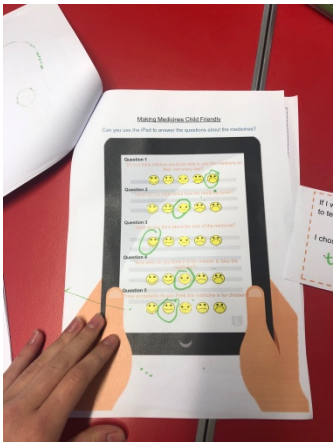


Figure 6.20: iPad scale

6.4.3 Other ways of acceptability testing

Children talked about the other ways that acceptability testing could be conducted. When asked how acceptability assessment could be improved, the main things children talked about was having a choice, being asked how they feel first, and being included.

Children are often included in acceptability testing at later stages of the approvals process but are rarely included in decisions about the ways that acceptability assessment is conducted. However, in this study children discussed how they believe it is important for them be involved in these decisions. Alex explained that he thought it would be useful if children were offered a choice of assessment scales so that each individual child could pick which one was most appropriate to them, taking into consideration whether the scale had words or did not have words:

> *"Umm not really, well they could have like a separate one where they copy it and it's the same, but it just doesn't have words and then the child could choose which one they use" (Alex, 8-12yrs, Boy, Hospital).*

Other children were also conscious that having a choice or option would be helpful 'G' explained that "*because [that] has got no words and what if you don't know what the faces mean? If it's got words somebody else could come and read the words" (G, Boy, 8-12yrs, School 2).* The children explained that not only did they think it was important for them to be involved, but that also that they thought it was important for children of different ages and abilities to be accounted for. Alex provided a detailed response:

"Beth: So, can you think of any ways to improve these to make them better?
Alex: Well, I mean you could put an extra one with three on so that one (hand gesturing) for maybe bad and good?
Beth: Oh, so with the thumbs up and down?
Alex: The little ones could do that (thumbs up and thumbs down gesture) in reception
Beth: So that is a little bit like this one- thumbs down and thumbs up
Alex: But I think they should probably be a bit bigger" (Alex, Boy, 8-12yrs, Hospital)

Here it is suggested that having a choice of an extra scale with just three images on, (a thumbs up, thumbs down and thumbs to the side) would be more appropriate for younger children, because they can 'do that' with their own hands. He also suggested that these should be bigger than the hand gestures that typically appear on the current scales.

Similarly, children in another workshop also believed it was important that children were involved in decisions about acceptability assessment because '*they can see if they actually like it or not and if it helps them' (Girl, 8-12yrs, Brownies)*. Children also considered that this assessment should come from both children in the hospital and children who are not in the hospital '*because they [adults] can just choose one child that is not actually like ill, and they can taste it… because if someone is really ill and then if the medicine makes them worse' (Girl, 8-12yrs, Brownies).* However, children in this workshop also showed an awareness that the medicines should not be tested on children initially '*because it could make them really poorly if it's not right' (Girl, 8-12yrs, Brownies)*.

However, they all agreed that children should have some say in their medicine and assessment. Here the children showed an awareness of the safety and effectiveness of the formulation to 'help them or make them worse', and the ability to separate this from the taste and feel of the medicine for children. It is clear that children understand that the medicine should be tested initially on adults to ensure its safety. However, they also demonstrated that it is important that children are involved in the development of the acceptability aspects of the medicines.

Children talked about how they thought it was important that adults '*ask how you feel about doing it [the assessment] first' (Joy, Girl, 8-12yrs, School 1).* They considered that:

> "*it [the medicine] might be like hard, it might be horrible if an adult tastes it because adults have different tastes to children" (Girl, 8-12yrs, Brownies).*

This is an important point, and one that all formulators undertake. It was also interesting that this was something that children chose to talk about, without any prompting. This finding demonstrates that children often have more of an insight to the process of medicines development and differences in preferences than we, as adults, sometimes consider. There was a belief from the children that '*people who are older than children are more important because like they have an adult brain' (Girl, 8-12yrs, Brownies),* in the context of the development of medicines. However, another child's response to this was, '*but as a child, as a kid they would understand more' (Girl, 8-12yrs, Brownies).* The idea that 'a kid would understand more' is a prominent reminder that children might be better placed about their own preferences and acceptability in regard to medicines and acceptability assessment and that this is something that should be considered in greater depth.

6.5 Conclusion

This chapter has explored the findings from the activities and discussions relating to the methods that are used to assess the acceptability of medicines and to the re-development and design of these methods. These findings have provided much needed insight and information about children's thoughts and opinions about the acceptability of medicine assessment and will help to expand knowledge about these assessment methods can be improved. This chapter has highlighted the wide range of aspects that influence the perceived appropriateness of acceptability assessment methods.

Chapter 7
Discussion

7 Discussion

7.1 Introduction

In this chapter the findings are discussed in relation to the aim and objectives of the study. The aim of this study was to explore the experiences of children in relation to medicines, to incorporate their views to develop a better understanding of the acceptability of medicine, and to relate this to the tools that are used to assess the acceptability of medicines. Crucially this study reveals the importance of involving children in improving acceptability and considering their ideas for the redevelopment of tools used to assess acceptability of medicines. This has been achieved by working with children and learning from them.

Three objectives were proposed to ensure that the overall aim of the study was achieved. These were to:

1. Explore children's experiences of medicines to gain a better understanding about what is acceptable to children in formulations.
2. Evaluate with children methods used to assess the acceptability of medicine.
3. Use this new information to propose ways that existing tools used to assess acceptability of formulations in a paediatric population can be re-designed to better reflect children's perspectives on the acceptability of medicine.

This chapter begins with a recap of the reasons underpinning the need for this study, and how the methods used were the most appropriate way of involving children in this research to achieve the study's aim and objectives.

7.1.1 A lack of theoretical frameworks

The importance of being able to develop acceptable medicines for the paediatric population is recognised in literature and regulations and outlined in Chapter 1. In order to develop acceptable medicines, it is important that formulators are aware of what is being referred to when talking about the acceptability of medicine, and how it can be measured.

Inconsistency and lack of clarity in how the acceptability of a medicine is defined and operationalised can be problematic for formulators attempting to develop an

acceptable medicine (Lallemant, 2018). Within the literature, many studies claim to assess the acceptability of medicines but fail to include a definition of the concept, this therefore limits the results if they cannot be interpreted or compared across studies (Chen et al, 2019). Furthermore, acceptability is often conflated with other constructs, such as palatability, usability, and swallowability (Table 2.5 presents a full synthesis). Whilst these factors are recognised as potentially relating to, or impacting on acceptability, they are not synonymous (EMA, 2018). Because of this inconsistency many studies fail to report how acceptability is assessed, and little to no information is provided about how data capture tools and measures are developed or validated.

It is widely acknowledged that the inconsistency in defining the acceptability of medicine can cause an issue when developing assessment measures. Within health psychology, it is recognised that applying a theory to a complex concept or intervention can enhance understanding (Rimer and Glanz, 2005). However, when searching the medicines-related literature no theoretical model or framework that defines or outlines the construct of the acceptability of medicines could be identified.

Broadening the search to wider health literature, the Theoretical Framework of Acceptability (TFA) developed by Sekhon, Cartwright, & Francis (2017) was identified, and presents a theoretical underpinning of acceptability specific to healthcare interventions. This was the only healthcare-related framework identified within the literature that provided specific sub-constructs of acceptability. The authors synthesised and systematically reviewed 43 papers, and applied Hox's (1997) four step process of theorising to provide a definition and theoretical framework. The four steps included: 1. Deciding on a concept to measure; 2. Defining the concept; 3. Describing the properties and scope of the concept; and 4. Identifying the empirical indicators and subdomains (constructs) of the concept. In order to do this, Sekhon et al. (2017) reviewed and evaluated the definitions and the end-point variables used to assess healthcare intervention acceptability within the 43 papers. By doing this they proposed the following conceptual definition of healthcare intervention acceptability:

> *"A multi-faceted construct that reflects the extent to which people delivering or receiving a healthcare intervention consider it to be appropriate, based on anticipated or experienced cognitive and emotional responses to the intervention." (p6)*

They then described the properties and scope of the concept of healthcare intervention acceptability, by reviewing the literature and identifying the variables that were reported to be measured by either observations or self-report techniques in acceptability assessment. The variables they identified were then operationalised and provided with definitions. This led to the proposed Theoretical Framework of Acceptability Version 2 (TFAv2) (Figure 7.1), composed of seven different sub-constructs: affective attitude, burden, ethicality, intervention coherence, opportunity costs, perceived effectiveness and self-efficacy (Sekhon et al, 2017).

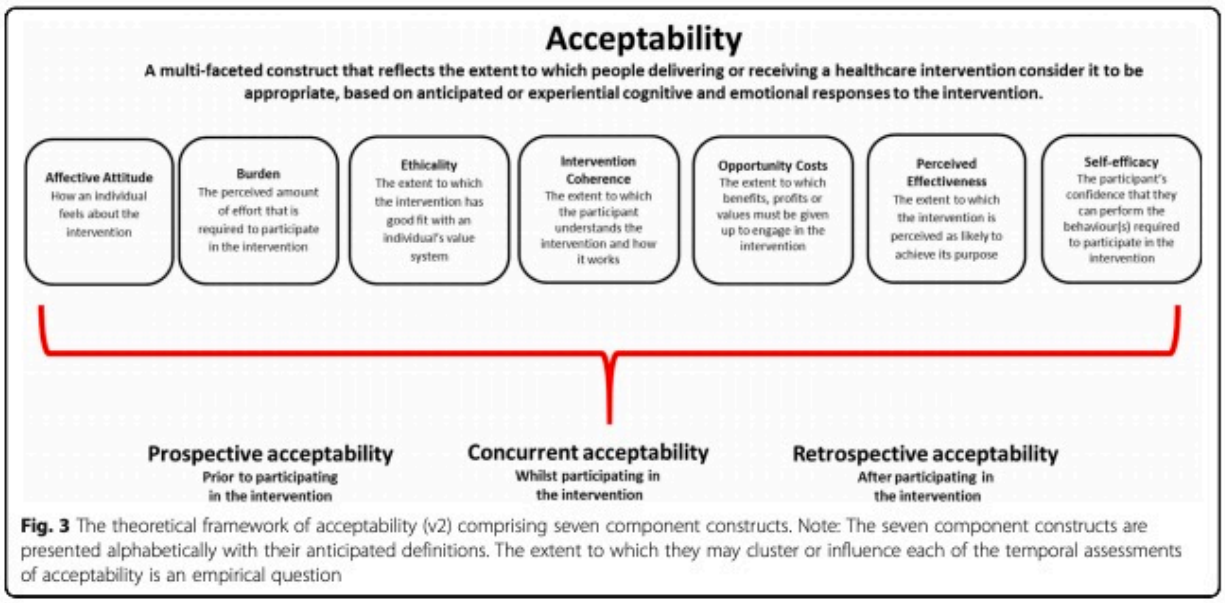


Fig. 3 The theoretical framework of acceptability (v2) comprising seven component constructs. Note: The seven component constructs are presented alphabetically with their anticipated definitions. The extent to which they may cluster or influence each of the temporal assessments of acceptability is an empirical question

Figure 7.1: Theoretical Framework of Acceptability (TFA v2) (Sekhon et al., 2017)

Sekhon et al. (2017) propose that theorising the concept of acceptability provides the foundations required to improve and develop more appropriate measures to assess healthcare intervention acceptability. However, the TFA also provides a basis for operationalising of the concept of acceptability across all health care. Since the framework was published in 2017 it has been validated within complex intervention acceptability studies (Kioskli, 2017) and applied to mobile health applications (health apps) (Chen et al, 2019), mental health programs (Murphy and Gardner, 2019), and healthcare delivery system interventions (Strait, 2018). However, to date, no paper has been identified that has attempted to apply the TFA to the acceptability of medicine.

Whilst acknowledged that there are differences between the acceptability of medicines and the acceptability of healthcare interventions, the current study demonstrates how the theorised concept of acceptability as proposed by Sekhon et al (2017) can be applicable in the context of medicines. The definition that Sekhon proposes considers acceptability as multi-dimensional, something which is already acknowledged in the acceptability of medicines (EMA, 2018). Additionally, Sekhon's definition indicates that acceptability is reliant on the individual's attitudes, perceptions and own assessment. Within wider healthcare definitions acceptability is also defined as relating to an individual's attitudes and perceptions (Sidani et al, 2009' Staninszewsa, 2010). Similarly, the inclusion of the child and their perceptions, beliefs and emotions toward medicines was found to impact acceptability in the current study. Finally, Sekhon's (2017) TFA describes seven domains, all of which were also identified in the findings as impacting on the acceptability of medicines in the current study.

Therefore, within this discussion I apply the theoretical understanding of acceptability developed by Sekhon (2017) to the acceptability of medicine and, based on the current study's findings, and I present:

a) a definition of the acceptability of medicine accounting for children's perceptions,
b) a framework of the acceptability of medicine with consideration of the user, and
c) recommendations for how these two factors can improve the assessment measures used to assess the acceptability of medicine.

7.2 A New Definition of the Acceptability of Medicines

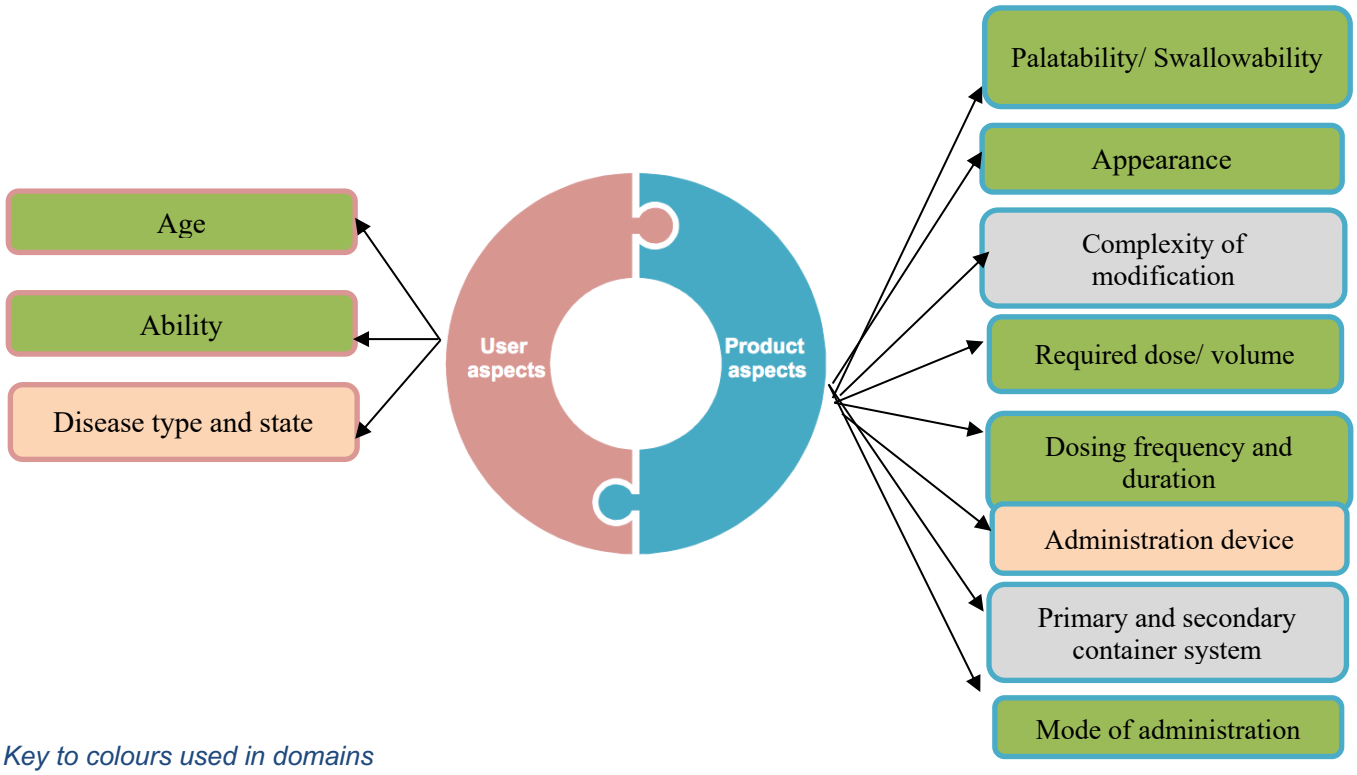
In the following section the general understanding of acceptability is explored, accounting for children's experiences and perceptions. The factors reported by the children that influence acceptability are presented in the Framework of Children's Medicine Acceptability (Section 7.3). The discussion of these two key areas demonstrate the achievement of the first objective of the study which was to explore children's experiences of medicines to gain a better understanding about what is acceptable to children in paediatric formulations.

In relation to the acceptability of medicines, the findings of the study presented in Chapter 5 (Exploring Children's Perspectives to Improve the Understanding of the Acceptability of Medicines), demonstrate that most children, whether they were familiar with taking medicines or not, understood that acceptability (a medicine was acceptable) meant the medicine was 'ok'. This is in line with the terminology used within the acceptability of medicines assessment studies (Mistry et al, 2018). Interestingly and perhaps not expectedly, children were quick to explain that different characteristics of medicines influenced how 'ok' medicine was.

The findings also show that children perceive the acceptability of medicines as a multi-dimensional concept. Whilst the children had differing interpretations of what was acceptable regarding specific characteristics, their perceptions included five of the seven dimensions outlined by the EMA (2013). In addition, children also discussed a range of other factors that they perceived as impacting on acceptability (referred to hereafter as User Aspects). Thus, children demonstrated they had a complex understanding of the acceptability of medicines and were able to contribute to the existing pool of knowledge regarding the concept (this is discussed in section 7.3).

However, current guidelines, papers and definitions focus heavily on the acceptability of the product, and little consideration is given to the user (see Figure 7.2). In a reflection paper, the EMA (2016, p4) reports capability as a potential influence on acceptability and state that the ability of a child to use a medicine product "will relate principally to age, physical development and ability to co-ordinate" but also "to psychological development and understanding" (p4). Whilst this is an important consideration and one that the current study considers, it is not expanded on within the guidance and no information regarding how this influence could be assessed or measured is provided. A major limitation of these existing definitions, models and guidelines is that there is little to no consideration of how children may contribute to, or influence, the acceptability of medicines. Without knowing the total extent of acceptability, it is a challenge for pharmaceutical companies, researchers and formulators to assess the complete concept of acceptability.

Based on the findings of the study, it was considered that the original EMA definition of acceptability might have to be adapted to encompass the perceptions and experiences of children.



Key to colours used in domains

Sufficient evidence generated; additional research beneficial
Some evidence generated; additional research needed
Minimal evidence generated; additional focused research needed

Figure 7.2: Characteristics of each aspect assessed during acceptability testing (EMA, 2018).

In a recent paper produced with the EuPFI, the requirement for additional information relating to the child is recognised (Lallemant, 2018). Lallemant (2018, p12) proposes that primary research involving the user should be undertaken by academic and formulation scientists and with the users of the formulations (children, caregivers, families, health professionals, and public health stakeholders), "to better understand the use of drugs in the economic, geographic and cultural context of their use". It is also argued that methodological research is required in order to validate the tools used for collecting acceptability data across age groups with a focus on developing "standardised, universal, objective, simple metrics… to evaluate the acceptability of

existing paediatric forms and optimise formulations under development… this research must necessarily involve concerned populations" (Lallemant, 2018, p13).

Children are often left out of initial stages of medicines development, and parents and caregivers are asked to provide acceptability evaluations as proxy (Angwa et al, 2020; Klingmann et al, 2020; Giralt et al., 2019). The concern within the pharmaceutical and medicines development industry that children do not, or cannot, understand what the acceptability of medicine is, produces a cycle whereby children are not involved. This was made clear to me when one of the doctors reviewing the patient information leaflets for this study had concerns that the word 'acceptability' was included on them, that the children would not know what was meant by acceptability. However, findings from this study demonstrate that children can and do, understand what the acceptability of medicine refers to and more importantly, are able to meaningfully add to the conversations regarding the acceptability of medicine.

Within the Literature Review (Chapter 2), although it was recognised that there are a multitude of definitions used within the literature, the EMA's (2017) definition of the acceptability of medicine was established as the most reliable and widely used definition:

> *"Patient acceptability can be defined as the ability and willingness of a patient to self-administer, and also of any of their lay or professional caregivers, to administer a medicinal product as intended." (EMA, 2017, p3).*

This definition of patient acceptability is crucial to explaining what acceptability is, as without it there would be no understanding about what acceptability refers to and how it should be evaluated. However, the findings from this research highlight additional component constructs (building blocks) that influence acceptability and argue that these should be included in a definition of the acceptability of medicine (see Section 7.3).

Therefore, the current study proposes an extended definition that can be operationalised for the purpose of measurement. This is grounded in the initial understanding provided by the EMA as well as the findings produced by the children in the study and is closely aligned with the definition of healthcare intervention

acceptability as proposed by Sekhon et al. (2017). This definition accounts for the newly identified constructs in 7.3.2 and explains how specific variables can be used as indicators to assess acceptability in order to provide a definition that will allow researchers to effectively measure the concept of acceptability.

The following definition of the acceptability of medicine is proposed:

> *"A multi-faceted construct that reflects the extent to which a child self-administering, or a parent or person administering, and a child receiving a medicine considers it to be appropriate, based on their anticipated or experienced cognitive and emotional responses to the medicine, resulting in the child's intention to engage with the medicine".*

This proposed definition draws on Sekhon et al. (2017) and incorporates the newly identified component constructs of acceptability (cognitive and emotional responses- see Section 7.3.2). It proposes that cognitive and emotional responses are likely to influence behavioural intent to engage with the medicine. Involving children emotional and cognitive responses to medicines aims to account for the full extent of acceptability, rather than solely focussing on product aspects. This definition is also more aligned with the definition proposed by Drumond (2017), who defines acceptability of medicine as the "sum of positive and negative experiences of a patient and/or caregiver with a pharmaceutical drug product before, during and after use, which will affect the ability and willingness to take or use the drug product as intended" (p296).

Whereas the original definition includes the willingness of the child, the definition developed from this study proposes that it is the child's intention rather than willingness that plays a bigger part as a predictor for engaging in the treatment. The intention of the child is driven by the characteristics of the user identified as impacting on acceptability in the current study. Willingness and intention have been reported as synonymous (Chen et al, 2018), however, whilst they are similar, there are distinct differences between intent and willingness that should be considered. Firstly, willingness is defined as "an individual's openness to opportunity, that is, his or her willingness to perform a certain behaviour in situations that are conducive to that behaviour" (Pomery et al, 2009, p3), however behavioural willingness is said to involve "little precontemplation of the behaviour or its consequences" (Pomery et al, 2009., Gerrard et al, 2002., Gerrard et al, 2009). Within the current study, it is clear that a

child's decision to take a medicine is not a passive act, children do consider whether or not to take a medicine, and the consequences of either taking, or not taking, the medicine. Therefore, behavioural intention seems a better fit. Azjen (1991) defines behavioural intention as, "Intentions are assumed to capture the motivational factors that influence a behaviour; they are indications of how hard people are willing to try, of how much of an effort they are planning to exert, in order to perform the behaviour" (p. 181). It is therefore argued that the intention of the child to engage in taking medicine is arguably more important than the willingness of the child. Furthermore, it is proposed that the user aspects influencing the acceptability of medicine within the model could be predictors (motivational factors) of the child's intention to take the medicine, and therefore by including these in acceptability assessment is more likely to result in a more accurate and valid acceptability rating. These motivational factors or constructs are discussed in section 7.3.2 Children and user aspects. Following this a discussion of the influence of product factors on acceptability can be found in Section 7.3.3.

7.3 Theoretical Framework of Children's Medicine Acceptability

The previous section outlined the newly developed definition of the acceptability of medicine, this definition was produced drawing on past literature and incorporating the data from the current study. The following section will discuss the newly developed framework, and its purpose in providing a conceptual model of the constructs that influence the acceptability of medicine.

As referred to in the previous section, current understanding of user aspects that influence acceptability is limited, and the findings from this study propose a number of aspects that should be considered. The Framework of Children's Medicine Acceptability proposes an additional seven constructs that influence acceptability. These constructs were identified by applying inductive methods to review the empirical data provided during data collection with the children (see Appendix 36 for preliminary framework).

7.3.1 Developing a new framework: Framework of Children's Medicine Acceptability

The Framework of Children's Medicine Acceptability accounts for the pre-existing constructs of the acceptability of medicine that relate to the user and product characteristics as outlined by the EMA (2018). This provides a framework that encompasses both: characteristics of the product and characteristics of the user and presents a structure to assess these factors together. Therefore, whilst the TFA (Sekhon, 2017) has been used as a basis for the theoretical underpinning of this model and has been applied to the new user constructs identified in the study, the new framework developed from this study is an updated and re-developed model (Figure 7.3). These findings, particularly those relating to user aspects, were also used to generate new items for the acceptability measurement tools in the following section.

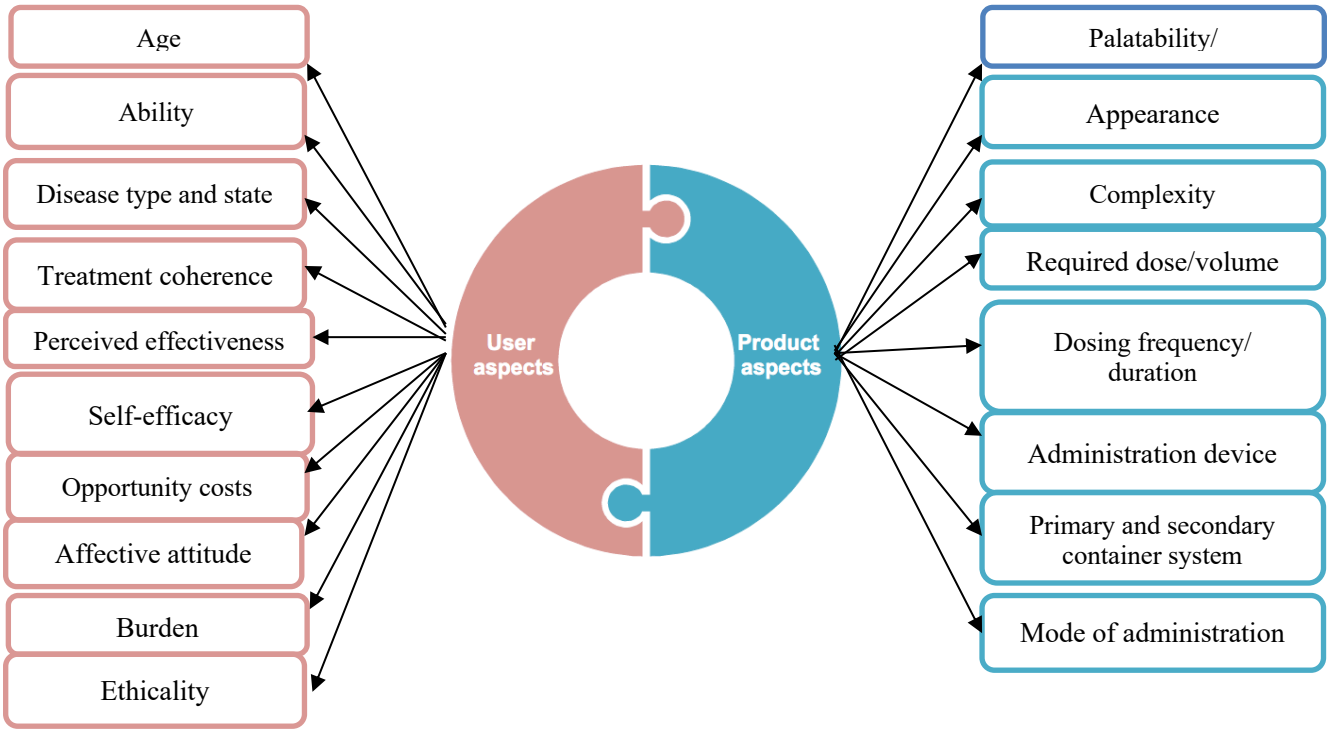


Figure 7.3: Framework of Children's Medicine Acceptability

This section will firstly discuss the necessity for the additional constructs to be included in a framework of the acceptability of medicine, it will then outline how both of these aspects (product aspects and user aspects) work together and can be evaluated as a whole.

7.3.2 Children and user aspects

Within this study children talked about discrete emotions, issues, beliefs and experiences that they identified as important to and/or impacting on acceptability. As

already mentioned, acceptability is often viewed from the perspective of adults and typically focusses on the product characteristics. However, as the Framework of Children's Medicine Acceptability highlights, there is a need for the inclusion of additional user characteristics as children reported that these influence the overall concept of acceptability. However, unlike the existing characteristics of the user which have been reported as important by adults (age, ability, disease type and state), the additional factors are inherent to children's experiences with medicine. The inclusion of these factors has the potential to improve how acceptability is viewed and ultimately assessed.

The following factors relate to either children's cognitive or affective responses to medicines or their impact on whether a medicine is deemed acceptable or not. The first four factors: treatment coherence, perceived effectiveness, self-efficacy and opportunity costs relate to cognitive factors, and the following three: affective attitude, burden, and ethicality relate to affective responses (the definitions provided for use in the Framework of Children's Medicine Acceptability can be found in Table 7.1). Within social psychology it is proposed that humans rely on affect, cognition and behaviour to effectively manoeuvre and make sense of life (Jhangiani & Tarry, 2014). Cognition helps people to understand and predict the behaviour of themselves and others. Over time, sets of knowledge are developed which allow quick judgements to be made about a person, object, or in this case a medicine. For example, a child's knowledge could be that needles hurt, or that medicines help. A person's set of knowledge and interpretation of events is dependent on past experience, for example: a child who takes a tablet every day might interpret the benefits of the medicines as more significant than a child who takes tablets less frequently, as they might not understand the benefits they provide.

Similarly, affect refers to the feelings that are experienced in day to day life (Shouse, 2005). Emotions can be strong and caused by specific events (such as taking a medicine) and are often accompanied by high levels of arousal (Steimer, 2002). They can serve as adaptive purposes, for example, being afraid of a needle because you believe they cause pain will lead to avoiding needles to protect yourself from the hurt. However, this can become harmful when it is left unregulated and unchecked i.e. a child's belief that needles are painful could adversely impact on them receiving

treatment for a condition that requires this mode of administration. Research has found a positive influence between affect and behavioural intention (Phua, 2012), if a person approaches a subject or experience with a positive attitude, they are more likely to be more prepared and willing to display more accepting behaviours (Selwyn, 1997).

The domains of the framework are used to structure the following sections of the Discussion.

Table 7.1: Framework of Children's Medicine Acceptability: User domains.

	Domain	Definitions
Cognitive factors	Treatment coherence	The extent to which the child understands the purpose for the medicine, and how the medicine works.
	Perceived effectiveness	Extent to which the child perceives the medicine as likely to achieve its purpose.
	Self-efficacy	A child's confidence in being able to use the medicine alone or with help.
	Opportunity costs	The extent to which the benefits of the medicine outweigh the negatives.
Affective factors	Affective attitude	How a child feels about the medicine.
	Burden	The perceived amount of effort required for the child to take the medicine.
	Ethicality	The extent to which the intervention has good fit with an individual's value system.

7.3.2.1 Treatment coherence

Treatment coherence is defined as the extent to which the child understands the purpose for the medicine, and how the medicine works.

Coherence and understanding of an illness or medical intervention has been reported as an indicator of intervention acceptability (Huddleston, 2012), and in his definition of treatment acceptability, Kazdin (1981, 2000) includes the extent to which a consumer finds an "intervention to be fair, appropriate, reasonable and consistent with their expectations of treatment". Similarly, Sekhon (2017) also included intervention coherence as an influencing factor in acceptability. By drawing on health psychology literature, Sekhon (2017, p9) provides a definition of intervention coherence as "the

extent to which the patient understands the intervention, and how the intervention works".

The findings from this study demonstrate that children's perceptions of acceptability are dependent on their understanding of their medicines and the purpose of medicines use in relation to the medical problem. In contrast to previous studies (Kameen-Anttila et al, 2006; Menacker et al, 1999), children in the current study had a good understanding about how medicines work and what they were used for. Older children in the study (8-12yrs) were more conscious of how medicines work in general, whereas younger children could explain about how they thought medicines they had specific experience with worked. This may be related to the cognitive development across different ages, and previous studies have demonstrated that the understanding of illness follows a cognitive development pattern (Bibace & Walsh, 1980; Hameen-Anttila & Bush, 2008). Therefore, a child may understand some topics of medicine use more easily depending on their operational stage of cognitive development (Hameen-Anttila & Bush, 2008).

Similarly, sources of children's knowledge about medicines was also varied in the current study and could also explain why coherence or understanding of medicines was so varied. Most children referred to their own prior experiences with specific medicines, or their observation of a family member using medicines. This is in line with studies from the US, Canada and Finland that report that parents, specifically the mother, is a child's primary source of information about medicines (Menacker et al, 1999; Bozoni et al, 2006; Chambers et al, 1997). In contrast to Stoelben et al (2000) children in the current study did not mention medicine packaging as a source of information.

7.3.2.2 Perceived effectiveness

Perceived effectiveness is defined as the extent to which the child perceives the medicine as likely to achieve its purpose.

The effectiveness of medicines was one of the first things that children discussed. Children, whether they had experience taking medicines or not, talked in general about how medicines help. In the current study, children generally viewed medicines

positively and discussed how medicines improve health; this is in accordance with other literature (Hameen-Anttila & Bush, 2008). Similarly, children also reported that medicines should mainly be used when you are sick to help you get better or when they were really needed, these findings are similar to that of work from Garcia et al (1996) and Hameen-Anttila et al (2006). However, children in the current study not only mentioned that medicines could help an existing illness but also reported the preventive value of medicines such as vitamins. This is at odds with previous literature; a systematic review (Hameen-Anttila & Bush, 2008) found that in most studies, children generally talked about medicines helping cure an existing illness rather than prevent an illness. The idea that positive past experiences might facilitate a child to develop a positive belief system about medicine is presented in the previous chapter and reiterated here. This aligns with work from the field of cognitive psychology which argues past experience influences our beliefs, attitudes and future behaviour (Albarracin & Wyer, 2000). Arguably, how effective a child believes a medicine to be is a key driver in children accepting a medicine, with a number of children explaining that they accept medicine because it helps, or because they believe that it helps.

As well as past experience, children also evaluated the effectiveness of a medicine based on how it looked. A systematic review (Hameen-Anttila & Bush, 2008) found that young children often identify a medicine by referring to its appearance (colour, form). The impact of colour and form is discussed as a product factor in section 7.3.3.2. However, studies have found that children often relate the efficacy of the medicine to external characteristics (Menacker et al, 1999; Bush et al, 1985). For example, children believe that the size, taste or colour of a medicine is related to how well the medicine works (Menacker et al, 1999; Bush et al, 1985).

7.3.2.3 Self-efficacy

Self-efficacy is defined as a child's confidence in being able to use the medicine alone or with help.

Children's participation in the medicine-taking process was regarded as an important influence on acceptability by children. This is in line with past research that has found that children regard themselves as active participants in their medicine use and report they are more autonomous in using medicines than parents indicate (Hameen-Anttila

& Bush, 2008). Autonomy was frequently mentioned in the current study, and children talked about a range of actions from knowing where medicine is kept in their homes, to administering and taking a medicine by themselves. These are in line with behaviours included on an 11-item medicine autonomy scale, used within previous research (Bush & Davidson, 1982). It is reported that autonomy, or self-efficacy, is one of the most influential cognitive variables on behaviour (Martos-Mendez, 2015). A number of psychosocial models include self-efficacy, such as The Attitude, Social influence and Self-efficacy model, which suggests that the patient (user) should have "sufficient self-efficacy to perceive herself/himself as being able to take the medicine as prescribed" (Lopez et al, 2003; in Martos-Mendez, 2015., p21).

A child being able to use a medicine independently improved acceptability of medicine for children who were required to take a medicine frequently for a condition such as Attention Deficit Hyperactivity Disorder. Self-administration and taking ownership of treatment is reported as fairly common for conditions that children are knowledgeable about (such as taking paracetamol for headaches) (Chambers et al, 1996). However, in the current study restriction by external factors, such as being at school or requiring a glass of water, reduced acceptability. Self-administration or autonomy in medication was related to children's knowledge and skills of their condition and treatment; this is also reported in a systematic review (Hameen-Anttila & Bush, 2008). Children who had more experience with a condition or treatment voiced a greater amount of empowerment and knowledge about their medicines, and for these children acceptability was improved when they could use their medicine independently. For other children with less experience of medicines and reduced awareness about the risks of medicines, having an adult involved in the process was fundamental to how they viewed the medicine taking process.

7.3.2.4 Opportunity costs

Opportunity costs are defined as the extent to which the benefits of the medicine outweigh the negatives.

Children discussed opportunity costs as the benefits of the medicine outweighing the negatives. This has been referred to in intervention acceptability as "the extent to which benefits, profits, or values must be given up to engage in an intervention"

(Sekhon et al, 2017, p8). Within healthcare this is often referred to as balancing the risk/benefit ratio. In the current study, children generally explained that they would accept negative aspects of a medicine, such as a bad taste, if they believed that taking the medicine was beneficial to their health, for example, one child described a time that he was in hospital for a procedure which required him to be put under general anaesthetic where the medicine was horrible but he understood that it helped him. His knowledge about the benefits of the medicine outweighed his emotional response to the bad taste.

The acknowledgement that people, both adults and children, should have access to the possible benefits and risks of a medicine has been recognised within the last decade (DoH, 2012), and this focus on health literacy has improved the access of information for patients. Raynor (2012) reported that low health literacy leads to worse mortality in the UK, and research has shown that for children the provision of patient information that is accessible, understandable and usable can reduce worry and fear about medical procedures (Bray et al, 2019).

In order for children to assess the opportunity costs of their medicines, it is crucial that they are informed about the reason they are taking their medicines. The findings from the current study suggest that if a child is not fully informed about the benefit of taking their medicine, or if they are administered a medicine without having its purpose explained, it could lead to children's affective responses dominating their behavioural response. Whereas if a child understands why they are being administered a medicine, they are more likely to use their knowledge and their cognition to evaluate the benefits and risks and make a behavioural decision rather than act on an emotional reaction. This has also been demonstrated in a study from Berry (2007), who found that parents who are fully informed are more likely to fully assess the benefits and risks of their child's treatment.

7.3.2.5 Affective attitude

Affective attitude is defined as how a child feels about the medicine.

Affective attitude, in relation to the findings of this study, can be understood as how an individual feels about taking the medicines. Children in the current study displayed that

they had developed attitudes towards medicine, this has previously been found in a study with 7-year-old children (Hameen-Anttila et al, 2006), and in 6-12-year-old children (Syofyan et al, 2019). These attitudes were either positive or negative, and specific factors of medicines were related to these attitudes. Positive attitudes were generally attributed to the clinical value and effectiveness of the medicine, as well as characteristics related to the palatability and appearance of the medicine. Children's attitudes toward medicine have been reported in a number of other studies (Dawood et al, 2011; Sharaideh et al, 2013) however reasoning was not provided (Syofyan et al, 2019). Similarly, children also expressed negative affective attitudes towards medicines, related to a bad prior experience or perceived risk of negative side effect (such as adverse drug reaction or choking), this is also reported in Syofyan et al (2019).

7.3.2.6 Burden

Burden is defined as the perceived amount of effort required for the child to take the medicine.

Whilst how easy the medicine was for children to use has been discussed in relation to self-efficacy in 7.3.2.3, children also talked about amount of effort required in using a medicine. Children talked about the frequency of taking their medicines being a burden, as well as the disruption caused to their routine such as when their medicine regime required regular attendance at hospital. It is clear that burden influences acceptability, with children expressing negative affective attitudes about their dislike for the amount of effort required in taking certain medicines. It is also clear that both burden and the associated emotions, can cause negative behavioural responses such as "kicking off". Whilst the behavioural response is typically used as the base for assessing acceptability (Blume et al, 2018; Rodd et al, 2011; Beck et al, 2005), understanding the reasons for the behaviour, and the ways in which this can be counteracted could be crucial to understanding and improving acceptability.

As well as practical burdens, psychological burdens were also referred to. Some children expressed fears about taking medicines, this is also reported by Bush & Joshi (2002). These fears were related to the dangers of medicines, such as taking a wrong

medicine or someone else's medicine (Menacker et al, 1999; Bush & Joshi, 2002). Children were also conscious of the dangers of taking a medicine for a condition that they do not have, being allergic to the medicine, or taking too much medicine for your age. These factors are also reported within a systematic review (Hameen-Anttila & Bush, 2008).

Finally, children were conscious of the safety of testing of medicines during the development process. They stated that medicines should be assessed with healthy adults and children before they were given to a sick child to ensure the medicine does not make the sick child's condition worse. Furthermore, the children in the current study were aware of adverse reactions such as being sick or not taking enough medicine, this finding is similar to the results provided by Stoelben et al (2000) who reported that 79% of German children (15-17 years) were aware that medicines can have harmful effects. The children in the current study were younger than the sample in the study from Stoelben et al (2000), and so this might imply that children of a younger age may also have an awareness of the risks associated with taking medicines.

The psychological burden of medicine-related pain in children has been extensively researched (Birnie et al, 2018), and research reveals that the past experience has a significant impact on children's perception. Findings from the current study reveal psychological burden and memory, particularly in relation to needles. Some children reported needles or tablets as scary and recounted traumatic past experiences of some medicines, some recalling episodes when they were younger and of which they had little clear memory but which they still talked of as being painful. Research by Chambers (2019) acknowledges this burden but states that "it's not so much how much pain children have from an injection, but how much pain they remember having, that impact their subsequent experiences". Noel (2012) builds on this proposing that when children remember previous pain as more severe, they experience future pain as more intense (Noel, 2012). Additionally, Chambers (2019) also reported that pain perspectives can be socially constructed and influenced largely by family members, in particular parents and siblings (Chambers, 2019). This was true for the children in the current study who had observed someone else, such as a sibling, in pain, or those

children who had been told about the pain by a friend or family member who had primed them with the awareness that needles are painful.

7.3.2.7 Ethicality

Ethicality, in the current study, is defined as the extent to which the medicine is a good fit with individual child's value system. Children in the current study displayed an awareness that taking medicines was the right thing to do to help them to get better. They demonstrated that they understood that taking medicines was the right course of action, even when they did not necessarily like the medicine. Ethicality was also reported as a factor in Sekhon's (2017) framework of intervention acceptability. There is little supporting evidence for ethicality in decision-making to take medicines in past literature, and no studies have asked children about this as yet. The current literature base is sparse in this area and a focus on this in future research would be beneficial.

7.3.3 Children and product aspects

In addition to the seven user aspects identified in the data and applied to the framework, children also discussed product aspects that influence acceptability. As outlined within the literature, the acceptability of a medicinal product is said to be dependent on the palatability/swallowability, the appearance, complexity, volume/amount, frequency and duration, administration device, primary/secondary container, and the mode of administration of the medicine (Kozarewicz, 2014; Ranmal, 2016). Children's perceptions of the acceptability of medicines related to specific aspects of medicines that either improved or reduced acceptability. Within this section the findings that relate to these aspects are discussed and provide a much-needed child's perspective on the product factors that influence acceptability. The aspects which improve or reduce acceptability are discussed in five sub-themes: palatability/swallowability, mode or form of administration, complexity/ease of use, size/volume/amount, frequency and duration.

7.3.3.1 Palatability/swallowability

Children reported that the smell, taste, and feel of a product would each improve the acceptability of a medicine. This finding is in line with the wider literature, with the

palatability of a medicine regarded as one of the most important factors relating to the product in paediatric medicine development (Mistry & Batchelor, 2016).

It was clear that taste and flavours were factors that dominated children's discussions and figured in their drawings and their responses to the activities; taste and flavours were considered by the children to be important measures of acceptability. However, it is worth reflecting on why these factors came through so strongly. As previously discussed (section 4.2.1) the nature of the activities that the children engaged with may have created a particular expectation and frame that might have triggered the children to talk about taste and flavours. In the Marvellous Medicine activity, the children were guided to think about shape, taste, colour and smell although no limits or constraints to their imagination were imposed (beyond only being able to access the colours of pencils that were available). Similar sorts of prompts were present in the other activity booklets. Although the activities provided a degree of direction, they did not prioritise particular factors, so the emphasis on taste and flavour can be reasonably confidently deemed to arise from the children rather than any bias within the research design or design of the tools. With the previous points in mind, the children reported that the smell, taste, and feel of a product would each improve the acceptability of a medicine. This finding is in line with the wider literature, with the palatability of a medicine regarded as one of the most important factors relating to the product in paediatric medicine development (Mistry & Batchelor, 2016).

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 (e.g. texture, cooling, heating, trigeminal response), and possibly also sound" (Kozarewicz, 2014, p245-248). Within the current study, whilst children did not specifically refer to the palatability of a product, they did talk about a number of these factors defined within palatability. Taste and palatability are reported as key barriers to completing treatment (Batchelor & Marriot, 2015; Milne & Bruss, 2008), and this is further complicated when considering the diversity of taste preferences in the paediatric population. Children in the current study had different ideas about what tastes would make a medicine acceptable, and one of the main ideas was that 'no taste' would be best. The taste of Calpol and strawberry flavours were also frequently mentioned and talked about in a positive way. These findings could reflect children's

biology, with past research revealing that children between the ages of 3-10 years reject bitter tastes (Mennella et al, 2005; Mennella et al, 2014) and unpleasant textures (Mennella et al, 2013), and favour sweet or pleasant tastes (Mennella et al, 2011).

7.3.3.2 Mode or form of administration

The mode and form of the medicine was also discussed as impacting on acceptability. Liquid formulations, often labelled as the formulation of choice for children, particularly by parents (Mennella et al, 2015), were talked about as being difficult to use and had more negative mouthfeel associations than other formulations. This is in line with prior research reporting that children find liquid formulations problematic to take (Mennella et al, 2015). In contrast, children talked more positively about tablets. In research about the acceptability of mini-tablets, it has been reported that children (aged 6months-6years) prefer mini-tablets in comparison to syrups (Musiime et al, 2014). Specifically, in the current study children liked tablets as they viewed them as a 'real' medicine that adults have, or perceived tablets as sweets or sweet-like. In recent years significant attention has been paid to the impact that 'sweet-like' medicine can have on paediatric adherence to treatment, and studies have already started to create three-dimensional tablets in the shape of sweets, such as Starmix ® (Scoutaris, Ross & Douroumis, 2018). However, there were also negative perceptions of tablets, and consistent with prior reports (Czynewski et al, 2000) some children voiced concerns about the fear of being sick or choking on tablets.

Whilst children generally regarded the colour and what the medicine looks like as the least important factor influencing acceptability (see Section 6.4.1.2), colour seemed to be an influencing factor in children's drawings. The majority of children explained their colour choices because it was their favourite colour, it made children feel magical, or it was the colour associated to the smell or taste of the medicine, or sweet. Within psychology, it is well understood that people make judgements based on colour (Morton, 2016). Colour of medication has been found to influence our emotional reaction to the medicine, a systematic review has found that different colours illicit different emotional responses to medicines, for example: red, yellow and orange are generally associated with stimulating medicines, whereas blue and green were generally regarded as tranquilising (Craen et al, 1996). The impact of a medicines

colour on patients' attitude is well reported in the literature (Craen et al, 1996), and one study has found that the colour of medication has an influence on patient's adherence (Fitzgerald, 2013). Differences in perception of medication colour has been reported between age and genders (Strivastava & More, 2010). Therefore, whilst children did not report the colour of medicine to be an important factor influencing on acceptability, this could be due to associations being subconscious and not something children are generally aware of. When developing medicines for children, being aware of the association's children have to certain colours is an important consideration.

7.3.3.3 Complexity/Ease of use

The complexity or ease of use of a product was voiced by the children as being one of the most important factors when considering the acceptability of a medicine. Children perceived medicines that they could use on their own, or without help from anyone else as more acceptable. Medicine that did not require any additional help (such as by parents or teachers administering or helping) were reported as more acceptable by some children who frequently used medicine (such as for ADHD), whereas other children who only used medicine when they were sick (such as calpol in a syringe or spoon) talked frequently about adults helping to administer medicines. This is supported by literature that reports that when children are unwell, autonomy in using medicines is not important (Gerrits et al, 1996). This suggests that the context around the medicines use could be an important factor to consider when prescribing medicines for children.

7.3.3.4 Size/volume/amount

The size or amount of medicine was also related to the acceptability of medicines, with most children explaining that a medicine that was too big or too much would reduce its acceptability. Tablet size is a frequently considered factor in formulation development, and tablet size has been deemed the most important factor relating to the acceptability of tablets in a feasibility study (Bracken et al, 2018). The size and amount of a medicine was the key reason for children voicing fears about the formulation, as reported in previous research (Czynewski et al, 2000) which reported that fears about choking or the medicine getting stuck in their throat reduced its acceptability. However, tablets up to 10mm in diameter have been demonstrated to be acceptable to children between the ages of 4-12 years when swallowed whole

(Bracken et al, 2018), and therefore it could be argued that the fear of the tablet is the cause of the issue rather than the formulation itself (fear as a barrier is discussed in detail in 5.4.2.2). Pill-swallowing training has been found to be related to improved medication adherence (Garvie, Lensing & Rai, 2007), and a recent systematic review reported that pill swallowing difficulties can be overcome with a variety of interventions (Patel et al, 2015).

7.3.3.5 Frequency and duration

Children reported that the extended frequency or duration of treatment would negatively affect acceptability. For children who were treated in hospitals, longer duration of treatment meant that they missed out on other aspects of their lives, such as school or weekends at home. The impact on longer duration of treatment has been reported as a barrier to compliance in adult treatment (Menzies et al, 1993; Dhanireddy et al, 2005). Whilst treatment duration was not reported as a barrier for children outside of hospitals, the frequency of having to take an inhaler or tablet each day to manage a condition was discussed by this group. Dosing frequency is reported as a consideration of acceptability in formulation development (Kozarewicz, 2014).

In summary, Section 7.3 has discussed how the conceptual TFA model developed by Sekhon et al (2017) has been applied to the empirical data collected from the children in the study, in order to better understand children's acceptability of medicine. This consideration of the TFA allowed the creation the Framework of Children's Medicine Acceptability which addresses both user aspects and product aspects which can be applied to the development and assessment of medicines. The Framework of Children's Medicine Acceptability is the first attempt at applying theory to the defining and operationalising of the acceptability of medicine.

7.4 Improving Acceptability Assessment

Involving children in this research regarding the understanding of the acceptability of medicines aimed to improve understanding of how children approach taking medicines and the barriers to an acceptable medicine. It is argued within the literature that "ensuring that formulations are suitably designed and acceptable to end-users reduces the risks that medicine quality could be compromised, supports patient adherence and consequently leads to safer and effective use of medicines" (Ranmal, 2018, p 2).

However, despite the wealth of literature and guidance provided about product aspects or characteristics of medicinal products that are said to impact acceptability (Liu, 2015), there is a recognised lack of empirical evidence on the suitability and end-user opinions of medicines in the child population (Ranmal, 2018).

In 2009, NICE published an extensive guideline about the inclusion of patients in their own healthcare. This outlines that "informed patient choice, rather than 'compliance' is the desired outcome" (NICE, 2009, pp53-54). It states, "facilitating informed choice involves more than the provision of information. Informing should be an active process… it also entails eliciting the patient's beliefs and identifying whether pre-existing beliefs might act as a barrier to an accurate interpretation of the evidence" (NICE, 2009, p53). In the current study, the findings demonstrate that children's beliefs and emotions about treatment and medicines impact on their perception of the acceptability of medicines. This therefore may impact their adherence to the treatment.

Involving children in this study has led to a better understanding of some of the influences that might play a part in a child regarding a medicine as acceptable or not. The NICE (2009, p56) guideline states that "the decision to take medicines and the continuing taking of medicines should be considered as a complex behaviour… internal factors represent the beliefs and experiences of the patient. These include the patient's beliefs about medicines in general and their own reaction to medicines. These will influence their intention to take a medicine as suggested by a health care professional." This mirrors the findings from the current study, which show that children's beliefs and experiences impact their intention to take a medicine. Similarly, the current study also demonstrated that factors such as prior experience, communication with family and friends, and information provided by other people who have had the same medicine or treatment also impacts on a number of the user factors and therefore children's intention to take a medicine. This is also reported in NICE guidelines (2009). Furthermore, within health risk-behaviour literature, 'experience' is reported as a moderator for engagement in behaviour. Individuals with more experience are reported as more likely to be increasingly aware of the consequences of engaging, or not engaging, in a health behaviour (Pomery et al, 2009).

A child's decision about the acceptability of a medicine is made within their own frames of reference and make sense within their own understanding. However, a key issue with this is that these factors are not currently given attention when developing or administering medicines for children. Researchers and healthcare professionals are generally focussed on improving the product, and rarely acknowledge that the child's reluctance to take medicine, or disagreement with the prescriber's recommendations may stem from the child's beliefs and attitudes and can be the cause of the issue for acceptability. NICE (2009) state that the onus is on health professionals to "elicit and explore patients' beliefs and experiences, and facilitate the patient making an informed choice about whether or not to take a prescribed medicine" (p56). Therefore, in order to do this, children need to be effectively involved in these discussions, and appropriate tools are required to facilitate this involvement; this was the focus of objectives two and three in the study.

As previously discussed, the ways that the acceptability of medicine is currently assessed in children is limited and often does not capture the total extent of acceptability. Throughout this discussion it has been argued that the inclusion of additional factors relating to the child would improve understanding of acceptability. The following section will discuss how measures can be improved to facilitate the effective involvement of the child in acceptability assessment.

7.4.1 Inclusion of user factors

The Framework of Children's Medicine Acceptability highlights additional constructs that should be considered during the acceptability assessment and proposes that these can be applied within the development stages of paediatric products. In guidance provided by the WHO it is stated that the "window of opportunity during which acceptability can be assessed and the formulation modified is short" (WHO, 2019, p92). This is because the "characteristics of the product only begin to be known when the paediatric investigation plan (PIP) or paediatric study plan (PSP) is submitted, and it is only when the first formulation prototype is available that acceptability can be truly evaluated in the target population" (WHO, 2019, p92).

However, in contradiction to this notion of a short window of opportunity, it is proposed that the Framework of Children's Medicine Acceptability can be applied both quantitatively and qualitatively to the development process. This would lengthen and/or widen that window of opportunity by enabling the assessment of acceptability prior to the development of the formulation prototype. At the planning stage of developing formulations, it is reported that little is known about specific needs of children (WHO, 2019, p95). However, the characteristics of the user outlined in the new framework provides additional information for formulators and developers to refer to in order to provide a more appropriate formulation. The framework also provides a method of considering the acceptability of a formulation prior to the formulation being developed. With the prospective assessment of medicine acceptability, children can provide their judgement of a potential medicine based on the user and product characteristics outlined in the framework.

It is theorised that patient acceptability will change across these time points (Sekhon, 2017) and therefore it is important within acceptability of medicines work for formulators and researchers to outline at what time point acceptability is assessed (e.g., prior to commencing medicine, whilst taking medicine, after completion of medication course) to ensure accurate acceptability assessments. It is a key feature of the framework that children can make a judgement about whether or not they expect the medicine to be acceptable prior to having had the medicine. These judgements are argued to be as a result of past experience influencing the new user factors outlined in the Framework of Children's Medicine Acceptability. Being able to effectively assess anticipated acceptability by evaluating these factors would provide the ability to highlight which aspects of the medicine would need to be changed or modified to improve acceptability or children's responses to the medicine.

Anticipated acceptability could encompass a timespan from the development stage through to clinical trials or a time close to the 'routine' administration of the medicine to a child. This would be significantly beneficial to pharmaceutical companies and their research divisions that often invest many years and funding into developing a medicine without a clear idea of acceptability until the final stages during clinical trials (IOM, 2009).

In the knowledge that it would not be possible to assess product factors and user factors separately during the acceptability of medicine assessment, Table 7.2 demonstrates how it might be possible to assess the collective acceptability of the medicines accounting for both the user aspects and product aspects.

Table 7.2: Proposed Framework of Children's Medicine Acceptability methods applicable to the development and assessment of formulations

Clinical development (anticipated acceptability)	**Administration assessment (concurrent acceptability)**	**Evaluation assessment (retrospective acceptability)**
Qualitative	**Qualitative**	**Qualitative**
e.g. semi-structured interviews or workshops based on constructs from Framework of Children's Medicine Acceptability with children to help guide development of formulation	e.g. semi-structured interviews based on constructs from the Framework of Children's Medicine Acceptability with children and deliverers about anticipated and/or experienced acceptability during the administration or treatment duration.	e.g. semi-structured interviews/focus groups based on constructs from the Framework of Children's Medicine Acceptability with children to assess experienced acceptability post-administration/treatment.
Quantitative	**Quantitative**	**Quantitative**
e.g. questionnaires or child-centred rating scales based on constructs from the Framework of Children's Medicine Acceptability to assess anticipated acceptability of the medicine or treatment.	e.g. questionnaires or child-centred rating scales based on constructs from the Framework of Children's Medicine Acceptability to assess acceptability during trials or administration with children.	e.g. questionnaires or child-centred rating scales based on constructs from the Framework of Children's Medicine Acceptability to assess acceptability post administration/treatment to assess retrospective acceptability.

The WHO states that "At the earliest conception of the strategy for developing formulations for children, all the dimensions of acceptability must be considered." (2018, p10). This might help to facilitate the consideration of acceptability earlier in the process. Furthermore, the findings from the current study also reveal that children have the agency to meaningfully contribute to these discussions about the acceptability of medicine. Children demonstrated not only that they believe they should be involved, but also how and why it was important for them to be involved in medicines development and assessment. They discussed the necessity of being involved in medicine development, and how assessment measures could be improved

through the involvement of children. It has been reported that children benefit from shared decision making in healthcare decisions in a number of ways. By influencing their wellbeing (Spinetta et al, 2002), improving effectiveness of services and enhancing communication skills (Cohen and Emanuel, 1998). The findings from the study reflect wider conversations regarding the inclusion of children, or the opportunity to participate, in decisions that affect their healthcare (Hinds et al, 2001).

7.4.2 Involving children in acceptability research improves knowledge

The EMA (2013) provides recommendations for the improvement of assessment measures and noted that the tools used to collect acceptability data need to be "developed… and validated… [and] must necessarily involve the concerned populations" (Lallemant 2018, p13). In the current study children provided their own input, and by drawing on their own experiences with acceptability assessment measures they worked to evaluate, and re-design current self-report measures used to assess the acceptability of medicines.

Children said that being involved in the development of assessment measures would be more appropriate than having the measures developed solely by adults. There were a number of reasons given for this, firstly children argued that there were distinct differences between adults and children in relation to the acceptability of medicine. Children have explained that "adults have different tastes to children", and it "might be horrible" if the testing of the medicine was left solely down to adults. Furthermore, there was a recognition that children would understand more about the acceptability of medicines to children than adults would, acknowledging the differences between the two population groups. Differences between adults and children in regard to acceptability of medicine is well recognised, and a number of studies demonstrate this (Lopez et al, 2018; EMA, 2013).

However, the findings also show that children had an awareness of the importance of the safety and effectiveness of the formulation, with the understanding that adults should initially ensure it was safe for use, with the assertion that adults were more important to medicine development than children. This was discussed in relation to the

formulation of medicines and children demonstrated an awareness that children are not equipped on their own to develop medicines.

7.4.3 Child-friendly design: Improving response categories

The findings of the Literature Review in Chapter 2 highlight considerable variety in the response images, words and anchors that are used on acceptability assessment measures (see Chapter 2). When evaluating and exploring ideas for re-designing these measures with the children in the study, children gave consideration to additional behaviours and facial expressions that they thought were easier to understand and use. The language used on the scales also seemed an important consideration, with the words 'ok' and 'acceptable' eliciting different responses from the children despite them being used interchangeably within acceptability assessment (Medeiros, 2016; Sjovall, 1984).

There were differences between how children interpreted and presented each of the response categories, and this seemed to be particularly dependent on the child's interpretation of how the question was posed and what wording was used. Although differences in children's responses were not clearly correlated to age in the current study, past research has considered the capacity of children to respond to scales, and wording has been identified as something to be carefully considered in research with children (e.g Piers-Harris Self-Concept Scale, 2002). In some studies, wording has been re-written depending on the population group to account for reading level (Mellor & Moore, 2014), and other studies have substituted the words entirely (Mellor et al, 2004). Interestingly, children in the current study voiced that having the choice between two scales- one with words and one without words, would mitigate issues regarding whether words were appropriate for children to read and understand.

The differences between how children interpreted and presented the response categories was particularly evident for the middle response/face which is generally assumed to be 'acceptable' in measurement (Medeiros, 2016). A number of children interpreted the middle face as a positive response, whereas some children explained that this face was 'in the middle' and this was accompanied by the use of a straight mouth on the face. Other children decided on a 'confused face' with a wavy mouth.

Interestingly, when re-designing the faces, some children chose to draw a straight line for the mouth of the faces labelled ‘I don’t like it’. Typically, in current assessment scales straight mouths are used to indicate the middle response- e.g. ‘ok’ or ‘acceptable’ (Thompson, 2013; Medeiros, 2012). Therefore, there are implications for the use of the straight face to indicate acceptability if the children using the scales interpret this to mean something else.

The variety of responses in relation to the wording on the scales may be related to children’s cognitive development. The findings demonstrated that children in the study could more easily interpret the end anchors, or the most positive and negative responses. This is in line with findings from wider literature that has found children between the ages of 5-12 years have a tendency to choose the extreme ends of the scales when presented with Likert scales (Chambers & Johnstone, 2002; von Baeyer et al, 1997). Similarly, when asked to re-design the faces on the scales, children generally added features to the ‘extremes’, such as making them more emotive, displaying more exaggerated body expressions, for example, a little smiley face, smiling with mouths open, crossing arms, frowning, and adding tears to the faces.

Another consideration when using scales with children is whether the results provide valid and accurate data (Chambers, 2014). The findings from the current study show that the child’s response depends on how the question on the scale is phrased. For example, past research has found that some scales refer to the questions in third person “What would this face look like if the medicine was good” (Sjovall, 1984), whereas the majority present the scales asking for a child’s subjective judgement “how would you feel if the medicine was good” (Thompson, 2013). Further research exploring this would be beneficial, as limited literature provides any conclusion to which format or phrasing is best for children. Other research by Chambers & Johnson (2002), has found that children between 5-11years old are able to accurately report judgements about physical objects and this accuracy did not change the younger the child was, or whether they were responding using a 3-point or 5-point scale. However, subjective judgements, such as emotions or judgements of the self, are more difficult for children to report accurately (Tyng et al. 2017). Suggesting that it is not the capacity of the child to use a scale, but what the scale is asking that might cause problems.

This has implications for the wording of questions on scales, particularly when the scale is asking for a response about a subjective feeling or judgement.

Cognitive developmentalists such as Piaget (1954) propose that between the ages of 7-11 years, children are able to make concrete judgements about physical objects, whereas from 12-16 years children enter the formal operation stage, in which abstract thinking typically evolves and judgements can be made about feelings and emotions. However, these are generalisable concepts and may not apply to every child. It is interesting to note that when children were discussing the faces and wording on the scales, many of the children referred to personal experiences and drew images that matched how they believed they would act when they did not or did like a medicine- rather than drawing how they would feel. It could be argued that this reflects the literature regarding cognitive development and children's capacity to report their subjective judgements, as a child would be able to make a judgement more easily about their behavioural reaction (physical and objective action), as opposed to reporting their emotional response or internal feelings (subjective reaction).

There was also an awareness from some of the older children that children younger than them might require additional help or different types of information in order to understand and use a measurement scale. In the current study children talked about how acceptability assessment could be improved if children were provided with a choice in which measures were used to assess acceptability, if they were asked how they felt about the measures, and if they were included in the development of the assessment measures. This has also been found in a study by Hall et al (2017), who found that children communicate judgements differently to adults and that in order to provide an appropriate differentiation in the sale points, scales need to be adapted to children's emotions. Children also explained that scales would be easier to understand if somebody helped to explain what the scales and responses meant. Some of the children considered that others might not be able to see, read or understand the images and words and therefore having someone help them before being administered the assessment measure would be useful. Bell (2007), reports that whilst having an adult on hand to help children make sense and understand the questions on the scales, it is important that the researcher is aware of potential biases.

7.4.4 Presentation of self-report acceptability assessment measures

When re-designing and developing the existing scales, the children thought that changing the presentation of the scales could improve how appropriate the scales were to children. The presentation of response scales has not been explored in the literature on children's acceptability of medicine and research is also limited in wider literature, with most papers focussing on adults. Wording, presentation and layout of a scale has been found to impact on adults (Dillman & Christianson, 2005; Schwarts & Oyserman, 2001; Hartley & Betts, 2010). In wider literature, the adaptation of likert scales for children has provided evidence that simple sentences and a lower number of responses improves children's participation in the scales (Royeen, 1985). Similarly, Royeen (1985) also found that presenting assessment scales in a game format was found to reduce anxiety in children. Whilst the current study did not measure the outcomes of using different formats, the children in the study generally demonstrated a preference for a game format scale. However, it is important that these factors are also studied in the wider child population (Betts & Hartley, 2012).

The current study demonstrates that the presentation of scales could be improved in a number of ways, specifically, the format of the scale (including scale items, anchor points and response images), and the layout of the whole self-report measure (positioning of the questions and response categories). The findings from the current study demonstrate how simply altering the design or layout of a measure or scale can take it from a boring scale and make it more engaging, interesting and child-friendly Bell (2007) notes that questionnaire format can help to avoid confusion, boredom and cognitive overload. This study shows that developing scales with children is possible and that their input could overcome some of these issues with engagement. Landoni et al (2017) also note that the inclusion of children in scale development provides unique insights and knowledge. This is important in terms of the quality of data collected and Betts & Hartley (2012) report that the format of children's questionnaires has the potential to influence data quality. However, further work needs to be undertaken on the presentation of assessment scales for children in relation to acceptability of medicines

An additional consideration of the findings relates to the cognitive ability of the children to use the scales effectively. Research has reported that children's ages and cognitive abilities may influence understanding of scale items and anchor points (Fuchs, 2005). However, in the current study, most children, regardless of age, identified the scales with pictures on as most appropriate. Whilst this was not quantitatively studied, it is in accordance with findings from Betts & Hartley (2012) who found that no differential effects were found for any of these factors in children aged 9, 10, and 11 years old. This is something that should be explored in future research.

7.5 Original Contributions to Knowledge

As earlier stated, the overall aim of the current study was to explore the experiences of children in relation to medicines, to use their views to develop a better understanding of the acceptability of medicine, and to re-develop the tools that are used to assess the acceptability of medicines. In this respect it has been successful. The study proposes three original contributions to knowledge.

The first original contribution is that this study proposes a new definition of the acceptability of medicine, which can be operationalised for use in practice. This is based on the engaging with children and drawing on their experiences to enhance current knowledge and understanding of the concept. From the review of past literature, this is the first study that has involved children in this way.

The second contribution to knowledge is the development of the "Framework of Children's Medicine Acceptability". This framework provides a conceptual contribution to knowledge. To date, this is the first study that has attempted to theorise the acceptability of medicine. This framework provides the foundations required to better define the concept and improve the assessment tools used to measure acceptability. An important contribution of this model is that it demonstrates that the acceptability of medicine is influenced by additional factors relating to the user that are not currently accounted for when developing and assessing the acceptability of medicines. Due to the nature of the model, there is clear scope for its potential transferability across other populations (e.g. older children, adolescents and adults), thus contributing to the broader existing knowledge regarding the acceptability of medicine outside of the child population.

The third contribution to knowledge is that this study provides a much-needed methodological contribution to existing knowledge regarding child-centred measures and assessment tools used to assess acceptability. Given the inconsistency in methods used to evaluate the acceptability of medicine, the improvement of this area is crucial to enhance medicines for children. This study contributes to improving assessment measures in two ways. Firstly, the study proposes new recommendations for the development of child-centred, child-friendly tools that could improve children's engagement, understanding and use of measurement tools. Secondly, the Framework of Children's Medicine Acceptability provides new and relevant items that should be included on assessment tools and measures that better reflects the acceptability of medicine to children, therefore providing an argument for a more valid set of items to assess acceptability.

7.5.1 Conclusion

The aim of this chapter was to discuss the findings in context of the broader body of literature. This study aimed to explore the perceptions and beliefs of children about the acceptability of medicine and the acceptability assessment measures. No previous research has focused on this in this population group and therefore the current study aimed to bridge this gap in knowledge. The original contributions to knowledge demonstrate that the aims and objectives of the study have been achieved. Knowledge has been developed in relation to children's perceptions of the acceptability of medicines and this has led to presenting a new definition of the acceptability of medicines. In addition, the study demonstrates new knowledge in relation to the factors that are thought to influence acceptability. Finally, the study has increased knowledge about children's perspectives of acceptability assessment measures. The following chapter offers strengths and limitations, reflections, and recommendations for future research, regulations and practise.

Chapter 8
Reflections

8 Reflections

8.1 Introduction

This concluding chapter will explore the quality of the study, its strengths and limitations, before offering recommendations for future research, researcher reflections and providing a final conclusion to close this thesis.

8.2 The Quality of the Study, Strengths and Limitations

When discussing the topic of evaluating quality in qualitative research, the current study draws on criteria from Lincoln and Guba (1985). These criteria are regarded as the "gold standard" (Whittemore, Chase and Mandle, 2001., p527), and represents the most used standards for evaluating qualitative research. It is suggested that quality should be evaluated on the study's 'trustworthiness', i.e. how closely a study represents the perspectives of the research participants. In order to assess trustworthiness, four concepts are highlighted: credibility, transferability, auditability and confirmability (Lincoln and Guba, 1985).

8.2.1 Credibility

The credibility of a qualitative study refers to the extent "to which a study's findings represents the meanings of the research participants" (Lietz & Zayas, 2010., p191). This relates to how authentic and accurate the study interpretations are to the descriptions provided by the participants (Drisko, 1997). In order to achieve credibility, it is reported that qualitative researchers should manage research reactivity and bias (Padgett, 2008). Research reactivity refers to any influence that either the researcher or the study procedures might have on the participants, whether that relates to the conduct of the study, questions asked, verbal and non-verbal communication and degree of participation (Lietz & Zayas, 2010). In order to manage this, it is proposed that researchers remain mindful of the research procedures and the potential influences.

In the current study the researcher was conscious of the imbalances that may be present between the child and adult, and the researcher aimed to balance their own roles between researcher, leader, and friendly person. This, in part, took shape in being conscious of the environment in which the data were collected, as well as the

conduct and behaviour engaged with during the study. Research has found that children perform more competently in environments they are familiar with (Alderson, 2004; Kellett and Ding, 2004), therefore each interview and workshop was purposely conducted in settings that the children were familiar with, whether this was the 'chill-out room' in the schools, or other spaces such as the church halls and public spaces for the larger groups. Children took pride in their schools and group meeting rooms, explaining why certain rooms are used and showing around. Similarly, consideration was given to how susceptible children are to adult influence, and the pressure of the child to conform to adult instruction or questioning (Flewitt, 2005; Tangen, 2008). Therefore, it was attempted to build rapport with the children before conducting the research by visiting each data collection site, where possible, prior to carrying out data collection. The researcher attempted to enter into the children's "culture of communication" (Christianson, 2004; p166), from introducing herself to the children by using her first name, rather than 'Miss' or an un-named visiting adult, to sitting on the floor alongside the children rather than sitting on a chair like the other adults or standing up like the other adults in the room might be.

As well as research reactivity, qualitative researchers should also be aware of how to minimise researcher bias and build self-awareness. Researcher bias relates to the perspectives, worldview, and preconceived ideas of the researcher that may influence the research process, design of the study, data analysis, and presentation of the findings (Lietz, Langer and Furman, 2006). In research with children this is particularly important, and in the current study particular consideration was given to ensuring that the children were viewed as meaningful contributors in the study, rather than being included in the study as research subjects or "transitional objects" (Yardley, 2000; Maconochie, 2008, p2).

In the current study the researcher was conscious of her position as a neophyte researcher, with little experience in healthcare, medicines, or research on the acceptability of medicine. It was initially feared that her lack of experience within this research topic would represent a significant limitation, not having the background or experience to connect with the children about their healthcare. However, the 'outsider' healthcare perspective became more a strength, as this allowed the researcher to engage in the research process with the belief/ orientation that the children were the

experts in the room. It was common during the process for the researcher to be unfamiliar with the names or purpose of particular medicines and would often end up asking the children to explain and expand when discussing certain topics regarding their experiences with medicines. This was found to encourage the children to take a more central role in the discussions, and this helped to balance the power between the researcher and the children. As well as this being a strength during the data collection in this study, it is also believed that this 'outsider status' in relation to healthcare also provided a strength during data analysis. Having never worked within pharmaceutical development the researcher did not come to analysis with any preconceived ideas about the typical considerations regarding medicines development and acceptability assessment and was therefore able to analyse the data without these views impacting on the interpretation.

Similarly, researcher bias also includes the influence of subjective interpretation (Bradshaw, Atkinson and Doody, 2017). This was considered extensively for the current study in the methodology chapter (Chapter 3) and it was recognised from the outset that "the research process… cannot be considered as independent of the researcher" (Emond, 2005; p126). The influence of the researcher on any study is becoming more widely recognised, and so in the methodology chapter of this thesis (Chapter 3) the underpinning philosophical stance is transparent. This research was conducted under the constant awareness that "reflexivity is not an activity that occurs at one point in time, but instead represents a process that unfolds throughout the entire research process" (Lietz & Zayas, 2010). Evidence of reflexivity is apparent throughout this thesis, from the earlier chapters regarding philosophical underpinnings and data collection techniques, to reflections regarding assumptions and preconceived ideas of the child population, and the interpretation of their data (Davis, 1998). This reflexivity was particularly useful when interpreting the data, and this was accompanied by 'Listener and Observer" techniques in order to ensure as far as possible that the interpretation of what the children said and drew made sense in the context in which they occurred (Leavitt, 1995).

Strategies to increase credibility include triangulation, member checking and thick descriptions (Padgett, 2008). For triangulation, Padgett (2008) defines it as the use of multiple sources to achieve a comprehensive picture. Therefore, by using a number

of sources to gather data qualitative researchers can achieve 'completeness' (Drisko, 1997). In the current study, triangulation was achieved through the use of number of sources to collect data, including small group workshops, large events and one-to-one interviews. Similarly, member checking was also undertaken, by "corroborating the research findings by seeking feedback from the research participants" (Lietz & Zayas, 2010; Creswell & Miller, 2000). Whilst this was not part of the formal data analysis process, the children were sought to be actively involved in the reviewing of observations or conclusions during the workshops and interviews, and were asked follow-up questions or for additional explanations in order to help clarify whether the researcher's observations were in line with the children's own perceptions (Clark, 2004). This is in line with how Shenton (2004) describes member viewing, providing participants with draft ideas of the analysis and ascertaining their sense of agreement with the findings (Lietz & Zayas, 2010).

Finally, within this thesis it is acknowledged that not all characteristics of the child population were measured, factors including health status, ethnicity and culture were not collected from the children. This therefore impacts on the extent that the study's findings represents the meanings provided by the research population, and limits the transferability of the conclusions made within this thesis. Recommendations for further research on this topic addresses this issues, and provides recommendations for the framework to be studied in other child populations.

8.2.2 Transferability

As well as credibility, displaying that the study can be applied, or of use, to theory, practice and future research is also important (Lincoln & Guba, 1985). This refers to how transferable the study findings are to situations outside of the study, and how they can fit in to other contexts in a meaningful way (Sandelowski, 1986). As reported in Lietz & Zayas (2010), qualitative studies cannot be generalised by quantitative standards, due to the fact that the sampling employed in qualitative research is generally purposive and not probability. However, whilst generalisability is not something sought in qualitative research, "transferability is achieved when the findings have applicability to another setting, to theory, to practice, or to future research (Lietz & Zayas, 2010., p195). Therefore, in order to demonstrate how a study is transferable

it is suggested that the researcher identify key aspects of the study and evaluate the extent that these might be applicable to other contexts (Devers, 1999). In the current study, the acceptability of medicine has been evaluated in a child population. The findings suggest a new definition and theoretical underpinning of the concept of the acceptability of medicine. This definition and proposed theory may be applicable to other population groups, such as adolescents, adults and older adults. Similarly, suggestions made in Section 8.4 demonstrate how the study findings can be applied to regulations, practice and to future research.

Race and ethnicity are being increasingly used as variables in health research (Sheldon & Parker, 1992), and the importance of recognising racial and ethnic differences is both a reflection of good science and social justice (Perez-Stable, 2018). In medicines research it is recognised that cultural differences influence perception of colour, shape and texture on the taste of a product (Wan et al, 2014), and therefore a limitation of this research is that race, ethnicity and culture data was not collected. However, this research relied solely on children self-reporting information about themselves, and the only data that was collected was their age and gender, both of which they could circle easily on the consent sheets. Following FDA guidance for collecting race and ethnicity data in clinical research, the children in the current study would have had to either self-report their race and ethnicity information, or a detailed race and ethnicity category page would have had to be included on patient consent forms (FDA, 2016). This was not thought to be appropriate, particularly when guidance for schools and local education authorities reports that parents should supply this data for children (Department for Children, 2009).

It could also be argued that the inclusion of caregivers and adults may have provided a more holistic view of medicines acceptability when considering that acceptability is defined as the ability and willingness of both the child and caregiver to administer a medicinal product. However, the current study was focussed specifically on the beliefs, perceptions and understanding of children regarding the acceptability of medicines. This study was conscious that the gaps in current knowledge are specific to considerations of children, and the methodology and methods section provides detailed information regarding why the focus on children's knowledge is so crucial to this topic area. Therefore, whilst the inclusion of parents and caregivers were outside

the scope of the current study, this is proposed as a recommendation to future research.

Finally, it is acknowledged that data were not collected from the children about factors including health status, ethnicity and culture. This absence of this data therefore limits the transferability of the findings and the framework that was proposed. It is recommended that future research on this topic should include data collection of these key demographic factors.

8.2.3 Auditability

The third of consideration of quality as identified by Lincoln and Guba (1985) is auditability. This refers to the extent that the study procedures are documented, allowing for another person outside of the study to follow and evaluate the process (Padgett, 2008). The qualitative process does not adhere to strict procedures, and it has been suggested that a flexible and iterative process is what makes for a high-quality qualitative project (Davies and Dodd, 2002; Morrow, 2007). Being iterative and allowing the process to change as the study went on was a key part of the development of the current study, as outlined in Chapter 4 Methodology the methods and data collection instruments were adapted for the different settings and individual children that took part. Data collection methods were adapted and revised as per feedback during the initial stages of the study (this is discussed in chapter 4), and sample sizes were flexible allowing for the recruitment of an additional data collection site following the commencement of the study (discussed in section 4.1).

In order to document the changes that occur during the process, it is suggested that the researcher keeps an audit trail (Lietz & Zayas, 2010). This is a written account of the research process, outlining what happened during the study and the accompanying reflexions of the researcher. Within Chapters 3 and 4 of this thesis, the study process is outlined and the researcher maintained a reflexive approach whilst outlining this. Furthermore, the researcher met with the supervisory team and kept a detailed account of each research meeting at least once a month over the three years. These meetings are also referred to as peer debriefing (Padgett, 2008), where members of the team can leave comments and discuss the project, as well as be the

place of research decisions, data analysis discussions and study feedback. The conduct of meetings such as these can enhance the quality of a project (Shenton, 2004). Peer debriefing is also said to promote reflexivity, generate new ideas and identify potential issues. In order to increase reflexivity and accountability in the current study, the research team consisted of both experts in academia, who were key in advising of the study set up and write up, as well as professionals in paediatric medicine and acceptability who could provide a more in-depth, expert view during certain points of the study (such as clinical data analysis and knowledge).

The literature review followed a search strategy that could be replicated but the search terms and strategy did not include all methods of assessment. For example, search terms such as 'visual analogue scale' and 'questionnaire' were not included. The absence of these search terms potentially limits the findings of the review as this absence may have caused some relevant papers to be missed during the electronic search stages.

8.2.4 Confirmability

Finally, confirmability refers to the findings being confirmed by others (Drisko, 1997; Lincoln & Guba, 1985). To achieve confirmability, a study must demonstrate that the findings and data are clearly linked, "that the works' findings are the result of the experiences of the informants, rather than the characteristics and preferences of the researcher" (Shenton, 2004., p72).

This can be achieved through a number of methods, see Table 5 for a summary of strategies. In the current study audit trails and peer debriefing have already been mentioned in Section 8.2.3, however member checking is also useful in allowing other collaborators that are external to the research team an opportunity to influence the research procedures. As outlined in the introduction chapter (Chapter 1), there is a growing interest in the acceptability of medicines, and the role of children in improving this. The current study was developed with patient and public involvement from the YPAG at Alder Hey Children's Hospital. In the first year of this study, research ideas were taken to one of the YPAG meetings, where the children and young people discussed, edited and contributed to the topics they thought would be useful to

research. Incorporating the perspectives of children and young people from the YPAG helped to ensure that the study was built with their ideas and perspectives in mind from the outset. This group was also fundamental in the reviewing and editing of the patient information leaflets and consent sheets, ensuring that the outward facing information was appropriate. The children at the YPAG thought that this study was important.

Table 8.1: Research strategies for increasing trustworthiness of qualitative research (Lincoln and Guba, 1985; Padgett, 2008; Shenton, 2004).

Reflexivity	A thoughtful consideration of how a researcher's standpoint can influence the research.
Observer Triangulation	Using more than one researcher to analyse the data.
Data triangulation	Collecting data from multiple sources such as interviews and focus groups.
Prolonged engagement	Conducting multiple interviews or spending extended time with participants to achieve an exhaustive look at the experience.
Member checking	Including participants in analysis or returning to a sample of participants to corroborate the findings.
Thick descriptions	A thorough representation of the phenomenon of inquiry and its context as perceived and experienced by study participants.
Audit trail	Keeping a detailed written account of the research procedures.
Peer debriefing	Meeting with mentors or other researchers engaged in qualitative research to dialogue regarding research decisions.

Negative case analysis	Seeking contrasting evidence through sampling and analysis.

In order to demonstrate trustworthiness and quality as outlined by Lincoln and Guba (1985), a qualitative research project must be shown to demonstrate some of the outlined strategies in Table 8.1. It is argued that whilst not required to employ all of these strategies, there should be evidence that the researcher has addressed research reactivity and bias and has addressed transferability, auditability and confirmability (Creswell & Miller, 2000). It is believed that the current study addresses these criteria of quality and provides evidence of this throughout this thesis.

8.3 Strengths Through Contributions to Knowledge

Although not a specific component of Lincoln and Guba's (1985) criteria it is proposed that the original contributions to knowledge can be seen as strengths. These contributions have been explored in depth in the discussion chapter (Chapter 7) but a summary of them is presented here as evidence of the quality and rigour of the study.

1. This study proposes a conceptual contribution based on a new definition of the acceptability of medicine, that can be operationalised for assessment.
2. The "Framework of Children's Medicine Acceptability" has been developed from this study. This model provides the operationalisation of the concept of acceptability in relation to children's medicine.
3. This study contributes to the methodological grounding of the acceptability of medicines for children. Involving the child in the re-development and design of acceptability assessment measures.
4. Finally, findings from this study indicate the importance of widening the window of opportunity to consult with children and young people at earlier stages of product development in order to improve product acceptability.

8.4 Recommendations

As mentioned in Section 8.2, the recommendations of a study are presented as a strength of quality, particularly in relation to the transferability of the study. The following recommendations are presented for regulators, practice and further research.

8.4.1 Recommendations for regulators

Based on the findings of this study, two recommendations are made for regulatory bodies to consider.

1. Currently, there is no extended guidance or suggestions about how formulation developers and researchers can address the user-related factors. The factors identified from this study relating to experience, psychological and affective responses should be considered in acceptability assessment as this would help provide a better measure of the acceptability of medicines.
2. Policy on acceptability assessment should include a definition that considers the acceptability of the user and of the product. The current study recommends a definition that has been developed from the findings and that can be operationalised for use in the development and assessment of acceptable formulations.
3. Existing policy should be reconsidered to include children's involvement in aspects of acceptability assessment in the early development stages.

8.4.2 Recommendations for practice

Based on the findings of this study, two key practice recommendations are presented:

1. Children should be included in acceptability assessment.
2. Acceptability testing with children should be carried out at an earlier stage of formulation development.

8.4.3 Recommendations for further research

The findings from this study are an important starting place for the inclusion of children in research related to the development of acceptable paediatric formulations and assessment of the acceptability of medicines.

Three key recommendations for further research are presented:

1. Research about the applicability and value of using the Framework of Children's Medicine Acceptability in acceptability assessment should be undertaken as this framework has the potential to improve the acceptability of medicine for children.
2. Research should investigate parents and caregivers' experiences of medicinal products and the factors contributing to the acceptability of medicine for children. This should build on the qualitative methods outlined in the current study.

3. Research is needed to develop and design acceptability measures suitable for use with children's formulations; these studies should involve children.
4. There is a need for future research to explore acceptability in more detail and also to examine the value of the proposed Framework of Children's Medicine Acceptability with a more focused population of children than those recruited to this study; this population would be with children with long-term conditions who require medication as this represent a group of children with a greater depth of experience in taking medicines. This would enable a wider exploration of acceptability and adherence.
5. Research is also needed to examine acceptability with children from a range of ethnicities and cultures.

8.5 Conclusion

In conclusion, the study reveals that children perceive the acceptability of medicine as a multi-dimensional construct related to two key aspects: the product and the user. The findings imply that improving knowledge and understanding about children's perceptions and beliefs of medicine, and its acceptability, can guide researchers and clinicians in better defining the concept of the acceptability of medicine.

Based on the literature underpinning this study it was apparent that children were largely omitted from acceptability research regarding medicines (Mistry & Batchelor, 2017; Ranmal et al, 2018). This research has explored the perceptions, experiences and knowledge of children in the acceptability of medicines and assessment measures. It is concluded that: 1) children are generally knowledgeable about their treatment and medicines; 2) children's beliefs and attitudes influence their acceptability of medicines; 3) children want to be involved in their medicines, and the improvement of their knowledge about the benefits of treatment may be a facilitator to improving acceptability and adherence; 4) children have contributed to the understanding of the acceptability of medicines; 5) the "Framework of Children's Medicine Acceptability" has the potential to improve medicine development and assessment; and 6) acceptability assessment measures can be made more child-friendly and age-appropriate by including children in their design and development.

It is hoped that this research will contribute to the limited literature that has involved children in medicines development and acceptability assessment. It is also hoped that this study emphasises that children can improve knowledge and understanding in topics that concern them, and their inclusion of the child contributes positively to such research. Finally, it is hoped that this study will help current practice, regulations and research to consider that multiple perspectives can only enhance understanding on topics such as these.

8.5.1 Final word

It seems fitting at the end of this child-centred thesis to hand the very final word back to the children as a reminder that they have much to say about the acceptability of medicines. So, this thesis ends with some wise words from three of the children. Alex clearly understands acceptability when he says:

> *"Acceptability means like if its ok for you, like yes or no. If you're fine taking it".*

And two of the girls I interviewed via Brownies sum up what is important to them in terms of the acceptability of medicine by mentioning taste, magic, children's preferences, children's understanding and the importance of choice:

> *It would have the taste of strawberry Calpol because I like the taste of Calpol, and people will feel magical with this medicine. It might be horrible if an adult tastes it, because adults have different tastes to children. But as a child, as a kid they'd understand more,*
>
> *And then the child could choose.*

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Appendices

Appendix 1: Ethical Approval Letter- FREC

Edge Hill University

Beth Gibson 13th November 2018

Dear Beth,

Thank you for submitting the amendments to your research ethics application '*Co-designing with children to develop child-centred methods for assessing the acceptability of children's medicines*' (FOHS 204) to the Faculty of Health & Social Care Research Ethics Committee.

I have pleasure in informing you that the Committee recommended that your study is granted Faculty of Health & Social Care research ethics approval, subject to the following conditions:

1. Ethical approval covers only the original study for which it is sought. If the study is extended, changed, and / or further use of samples or data is needed the Committee Administrator, Daniel Brown, must be contacted for advice as to whether additional ethical approval is required.

2. (NHS studies only) NHS Research governance processes must be adhered to. If required, an application must be made to the HRA for approval for the research to be conducted in the NHS. NHS R&D departments (in Trusts where data is being collected) may also need to be approached for Trust permission to proceed.

3. If the project requires HRA approval and/or NHS ethical approval, please forward evidence of the approval(s) to Daniel Brown (browdan@edgehill.ac.uk) before commencing the study. FREC approval is subject to the receipt of evidence of appropriate external approvals.

4. The Principal Investigator is responsible for ensuring that all data are stored and ultimately disposed of securely in accordance with the Data Protection Act (1998) / General Data Protection Regulation (GDPR) (2018) and as detailed within the approved proposal.

5. The Principal Investigator is responsible for ensuring that an annual monitoring form and an end of study form, where appropriate, is sent to the Committee Administrator (browdan@edgehill.ac.uk). The form will be sent to you at the appropriate time by the Committee Administrator.

6. Ethical approval for this research will expire on 01-09-2020. Any extensions to this date will require additional approval from the committee.

The study documentation that has been reviewed and approved is detailed below:

<doc title>	**<version no & date>**

FOHSC Research Proposal	**V2, 15-05-2018**
Appendix 1 Child info sheet, 5-7 yrs	**V2, 15-05-2018**
Appendix 2 Child info sheet, 8-12 yrs	**V2, 15-05-2018**
Appendix 3 Activity Sheet, 5-7 yrs	**V1, 15-02-2018**
Appendix 4 Activity Sheet, 8-12 yrs	**V1, 15-02-2018**
Appendix 5 Child Consent sheets, 5-7 yrs	**V2, 15-05-2018**
Appendix 6 Parent Consent sheets	**V2, 15-05-2018**
Appendix 7 Parent information sheets	**V2, 15-05-2018**
Appendix 8 Semi structured workshop guide	**V1, 15-02-2018**
Appendix 9 Professionals Summary sheet	**V2, 15-05-2018**
Appendix 10 FOHSC Recruitment Flowchart	**V2, 15-05-2018**
Appendix 11 Flyer	**V1, 15-02-2018**
Appendix 12 thank you and info sheets	**V1, 15-02-2018**
Appendix 13 Certificate of participation	**V1, 15-02-2018**
Appendix 14 5-7 Information sheets Multiple workshops	**V1, 15-05-2018**
Appendix 15 8-12 Information sheets Multiple workshops	**V1, 15-05-2018**
Appendix 16 Parent information sheets Multiple workshops	**V1, 15-05-2018**
Appendix 17 Parent consent forms Multiple workshops	**V1, 15-05-2018**
Appendix 18 Child Consent sheets Multiple workshops	**V1, 15-05-2018**
Appendix 19 Museum Activity Sheet, 5-7yrs	**V1, 18-10-2018**
Appendix 20 Museum Activity Sheet, 8-12	**V1, 22-10-2018**
Appendix 21 Museum Information Sheet Parents	**V1, 25-10-2018**
Appendix 22 Museum Information Poster	**V1, 25-10-2018**
Appendix 23 Certificate of Participation	**V3, 30-10-2018**

Yours sincerely

Professor Mary O'Brien

Chair of Faculty of Health & Social Care Research Ethics Committee
Edge Hill University
St Helens Road
Ormskirk
Lancashire
L39 4QP
obrienm@edgehill.ac.uk

Appendix 2: Ethical Approval Letter- HRA

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Miss Bethany Gibson
PhD Student
Edge Hill University
Edge Hill University
St Helens Road
Ormskirk
L39 4QP

Email: hra.approval@nhs.net
HCRW.approvals@wales.nhs.uk

06 August 2019

Dear Miss Gibson

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Using participatory methods with children to develop child-centred measures for assessing the acceptability of medicine for children**
IRAS project ID:	**244188**
Protocol number:	**1**
REC reference:	**19/LO/0918**
Sponsor	**Edge Hill University**

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.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

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 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) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

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

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

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 **244188**. Please quote this on all correspondence.

Yours sincerely,
Nicole Curtis

Approvals Specialist

Email: hra.approval@nhs.net

Copy to: *Miss Katelyn Williams*

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 [Recruitment poster]	1	13 March 2019
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Insurance and indemnity]	1	03 August 2018
HRA Schedule of Events [HRA Schedule of Events (HRA Assessed)]	2	26 July 2019
HRA Statement of Activities [HRA Statement of Activities (HRA Assessed)]	1	25 June 2019
Interview schedules or topic guides for participants [Semi-structured activity guide]	2	20 March 2019
IRAS Application Form [IRAS_Form_21062019]		21 June 2019
Other [Ethical review response]	1	19 June 2019
Other [Track research protocol]	2	19 June 2019
Other [Appendix 29a Activity Booklet 8-12 years]	2	10 June 2019
Other [Appendix 29b Activity Booklet 5-7 years]	2	10 June 2019
Other [Certificate of participation]	3	13 March 2019
Other [HRA ethical response]	2	18 July 2019
Other [HRA ethical response]	3	01 August 2019
Participant consent form [Parent for child to participate consent form]	6	01 August 2019
Participant consent form [Track Appendix 27]	6	01 August 2019
Participant consent form [Child assent form 5-12 years]	4	10 June 2019
Participant consent form [Track Appendix 26]	4	10 June 2019
Participant consent form [Parent for child to participate consent form]	3	26 February 2019
Participant consent form [Parent for child to participate consent form]	4	12 June 2019
Participant consent form [Track Appendix 27]	4	12 June 2019
Participant information sheet (PIS) [Track Appendix 24]	4	12 June 2019
Participant information sheet (PIS) [Track Appendix 25]	4	12 June 2019
Participant information sheet (PIS) [8-12 year Information sheet]	4	12 June 2019
Participant information sheet (PIS) [5-7 year Information sheet]	4	12 June 2019
Participant information sheet (PIS) [Parent information sheet]	6	01 August 2019
Participant information sheet (PIS) [Track Appendix 28]	6	01 August 2019
Research protocol or project proposal [Protocol]	2	19 June 2019
Summary CV for Chief Investigator (CI) [IRAS CV]	1	13 March 2019
Summary CV for student [Summary CV for student]	1	13 March 2019
Summary CV for supervisor (student research) [Supervisor CV]	1	18 March 2019
Summary CV for supervisor (student research) [Supervisor CV]	1	18 March 2019
Summary CV for supervisor (student research) [Supervisor CV]	1	04 March 2019
Summary CV for supervisor (student research) [Supervisor CV]	1	26 March 2019

Appendix 3: Research Governance: Letter of Access

Alder Hey Children's NHS
NHS Foundation Trust

Alder Hey
Eaton Road
Liverpool
L12 2AP

Telephone: 0151 228 4811
www.alderhey.com

16th January 2018

Bethany Gibson

Dear Bethany,

Letter of Access for Research

This letter confirms your right of access to conduct research through Alder Hey Children's NHS Foundation Trust for the purpose and on the terms and conditions set out below. This right of access commences on 16th January 2018 and will end 16th January 2021, 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 this NHS organisation. Please note that you cannot start the research until the Principal Investigator for the research project has received a letter from us giving permission to conduct the project.

The information supplied about your role in research at Alder Hey Children's NHS Foundation Trust has been reviewed and you do not require an honorary research contract with this NHS organisation. 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 Alder Hey Children's NHS Foundation Trust premises. You are not entitled to any form of payment or access to other benefits provided by this NHS organisation to employees and this letter does not give rise to any other relationship between you and this NHS organisation, in particular that of an employee.

While undertaking research through Alder Hey Children's NHS Foundation Trust you will remain accountable to your employer, Edge Hill University, but you are required to follow the reasonable instructions of your Research Supervisor, Prof Matthew Peak, in this NHS organisation or those 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 this NHS organisation 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 Alder Hey Children's NHS Foundation Trust policies and procedures, which are available to you upon request, and the Research Governance Framework.

You are required to co-operate with Alder Hey Children's NHS Foundation Trust in discharging its 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 Alder Hey Children's NHS Foundation Trust 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.

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 (http://www.dh.gov.uk/assetRoot/04/06/92/54/04069254.pdf) 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.

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 premises you wear your ID badge at all times, or are able to prove your identity if challenged. Please note that this NHS organisation accepts no responsibility for damage to or loss of personal property.

We 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 this NHS organisation or if you are convicted of any criminal offence. Your substantive employer is responsible for your conduct during this research project and may in the circumstances described above instigate disciplinary action against you.

Alder Hey Children's NHS Foundation Trust will not 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.

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 this NHS organisation.

Yours sincerely

Chloe
HR Assistant
Alder Hey Children's NHS Foundation Trust

Appendix 4: Capacity and Capability

Staunton Edward (RQ6) RLBUHT <edward.staunton@rlbuht.nhs.uk>
Mon 16/09/2019 09:56
To: Katelyn Williams; Beth Gibson
Cc: Moorcroft Theresa <Theresa.Moorcroft@alderhey.nhs.uk>; Orton Charlie <Charlie.Orton@alderhey.nhs.uk>; Peak Matthew <Matthew.Peak@alderhey.nhs.uk>; Blair Jo <Jo.Blair@alderhey.nhs.uk> **+2 others**

HRA_Statement_of_activities_...
311 KB

Dear Sponsor Representative,

RE: IRAS. 244188 Using participatory methods with children to develop child-centred measures for assessing the acceptability of medicine for children

This email confirms that Alder Hey Children's NHS Foundation Trust has the capacity and capability to deliver the above referenced study.

We agree to start this study on 16/9/19 & expect the study to run until 30/9/20 (all study activity).

The supervisor at Alder Hey is Prof Peak.

If you wish to discuss further, please do not hesitate to contact me.

The SoA document attached, forms the agreement between sponsor & trust.

Regards,

Eddie Staunton.
Portfolio & Performance Co-ordinator.
NIHR CRN: North West Coast Children's Speciality
1st Floor Institute in the Park
Clinical Research Division
Alder Hey Children's NHS Foundation Trust
Eaton Road, Liverpool L12 2AP

Direct line 0151 282 6654 (Science Park).
Main Switch (AH) 0151 228 4811
Office 0151 252 5570 Ext 3943
edward.staunton@alderhey.nhs.uk

Appendix 5: Child information sheet (5-7yrs)

Edge Hill University

Alder Hey Children's NHS Foundation Trust

Designing acceptability tools for children's medicine

Information for children

5-7 years old

Colour me in!

I am asking if you would like to take part in a workshop about making medicines more child-friendly.

Before you decide if you would like to help, read this booklet with a parent or guardian to find out more!

What is this study about?

This project wants to make medicine better for children by improving the methods used to evaluate it.

Who?

My name is Beth and I am doing this project. I will always be with you during the workshops, and sometimes might bring along a friend to help me! Your friends and teacher, leader or other trusted adult will also be with us.

Why?

When you are poorly the doctor can give you medicine to make you better. Sometimes children and young people don't like their medicine and that makes them grumpy or sad. Sometimes children even stop taking their medicine.

Where?

Name of group: *(Please circle your group)*

Rainbows/Brownies/Cubs/Beavers/Libraries/Schools/

Alder Hey

What will I have to do if I take part?

If you want to take part, I will arrange for some workshops to take place at your group or arrange for you to come to some workshops. There will be about 10 people in each workshop.

In the workshops we will talk a little bit about medicine.

You will get to draw and design your very own medicine.

We will play some games that will help us to arrange the medicine into what we like most and what we like least about it.

We will look at some packages of real medicine and some of the ways that medicine is tested and evaluated now.

You will have the opportunity to interact with all of the activities, if you want to. These may be shortened depending on time!

You **won't** need to take any real medicines!

When?

Date: This will be arranged and I will let your parent or guardian know when the workshops are.

If it is ok, I will voice and video record the workshop so that I can look and listen back to all your great ideas!

If you say it is ok, I might also ask if I can take pictures of you and your work.

It is important that you understand that you do not have to take part if you don't want to.

No-one will mind if you don't want to join in the workshops.

Thank you lots for reading this!

If you have any questions you can ask Beth in person when she visit's your group, OR you can ask your parent or guardian to call or e-mail Beth.

Number: 01695 654314

E-mail: Gibsonb@edgehill.ac.uk

Appendix 6: Child information sheet (8-12yrs)

Edge Hill University

Alder Hey Children's NHS
NHS Foundation Trust

Designing acceptability tools for children's medicine

Information for children

8-12 years old

Can you label the medicine equipment?

I am asking if you would like to take part in a project about making medicines more child-friendly.

Before you decide if you would like to help, read this booklet with a parent or guardian to find out more!

What is this study about?

This project wants to make medicine better for children by improving the methods used to evaluate it. I think you can help me to do this by telling me what is good and bad about medicine and the ways we test it.

I think that together, we can re-design and develop some new ways of testing how acceptable medicine is.

Who?

My name is Beth and I am running this project. I will always be with you during the workshops, and sometimes might bring along a friend who will draw and write for us! Your friends and teacher, leader or other trusted adult will also be with us.

Why?

When we are unwell our doctor's or parents give us medicine to make us better. Sometimes children and young people don't like their medicine and that makes them upset. Some even stop taking their medicine.

It is important that our medicine is OK to take, because we need it to get better!

Designing new ways to tell the doctor what is good and bad about our medicine, helps them to understand more.

Where?

Name of group: *(Please circle your group)*

Rainbows/Brownies/Cubs/Beavers/Libraries/Schools/Alder Hey

What will I have to do if I take part?

If you want to take part, I will visit you at your group or arrange for you to come to a workshop. There will be about 10 other people in your workshop.

In the workshops we will discuss different types of medicines and what we like and don't like about it.

I will ask you to design your very own medicine that you think would best for children to take.

We will play some games that will help us to arrange the medicine into what we like most and what we like least.

We will look at some real medicine and some of the scales that are currently used to assess medicine.

You will get to use these scales to develop your own way of evaluating whether a medicine is OK to take.

You will have the opportunity to take part in all of the activities, if you want to. These may be shortened, depending on time! You **won't** have to take any real medicines!

When?

Date: This will be arranged and I will let your parent or guardian know when the workshop is!

It is important that you understand that you do-not have to take part in the project if you don't want to.

No-one will mind if you don't want to join in the workshops.

No-one will know what you say to Beth unless you say something that makes her worried about you.

If you decide you don't want to take part in the workshop when you arrive, you can do a different activity or ask Beth to call your parent/guardian to pick you up.

If it is OK, I will voice and video record the workshop so that I can look and listen back to all your great ideas!

If you say it is OK, I might also ask if I can take pictures of you and your work.

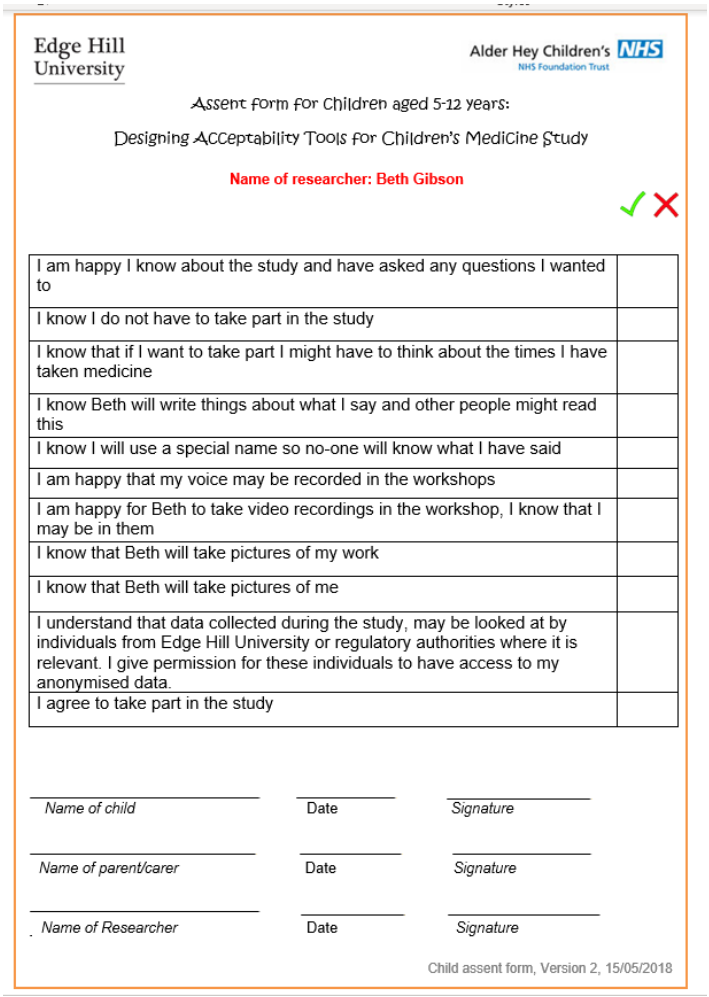
Thank you for reading this!

If you have any more **questions** about the project you can ask Beth when she next visits your group, OR you can ask your parent/guardian to contact her...

Number: 01695 654314

E-mail: Gibsonb@edgehill.ac.uk

Appendix 7: Child assent form



Edge Hill University

Alder Hey Children's NHS
NHS Foundation Trust

Assent form for children aged 5-12 years:

Designing Acceptability Tools for Children's Medicine Study

Name of researcher: Beth Gibson

I am happy I know about the study and have asked any questions I wanted to	
I know I do not have to take part in the study	
I know that if I want to take part I might have to think about the times I have taken medicine	
I know Beth will write things about what I say and other people might read this	
I know I will use a special name so no-one will know what I have said	
I am happy that my voice may be recorded in the workshops	
I am happy for Beth to take video recordings in the workshop, I know that I may be in them	
I know that Beth will take pictures of my work	
I know that Beth will take pictures of me	
I understand that data collected during the study, may be looked at by individuals from Edge Hill University or regulatory authorities where it is relevant. I give permission for these individuals to have access to my anonymised data.	
I agree to take part in the study	

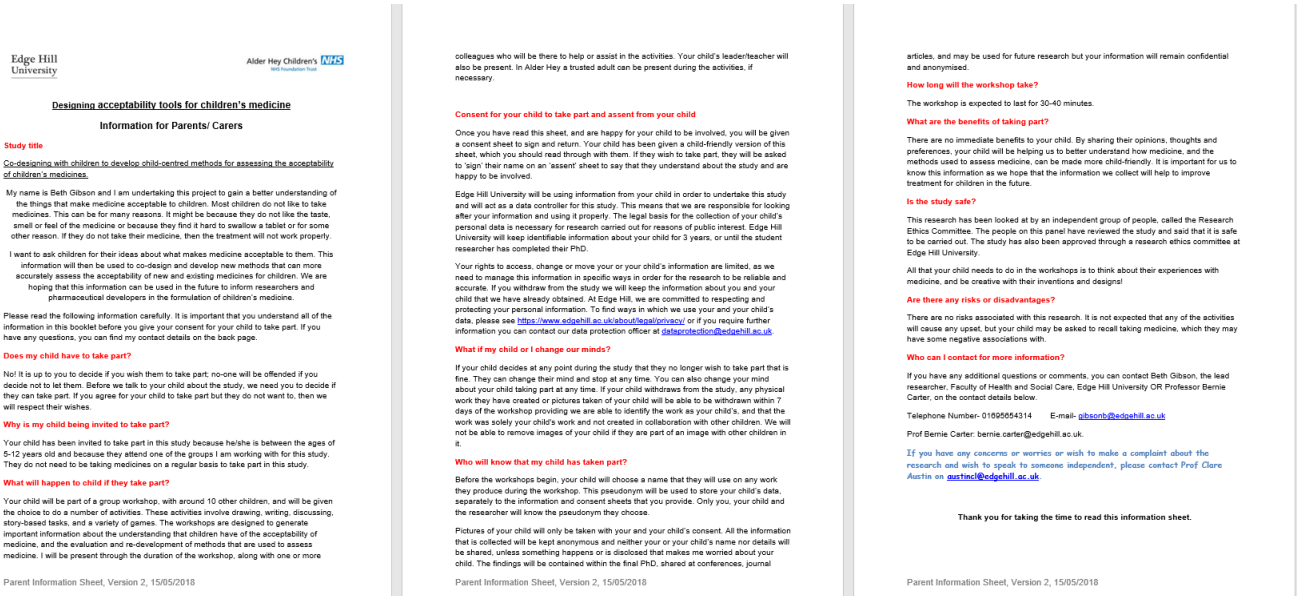
Name of child Date *Signature*

Name of parent/carer Date *Signature*

Name of Researcher Date *Signature*

Child assent form, Version 2, 15/05/2018

Appendix 8: Parent information sheet



Edge Hill University

Alder Hey Children's NHS

Designing acceptability tools for children's medicine

Information for Parents/ Carers

Study title

Co-designing with children to develop child-centred methods for assessing the acceptability of children's medicines.

My name is Beth Gibson and I am undertaking this project to gain a better understanding of the things that make medicine acceptable to children. Most children do not like to take medicines. This can be for many reasons. It might be because they do not like the taste, smell or feel of the medicine or because they find it hard to swallow a tablet or for some other reason. If they do not take their medicine, then the treatment will not work properly.

I want to ask children for their ideas about what makes medicine acceptable to them. This information will then be used to co-design and develop new methods that can more accurately assess the acceptability of new and existing medicines for children. We are hoping that this information can be used in the future to inform researchers and pharmaceutical developers in the formulation of children's medicine.

Please read the following information carefully. It is important that you understand all of the information in this booklet before you give your consent for your child to take part. If you have any questions, you can find my contact details on the back page.

Does my child have to take part?

No! It is up to you to decide if you wish them to take part; no-one will be offended if you decide not to let them. Before we talk to your child about the study, we need you to decide if they can take part. If you agree for your child to take part but they do not want to, then we will respect their wishes.

Why is my child being invited to take part?

Your child has been invited to take part in this study because he/she is between the ages of 5-12 years old and because they attend one of the groups I am working with for this study. They do not need to be taking medicines on a regular basis to take part in this study.

What will happen to child if they take part?

Your child will be part of a group workshop, with around 10 other children, and will be given the choice to do a number of activities. These activities involve drawing, writing, discussing, story-based tasks, and a variety of games. The workshops are designed to generate important information about the understanding that children have of the acceptability of medicine, and the evaluation and re-development of methods that are used to assess medicine. I will be present through the duration of the workshop, along with one or more

colleagues who will be there to help or assist in the activities. Your child's leader/teacher will also be present. In Alder Hey a trusted adult can be present during the activities, if necessary.

Consent for your child to take part and assent from your child

Once you have read this sheet, and are happy for your child to be involved, you will be given a consent sheet to sign and return. Your child has been given a child-friendly version of this sheet, which you should read through with them. If they wish to take part, they will be asked to 'sign' their name on an 'assent' sheet to say that they understand about the study and are happy to be involved.

Edge Hill University will be using information from your child in order to undertake this study and will act as a data controller for this study. This means that we are responsible for looking after your information and using it properly. The legal basis for the collection of your child's personal data is necessary for research carried out for reasons of public interest. Edge Hill University will keep identifiable information about your child for 3 years, or until the student researcher has completed their PhD.

Your rights to access, change or move your or your child's information are limited, as we need to manage this 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 and your child that we have already obtained. At Edge Hill, we are committed to respecting and protecting your personal information. To find ways in which we use your and your child's data, please see https://www.edgehill.ac.uk/about/legal/privacy/ or if you require further information you can contact our data protection officer at dataprotection@edgehill.ac.uk.

What if my child or I change our minds?

If your child decides at any point during the study that they no longer wish to take part that is fine. They can change their mind and stop at any time. You can also change your mind about your child taking part at any time. If your child withdraws from the study, any physical work they have created or pictures taken of your child will be able to be withdrawn within 7 days of the workshop providing we are able to identify the work as your child's, and that the work was solely your child's work and not created in collaboration with other children. We will not be able to remove images of your child if they are part of an image with other children in it.

Who will know that my child has taken part?

Before the workshops begin, your child will choose a name that they will use on any work they produce during the workshop. This pseudonym will be used to store your child's data, separately to the information and consent sheets that you provide. Only you, your child and the researcher will know the pseudonym they choose.

Pictures of your child will only be taken with your and your child's consent. All the information that is collected will be kept anonymous and neither your or your child's name nor details will be shared, unless something happens or is disclosed that makes me worried about your child. The findings will be contained within the final PhD, shared at conferences, journal

articles, and may be used for future research but your information will remain confidential and anonymised.

How long will the workshop take?

The workshop is expected to last for 30-40 minutes.

What are the benefits of taking part?

There are no immediate benefits to your child. By sharing their opinions, thoughts and preferences, your child will be helping us to better understand how medicine, and the methods used to assess medicine, can be made more child-friendly. It is important for us to know this information as we hope that the information we collect will help to improve treatment for children in the future.

Is the study safe?

This research has been looked at by an independent group of people, called the Research Ethics Committee. The people on this panel have reviewed the study and said that it is safe to be carried out. The study has also been approved through a research ethics committee at Edge Hill University.

All that your child needs to do in the workshops is to think about their experiences with medicine, and be creative with their inventions and designs!

Are there any risks or disadvantages?

There are no risks associated with this research. It is not expected that any of the activities will cause any upset, but your child may be asked to recall taking medicine, which they may have some negative associations with.

Who can I contact for more information?

If you have any additional questions or comments, you can contact Beth Gibson, the lead researcher, Faculty of Health and Social Care, Edge Hill University OR Professor Bernie Carter, on the contact details below.

Telephone Number- 01695654314 E-mail- gibsonb@edgehill.ac.uk

Prof Bernie Carter: bernie.carter@edgehill.ac.uk.

If you have any concerns or worries or wish to make a complaint about the research and wish to speak to someone independent, please contact Prof Clare Austin on austinc@edgehill.ac.uk.

Thank you for taking the time to read this information sheet.

Appendix 9 Parent consent form

Edge Hill University

Alder Hey Children's NHS
NHS Foundation Trust

CONSENT FORM FOR RESEARCH

TO BE COMPLETED BY PARENT/GUARDIAN

Title of Project: Designing acceptability tools for children's medicine

Name of Researcher: Beth Gibson

Please read all of the information below and initial each box if you consent: Initials

I confirm that I have read and understood the Information Sheet (Parent information sheet, Version 2, 15.05.2018) for the above study and have explained the study to my child. We have had the opportunity to consider the information, ask questions, and have had these answered satisfactorily.	
I understand that my child's participation is voluntary and that I am free to withdraw my child at any time without reason. If I do withdraw, his/her medical and legal rights will not be affected in any way.	
I understand and agree that the workshop my child takes part in will be audio-recorded with their permission, and will form part of the data collection for this study.	
I understand and agree that the workshop my child takes part in will be video-recorded with their permission, and will form part of the data collection for this study.	
I understand and agree that any written notes/transcription that the researcher may take during the workshop will also form part of the data collection for this study.	
I agree for the photographing of my child's work created during the workshops, and understand that this will form part of the data collection for this study.	
I am happy for my child's photograph to be taken and used as part of the final PhD thesis.	
I understand that the information collected during the study may be included in study reports. I understand that nobody will be able to identify any participants in these reports.	
I understand that within 7 days of a workshop, I can ask for any physical work my child has created or pictures of my child to be withdrawn. I understand this is only possible if the work is identifiable as my child's and providing it was not collaboratively created with other children. I understand that if they appear in photographs with other children, these images will not be able to be withdrawn.	
I understand that data collected during the study, may be looked at by individuals from Edge Hill University or regulatory authorities where it is relevant. I give permission for these individuals to have access to my anonymised data.	
I would like to receive a copy of the workshop outputs and the children's booklet.	☐ Yes ☐ No
I agree for my child to take part in the above study if they want to.	

Name of child _____ DOB of child _____

Name of parent/guardian _____ Date _____ Signature _____

Name of Researcher _____ Date _____ Signature _____

Parent consent form, Version 2, 15/05/2018

Appendix 10: Child information sheet (multiple workshops 5-7yrs)

Edge Hill University

Alder Hey Children's NHS
NHS Foundation Trust

Designing acceptability tools for children's medicine

Information for children (multiple workshops)

5-7 years old

Colour me in!

I am asking if you would like to take part in a workshop about making medicines more child-friendly.

Before you decide if you would like to help, read this booklet with a parent or guardian to find out more!

What is this study about?

This project wants to make medicine better for children by improving the methods used to evaluate it.

Who?

My name is Beth and I am doing this project. I will always be with you during the workshops, and sometimes might bring along a friend to help me! Your friends and teacher, leader or other trusted adult will also be with us.

Why?

When you are poorly the doctor can give you medicine to make you better. Sometimes children and young people don't like their medicine and that makes them grumpy or sad. Sometimes children even stop taking their medicine.

Where?

Name of group: *(Please circle your group)*

Rainbows/Brownies/Cubs/Beavers/Libraries/Schools/Alder Hey

What will I have to do if I take part?

If you want to take part, I will arrange for some workshops to take place at your group or arrange for you to come to some workshops. There will be about 10 people in each workshop.

In the **first** workshops we will talk a little bit about medicine and you will get to draw and design your very own medicine. We will play some games that will help us to arrange the medicine into what we like most and what we like least about it.

In the **second** workshops, we will look at some packages of real medicine and some of the ways that medicine is tested and evaluated now.

You are being invited to take part in at least two workshops, where you can do all of the activities, if you want to!

You **won't** need to take any real medicines!

When?

Date: This will be arranged and I will let your parent or guardian know when the workshops are.

If it is ok, I will voice and video record the workshop so that I can look and listen back to all your great ideas!

If you say it is ok, I might also ask if I can take pictures of you and your work.

It is important that you understand that you do not have to take part if you don't want to.

No-one will mind if you don't want to join in the workshops.

Thank you lots for reading this!

If you have any questions you can ask Beth in person when she visit's your group, OR you can ask your parent or guardian to call or e-mail Beth.

Number: 01695 654314

E-mail: Gibsonb@edgehill.ac.uk

Appendix 11: Child information sheet (multiple workshops 8-12yrs)

Edge Hill University

Alder Hey Children's NHS
NHS Foundation Trust

Designing acceptability tools for children's medicine

Information for children

(Multiple workshops)

8-12 years old

Can you label the medicine equipment?

I am asking if you would like to take part in a project about making medicines more child-friendly.

Before you decide if you would like to help, read this booklet with a parent or guardian to find out more!

What is this study about?

This project wants to make medicine better for children by improving the methods used to evaluate it. I think you can help me to do this by telling me what is good and bad about medicine and the ways we test it.

I think that together, we can re-design and develop some new ways of testing how acceptable medicine is.

Who?

My name is Beth and I am running this project. I will always be with you during the workshops, and sometimes might bring along a friend who will draw and write for us! Your friends and teacher, leader or other trusted adult will also be with us.

Why?

When we are unwell our doctors or parents give us medicine to make us better. Sometimes children and young people don't like their medicine and that makes them upset. Some even stop taking their medicine.

It is important that our medicine is OK to take, because we need it to get better!

Designing new ways to tell the doctor what is good and bad about our medicine, helps them to understand more.

Where?

Name of group: *(Please circle your group)*

Rainbows/Brownies/Cubs/Beavers/Libraries/Schools/Alder Hey

What will I have to do if I take part?

If you want to take part, I will visit you at your group or arrange for you to come to a number of workshops. There will be about 10 other people in your workshops.

In the **first** workshops we will discuss different types of medicines and what we like and don't like about it. I will ask you to design your very own medicine that you think would be best for children to take.

We will play some games that will help us to arrange the medicine into what we like most and what we like least.

In the **second** workshops, we will look at some real medicine and some of the scales that are currently used to assess medicine.

You will get to use these scales to develop your own way of evaluating whether a medicine is OK to take.

You will have the opportunity to take part in all of the workshops, if you want to!

You **won't** have to take any real medicines!

When?

Date: This will be arranged and I will let your parent or guardian know when the workshops are!

If it is OK, I will voice and video record the workshop so that I can look and listen back to all your great ideas!

If you say it is OK, I might also ask if I can take pictures of you and your work.

It is important that you understand that you do not have to take part in the project if you don't want to.

No one will mind if you don't want to join in the workshops.

No one will know what you say to Beth unless you say something that makes her worried about you.

If you decide you don't want to take part in the workshop when you arrive, you can do a different activity or ask Beth to call your parent/guardian to pick you up.

Thank you for reading this!

If you have any more **questions** about the project you can ask Beth when she next visits your group, OR you can ask your parent/guardian to contact her…

Number: 01695 654314

E-mail: Gibsonb@edgehill.ac.uk

Appendix 12: Child assent form (multiple workshops)

Edge Hill University

Alder Hey Children's NHS
NHS Foundation Trust

Assent form for children aged 5-12 years Multiple Workshops:

Designing ACCeptability Tools for Children's Medicine Study

Name of researcher: Beth Gibson

I am happy I know about the study and have asked any questions I wanted to	
I know I do not have to take part in the study	
I know that if I want to take part I might have to think about the times I have taken medicine	
I know Beth will write things about what I say and other people might read this	
I know I will use a special name so no-one will know what I have said	
I am happy that my voice may be recorded in the workshops	
I am happy for Beth to take video recordings in the workshop, I know that I may be in them	
I know that Beth will take pictures of my work	
I know that Beth will take pictures of me	
I know that there will be another workshop and I am happy to take part in it	
I agree to take part in the study	

Name of child	Date	*Signature*
Name of parent/carer	Date	*Signature*
Name of Researcher	Date	*Signature*

Child assent form Multiple Workshops, Version 1, 15/05/2018

Appendix 13: Parent information sheet (multiple workshops)

Edge Hill University

Alder Hey Children's NHS
NHS Foundation Trust

Designing acceptability tools for children's medicine

Information for Parents/Carers

(Multiple workshops)

Study title

Co-designing with children to develop child-centred methods for assessing the acceptability of children's medicines.

My name is Beth Gibson and I am undertaking this project to try and make medicine more acceptable for children by improving the methods that are currently used to do this. Most children do not like to take medicines. This can be for many reasons. It might be because they do not like the taste, smell or feel of the medicine or because they find it hard to swallow a tablet or for some other reason. If they do not take their medicine, then the treatment will not work properly.

I want to ask children for their ideas about what makes medicine acceptable to them. This information will then be used to co-design and develop new methods that can more accurately assess the acceptability of new and existing medicine for children. We are hoping that this information can be used in the future to inform researchers and pharmaceutical developers in the formulation of children's medicine.

Please read the following information carefully. It is important that you understand all of the information in this booklet before you give your consent for your child to take part. If you have any questions, you can find my contact details on the back page.

Does my child have to take part?

No, it is up to you to decide if you wish them to take part; no-one will be offended if you decide not to let them. Before we talk to your child about the study, we need you to decide if they can take part.

Why is my child being invited to take part?

Your child has been invited to take part in this study because he/she is between the ages of 5-12 years old and they attend one of the groups I am working with for this study. They do not need to be taking medicines on a regular basis to take part in this study.

What will happen to child if they take part?

Your child will be part of a number of group workshops, with 10 other children. The first workshop is designed to generate information about the understanding that children have of the acceptability of medicine. This will involve activities such as drawing, writing and discussing, and a variety of games. The second workshop will focus on the evaluation and re-development of methods that are used to assess medicine. I will be present through the duration of the workshop, along with my colleague(s) who will be there to help with the activities. Your child's leader/teacher or other trusted adult will also be present.

Consent for your child to take part and assent from your child

Once you have read this sheet, and are happy for your child to be involved, you will be given a consent sheet to sign and return. Your child has been given a child-friendly version of this sheet, which you should read through with them. If they wish to take part, they will be asked to sign their name on an 'assent' sheet to say that they understand about the study and are happy to be involved.

What if my child or I change our minds?

If your child decides at any point during the study that they no longer wish to take part that is fine. They can change their mind and stop at any time. You can also change your mind about your child taking part at any time. If your child withdraws from the study, any physical work they have created or pictures taken of your child will be able to be withdrawn within 7 days of the workshop providing we are able to identify the work as your child's, and that the work was solely your child's work and not created in collaboration with other children. We will not be able to remove images of your child if they are part of an image with other children in it.

Edge Hill University will be using information from your child in order to undertake this study and will act as a data controller for this study. This means that we are responsible for looking after your information and using it properly. The legal basis for the collection of your child's personal data is necessary for research carried out for reasons of public interest. Edge Hill University will keep identifiable information about your child for 3 years, or until the student researcher has completed their PhD.

Your rights to access, change or move your or your child's information are limited, as we need to manage this 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 and your child that we have already obtained. At Edge Hill, we are committed to respecting and protecting your and your child's personal information. To find ways in which we use your data, please see https://www.edgehill.ac.uk/about/legal/privacy/ or if you require further information you can contact our data protection officer at dataprotection@edgehill.ac.uk.

Who will know that my child has taken part?

Before the workshops begin, your child will choose a name that they will use on any work they produce during the workshop. This pseudonym will be used to store your child's drawings and work, and will be stored separately to any information containing your child's name, only you, your child and the researcher will know the pseudonym. Pictures of your child will only be taken with your, and your child's consent. All the information that is collected will be kept anonymous and neither your or your child's name nor details will be shared, unless something happens or is disclosed that makes me worried about your child. The findings from this study will be contained within the final PhD, shared at conferences, journal articles, and may be used for future teaching but your information will remain confidential and anonymised.

What are the benefits of taking part?

There are no immediate benefits to your child. However, by sharing their opinions, thoughts and preferences, your child will be helping us to better understand how medicine, and the methods used to assess medicine, can be made more child-friendly.

Is the study safe?

This research has been looked at by an independent group of people, called the Research Ethics Committee. The people on this panel have reviewed the study and said that it is safe to be carried out. The study has also been approved through a research ethics committee at Edge Hill University.

The only thing we will ask of your child is to think about their experiences with medicine, and be creative with their inventions and designs!

Are there any risks or disadvantages?

There are no risks associated with this research. It is not expected that any of the activities will cause any upset, but your child may be asked to remember taking a medicine they did not like.

Who can I contact for more information?

If you have any additional questions, comments or worries, you can contact Beth Gibson, the lead researcher, Faculty of Health and Social care, Edge Hill University on the contact details below, or Professor Bernie Carter.

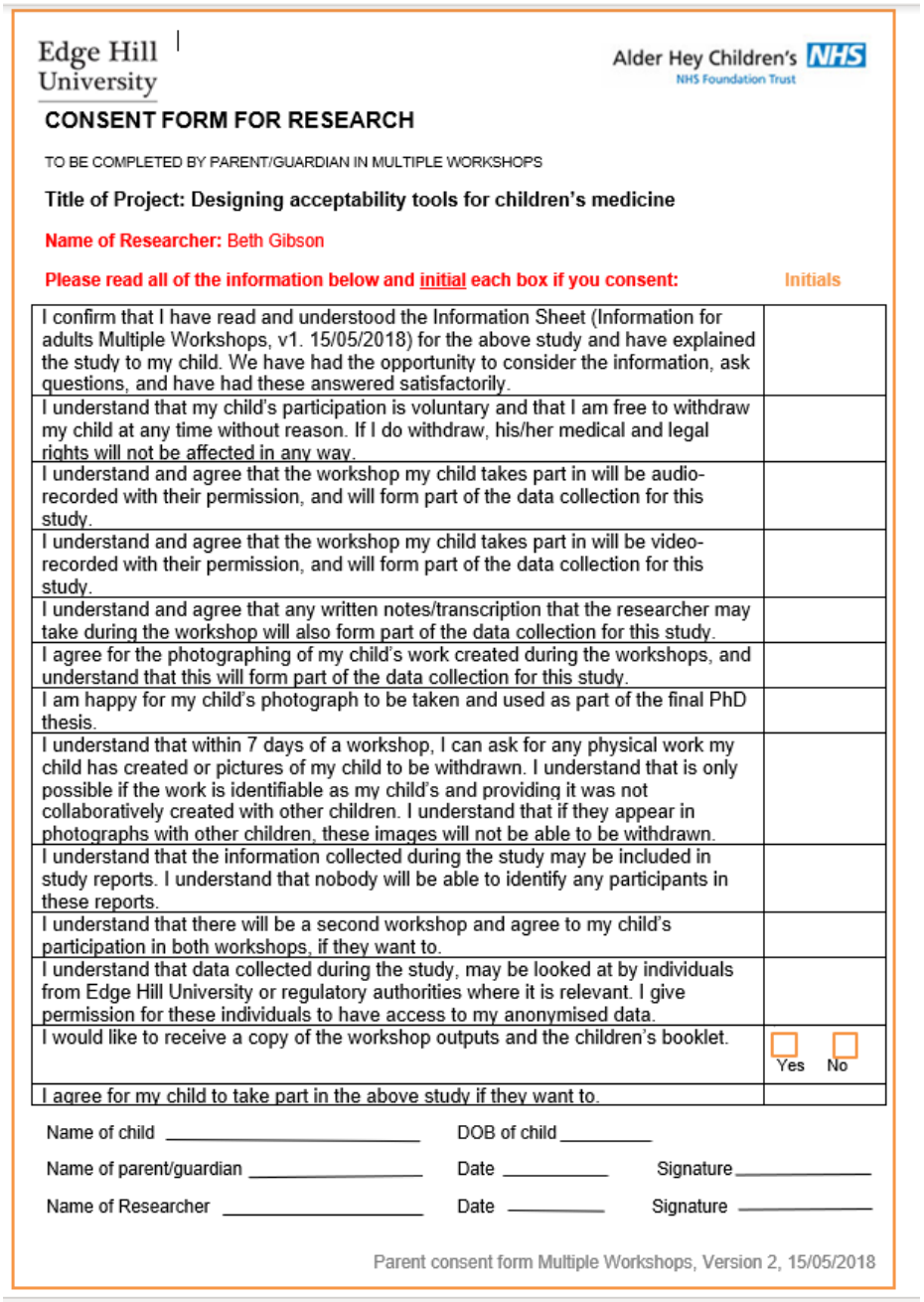
Number- 01695654314 E-mail- gibsonb@edgehill.ac.uk

Professor Bernie Carter: Bernie.carter@edgehill.ac.uk

If you have any concerns or wish to make a complaint about the research and wish to speak to someone independent, please contact Professor Clare Austin, Associate Dean, Research and Innovation on 01695 650772 or austincl@edgehill.ac.uk.

Thank you for taking the time to read this information!

Appendix 14: Parent consent form (multiple workshops)



Edge Hill University

Alder Hey Children's NHS
NHS Foundation Trust

CONSENT FORM FOR RESEARCH

TO BE COMPLETED BY PARENT/GUARDIAN IN MULTIPLE WORKSHOPS

Title of Project: Designing acceptability tools for children's medicine

Name of Researcher: Beth Gibson

Please read all of the information below and initial each box if you consent: Initials

I confirm that I have read and understood the Information Sheet (Information for adults Multiple Workshops, v1. 15/05/2018) for the above study and have explained the study to my child. We have had the opportunity to consider the information, ask questions, and have had these answered satisfactorily.	
I understand that my child's participation is voluntary and that I am free to withdraw my child at any time without reason. If I do withdraw, his/her medical and legal rights will not be affected in any way.	
I understand and agree that the workshop my child takes part in will be audio-recorded with their permission, and will form part of the data collection for this study.	
I understand and agree that the workshop my child takes part in will be video-recorded with their permission, and will form part of the data collection for this study.	
I understand and agree that any written notes/transcription that the researcher may take during the workshop will also form part of the data collection for this study.	
I agree for the photographing of my child's work created during the workshops, and understand that this will form part of the data collection for this study.	
I am happy for my child's photograph to be taken and used as part of the final PhD thesis.	
I understand that within 7 days of a workshop, I can ask for any physical work my child has created or pictures of my child to be withdrawn. I understand that is only possible if the work is identifiable as my child's and providing it was not collaboratively created with other children. I understand that if they appear in photographs with other children, these images will not be able to be withdrawn.	
I understand that the information collected during the study may be included in study reports. I understand that nobody will be able to identify any participants in these reports.	
I understand that there will be a second workshop and agree to my child's participation in both workshops, if they want to.	
I understand that data collected during the study, may be looked at by individuals from Edge Hill University or regulatory authorities where it is relevant. I give permission for these individuals to have access to my anonymised data.	
I would like to receive a copy of the workshop outputs and the children's booklet.	☐ Yes ☐ No
I agree for my child to take part in the above study if they want to.	

Name of child _____ DOB of child _____

Name of parent/guardian _____ Date _____ Signature _____

Name of Researcher _____ Date _____ Signature _____

Parent consent form Multiple Workshops, Version 2, 15/05/2018

Appendix 15: Child information sheet (Hospital, 5-7yrs)

Edge Hill University

Alder Hey Children's NHS
NHS Foundation Trust

Designing acceptability tools for children's medicine

Information for children

5-7 years old

Colour me in!

A study to improve medicines for children and young people.

Before you decide if you would like to help, read this booklet with a parent or guardian to find out more!

What is this study about?

This project wants to make medicine better for children by improving the ways it is tested.

Why?

When you are poorly the doctor can give you medicine to make you better. Sometimes children and young people don't like their medicine and that makes them grumpy or sad. Sometimes children even stop taking their medicine.

What will I have to do if I take part?

If you want to take part, we will ask your parent if it is OK with them, they will need to sign some papers for you.

We will talk a little bit about medicine and you will get to complete your very own activity booklet.

We will play some games that will help us to find out about what you think about medicines.

We will look at some of the ways that children are involved in thinking about how medicines are tested, and you will be asked what you think of each method.

You **won't** need to take any real medicines!

Will taking part help me now?

No, but we hope it will help children and young people in the future.

Do I have to take part?

No, it is up to you, if you change your mind and do not want to take part anymore, let me know.

Is the study safe?

Yes. We will not ask you to do anything that will put you in harm and we do not think any of the activities will upset you. You do not have to answer anything that you do not want to.

Pictures

If it ok with you, Beth will take pictures of any drawings or activities you produce. These may be used in her work. You won't be in any pictures. If your real name is on your work Beth will remove it before she uses the picture.

If it is ok, I will use a voice recorder so that I can listen back to all your great ideas!

It is important that you understand that you do not have to take part if you don't want to.

Thank you lots for reading this!

If you have any questions you can ask Beth in person, OR you can ask your parent or guardian to call or e-mail Beth.

Number: 01695 654314

E-mail: Gibsonb@edgehill.ac.uk

Appendix 16: Child information sheet (Hospital, 8-12 yrs)

Edge Hill University

Alder Hey Children's NHS
NHS Foundation Trust

Designing acceptability tools for children's medicine

Information for children

8-12 years old

Can you label the medicine equipment?

A study to improve medicines for children and young people.

Before you decide if you would like to help, read this booklet with a parent or guardian to find out more!

What is this study about?

This project wants to make medicine better for children by improving the methods used to evaluate it. I think you can help me to do this by telling me what is good and bad about medicine and the ways we test it. I think that together, we can re-design and develop some new ways of testing how acceptable medicine is.

Why?

When we are unwell our doctor's or parents give us medicine to make us better. Sometimes children and young people don't like their medicine and that makes them upset. Some even stop taking their medicine.

What will I have to do if I take part?

If you want to take part, we will ask your parent if it is OK with them, they will need to sign some papers for you.

We will talk a little bit about medicine and you will get to complete your very own activity booklet.

We will play some games that will help us to find out about what medicines are acceptable to you.

We will look at some of the ways that are currently used to assess medicine acceptability. You will be able to use these measures to develop your own way of evaluating whether a medicine is OK to take.

You **won't** have to take any real medicines!

Will taking part help me now?

No, but we hope it will help children and young people in the future.

Do I have to take part?

No, it is up to you, if you change your mind and do not want to take part anymore, let me know.

Is the study safe?

Yes. We will not ask you to do anything that will put you in harm and we do not think any of the activities will upset you. You do not have to answer anything that you do not want to.

Pictures

If it ok with you, Beth will take pictures of any drawings or activities you produce. These may be used in her work. You won't be in any pictures. If your real name is on your work, Beth will remove it before she uses the picture.

It is important that you understand that you do-not have to take part in the project if you don't want to.

No-one will know what you say to Beth unless you say something that makes her worried about you.

If it is ok, I will use a voice recorder so that I can listen back to all of your great ideas!

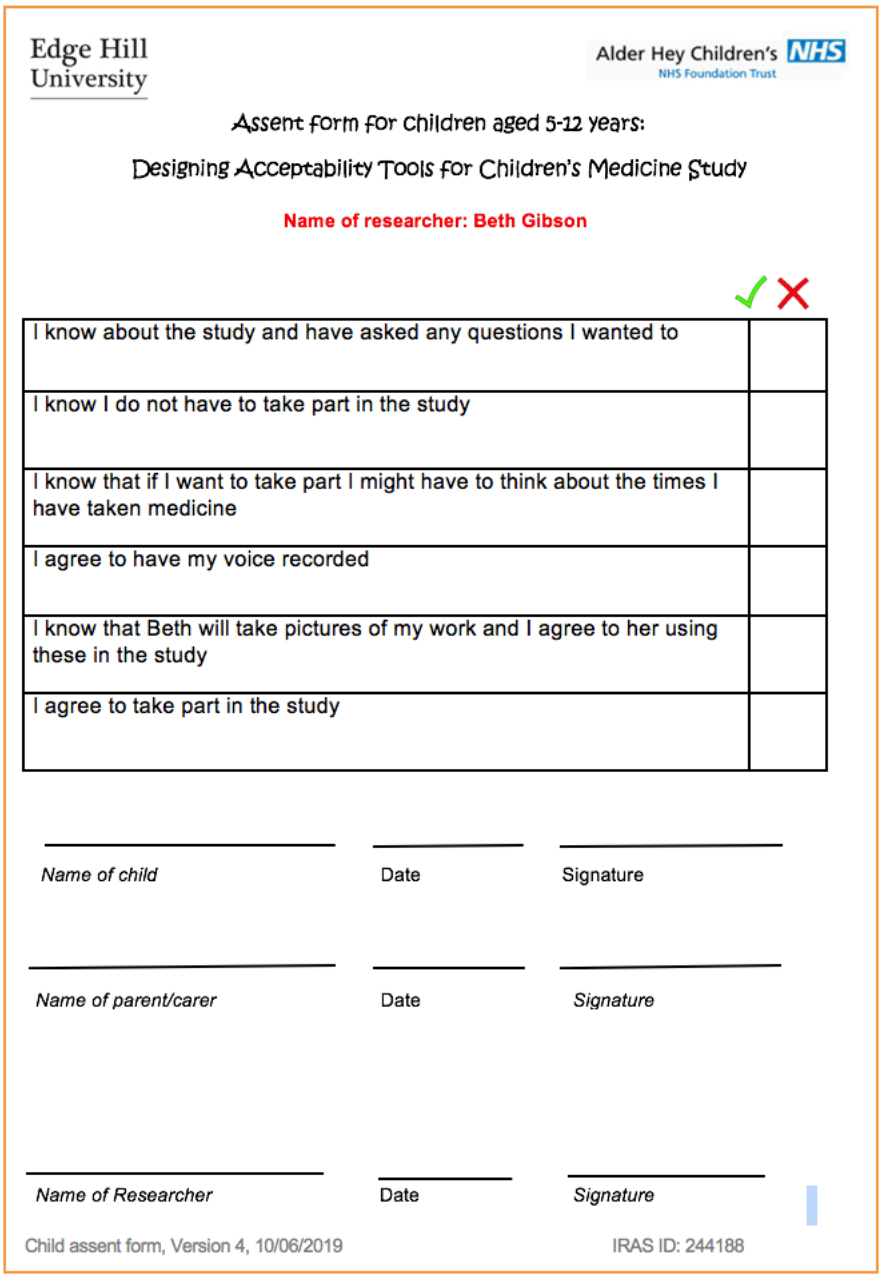
Thank you for reading this!

If you have **any** more questions about the project you can ask Beth in person, OR you can ask your parent/guardian to contact her...

Number: 01695 654314

E-mail: Gibsonb@edgehill.ac.uk

Appendix 17: Child assent form (hospital)



Edge Hill University

Alder Hey Children's NHS
NHS Foundation Trust

Assent form for children aged 5-12 years:

Designing Acceptability Tools for Children's Medicine Study

Name of researcher: Beth Gibson

	✓ / ✗
I know about the study and have asked any questions I wanted to	
I know I do not have to take part in the study	
I know that if I want to take part I might have to think about the times I have taken medicine	
I agree to have my voice recorded	
I know that Beth will take pictures of my work and I agree to her using these in the study	
I agree to take part in the study	

Name of child	Date	Signature
Name of parent/carer	Date	*Signature*
Name of Researcher	Date	*Signature*

Child assent form, Version 4, 10/06/2019 IRAS ID: 244188

Appendix 18: Parent information sheet (hospital)

Edge Hill University

Alder Hey Children's NHS Foundation Trust

Information for Parents/ Carers

Study title

Using participatory methods with children to develop child-centred measures for assessing the acceptability of medicine for children

Please read the following information carefully. It is important that you understand all of the information in this booklet before you give your consent for your child to take part. If you have any questions, you can find my contact details on the back page.

Why are we doing this?

My name is Beth Gibson and I am undertaking this project to gain a better understanding of the things that make medicine acceptable to children. Most children do not like to take medicines. This can be for many reasons. It might be because they do not like the taste, smell or feel of the medicine or because they find it hard to swallow a tablet or for some other reason. If they do not take their medicine, then their treatment will not work properly.

I want to ask children for their ideas about what makes medicine acceptable to them. This information will then be used to co-design and develop new methods that can more accurately assess the acceptability of new and existing medicines for children. We are hoping that this information can be used in the future to inform researchers and pharmaceutical developers in the formulation of children's medicine.

Why is my child being invited to take part?

Your child has been invited to take part in this study because he/she is between the ages of 5-12 years old and because they attend Alder Hey Children's Hospital. They do not need to be taking medicines on a regular basis to take part in this study.

What will happen to child if they take part?

Your child will be given a short, interactive activity booklet. The booklet contains drawing, writing and discussion activities. The activity booklet is designed to generate important information about the understanding that children have of the acceptability of medicine, and the evaluation and re-development of methods that are used to assess medicine. I will stay with your child whilst they complete the booklet.

Does my child have to take part?

No! It is up to you to decide if you wish them to take part; no-one will be offended if you decide not to let them. Before we talk to your child about the study, we need you to decide if they can take part. If you agree for your child to take part but they do not want to, then we will respect their wishes.

Consent for your child to take part and assent from your child

Once you have read this sheet, and are happy for your child to be involved, you will be given a consent sheet to sign and return. Your child has been given a child-friendly version of this sheet, which you should read through with them. If they wish to take part, they will be asked to 'sign' their name on an 'assent' sheet to say that they understand about the study and are happy to be involved.

Edge Hill University will be using information from your child in order to undertake this study and will act as a data controller for this study. This means that we are responsible for looking after your information and using it properly. The legal basis for the collection of your child's personal data is necessary for research carried out for reasons of public interest. Edge Hill University will keep identifiable information about your child for 10 years, or until the student researcher has completed their PhD.

Your rights to access, change or move your or your child's information are limited, as we need to manage this 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 and your child that we have already obtained. At Edge Hill, we are committed to respecting and protecting your personal information. To find ways in which we use your and your child's data, please see https://www.edgehill.ac.uk/about/legal/privacy/ or if you require further information you can contact our data protection officer at dataprotection@edgehill.ac.uk.

What if my child or I change our minds?

If your child decides at any point during the study that they no longer wish to take part that is fine. They can change their mind and stop at any time. You can also change your mind about your child taking part at any time. If your child withdraws from the study, any physical work they have created, or pictures taken of your child's drawings will be able to be withdrawn within 7 days of them participating providing we are able to identify the work as your child's.

Who will know that my child has taken part?

Before your child completes any activities, they will choose a name that they will use on any work they produce. This pseudonym will be used to store your child's data, separately to the information and consent sheets that you provide. Only you, your child and the researcher will know the pseudonym they choose.

Pictures of your child's drawings and activity booklets will be taken with your and your child's consent. All the information that is collected will be kept anonymous and neither your or your child's name nor details will be shared, unless something happens or is disclosed that makes me worried about your child. The findings, including pictures of their drawings and booklets, may be contained within the final PhD, shared at conferences, journal articles, and may be used for future research but your information will remain confidential and anonymised.

How long will the activities take?

The activities will take around 30 minutes.

What are the benefits of taking part?

There are no immediate benefits to your child. By sharing their opinions, thoughts and preferences, your child will be helping us to better understand how medicine, and the methods used to assess medicine, can be made more child-friendly. It is important for us to know this information as we hope that the information we collect will help to improve treatment for children in the future.

Is the study safe?

This research has been looked at by an independent group of people, called the Research Ethics Committee. The people on this panel have reviewed the study and said that it is safe to be carried out. The study has also been approved through a research ethics committee at Edge Hill University.

Are there any risks or disadvantages?

There are no risks associated with this research. It is not expected that any of the activities will cause any upset, but your child may be asked to recall taking medicine, which they may have some negative associations with.

Edge Hill University, as Sponsor, has appropriate insurance in place in the unlikely event that you suffer harm a direct consequence of your participation in this study.

Who can I contact for more information?

If you have any additional questions or comments, you can contact Beth Gibson, the lead researcher, Faculty of Health and Social Care, Edge Hill University OR Professor Bernie Carter, on the contact details below.

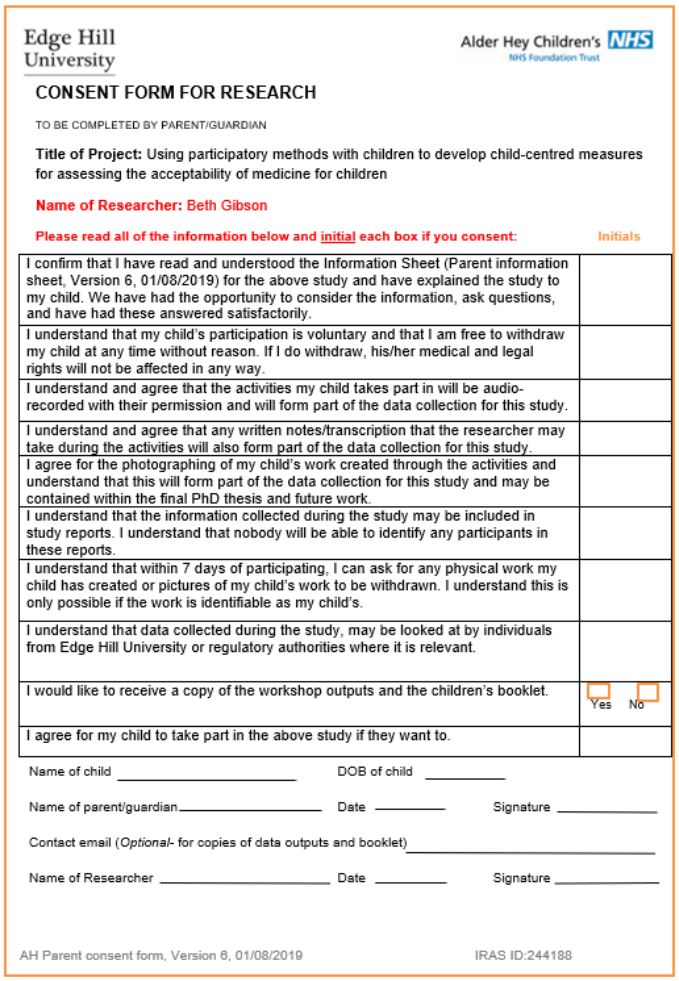
Telephone Number- 01695654314 E-mail- gibsonb@edgehill.ac.uk

Prof Bernie Carter: bernie.carter@edgehill.ac.uk.

If you have any concerns or worries or wish to make a complaint about the research and wish to speak to someone independent, please contact Prof Clare Austin on austincl@edgehill.ac.uk.

Thank you for taking the time to read this information sheet.

Appendix 19: Parent consent form (hospital)



Edge Hill University

Alder Hey Children's NHS
NHS Foundation Trust

CONSENT FORM FOR RESEARCH

TO BE COMPLETED BY PARENT/GUARDIAN

Title of Project: Using participatory methods with children to develop child-centred measures for assessing the acceptability of medicine for children

Name of Researcher: Beth Gibson

Please read all of the information below and initial each box if you consent: Initials

I confirm that I have read and understood the Information Sheet (Parent information sheet, Version 6, 01/08/2019) for the above study and have explained the study to my child. We have had the opportunity to consider the information, ask questions, and have had these answered satisfactorily.	
I understand that my child's participation is voluntary and that I am free to withdraw my child at any time without reason. If I do withdraw, his/her medical and legal rights will not be affected in any way.	
I understand and agree that the activities my child takes part in will be audio-recorded with their permission and will form part of the data collection for this study.	
I understand and agree that any written notes/transcription that the researcher may take during the activities will also form part of the data collection for this study.	
I agree for the photographing of my child's work created through the activities and understand that this will form part of the data collection for this study and may be contained within the final PhD thesis and future work.	
I understand that the information collected during the study may be included in study reports. I understand that nobody will be able to identify any participants in these reports.	
I understand that within 7 days of participating, I can ask for any physical work my child has created or pictures of my child's work to be withdrawn. I understand this is only possible if the work is identifiable as my child's.	
I understand that data collected during the study, may be looked at by individuals from Edge Hill University or regulatory authorities where it is relevant.	
I would like to receive a copy of the workshop outputs and the children's booklet.	☐ Yes ☐ No
I agree for my child to take part in the above study if they want to.	

Name of child _____ DOB of child _____

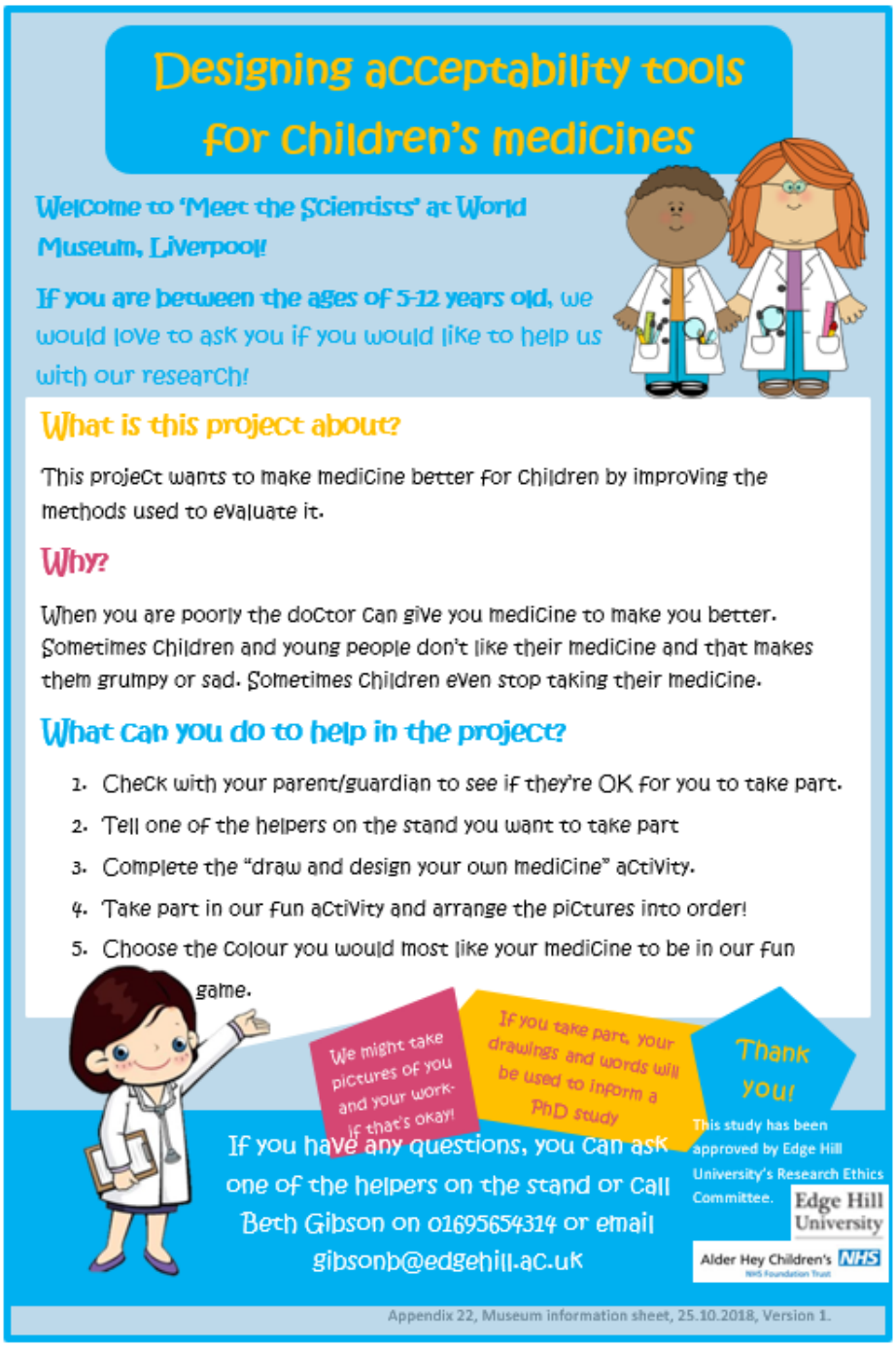
Name of parent/guardian _____ Date _____ Signature _____

Contact email (*Optional*- for copies of data outputs and booklet) _____

Name of Researcher _____ Date _____ Signature _____

AH Parent consent form, Version 6, 01/08/2019 IRAS ID:244188

Appendix 20: Museum information poster



Appendix 21: Museum information sheets

Designing acceptability tools for children's medicines research study

Information for parents/carers

attending the World Museum, Liverpool 2018

Edge Hill University

Alder Hey Children's NHS

Most children don't like to take medicines. This might be because they do not like the taste, smell or feel of the medicine or because they find it hard to swallow a tablet or something else. If they do not take their medicine, then their treatment will not work properly. I am asking children for their ideas about what makes medicine acceptable to them.

What will my child have to do?

During their visit to my stand at the museum your child will be able take part in some **research activities** including drawing and writing to help us understand what they think about the acceptability of medicine, and the methods that are used to assess medicine.

The activities won't take long, about 3-5 minutes for each activity.

Consent for your child to take part and assent from your child

If you are happy for your child to take part, one of our helpers will ask whether you have read and understood the information sheet and give you a chance to ask any questions. Please stay with your child whilst they are completing the activities.

Once they have completed an activity, a helper will ask you (and your child) again if you are happy for your child's drawing or writing to be part of the study. If you and your child are OK about this, we will let your child post their drawing or writing into Dr. Diamond's post-box.

The act of posting the activity into the post box is your consent for your child to take part in study. Once they have posted their work, they will not be able to withdraw from the study.

Who will know that my child has taken part?

We will not tell anyone that your child has taken part. We are not collecting any personal information from you or your child. If they do share personal information in their drawings or writing, we will anonymise this.

What are the benefits of taking part?

There are no benefits to your child taking part, but we hope they will enjoy sharing their ideas with us.

Is the study safe?

An independent group called the Research Ethics Committee have said this study is safe.

Are there any risks or disadvantages?

We do not think there any risks or disadvantages to your child if they take part.

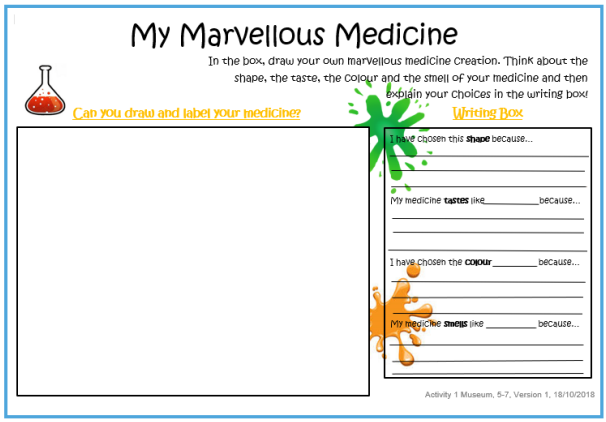
Who can I contact for more information?

If you have any additional questions or comments, you can contact **Beth Gibson** (the lead researcher), Faculty of Health and Social Care, Edge Hill University on 01695654314 or email gibsonb@edgehill.ac.uk or contact Prof. Bernie Carter, (Beth's PhD supervisor) by email on bernie.carter@edgehill.ac.uk

If you have any concerns or worries or wish to make a complaint about the research and wish to speak to someone independent, please contact Prof Clare Austin on austincl@edgehill.ac.uk.

Appendix 21, Museum information sheet for parents, 25.10.2018, Version 1.

Appendix 22: Museum activity sheet (5-7yrs)



My Marvellous Medicine

In the box, draw your own marvellous medicine creation. Think about the shape, the taste, the colour and the smell of your medicine and then explain your choices in the writing box!

Can you draw and label your medicine?

Writing Box

I have chosen this **shape** because...

My medicine **tastes** like_____because...

I have chosen the **colour**_____because...

My medicine **smells** like _____because...

Activity 1 Museum, 5-7, Version 1, 18/10/2018

Designing acceptability tools for children's medicine-
Research Study
at the World Museum, Liverpool

How old are you? (Circle your age)

5 6 7 8 9 10 11 12

Are you:

Boy Girl

Activity 1 Museum, 5-7, Version 1, 18/10/2018

Appendix 23: Museum activity sheet (8-12yrs)

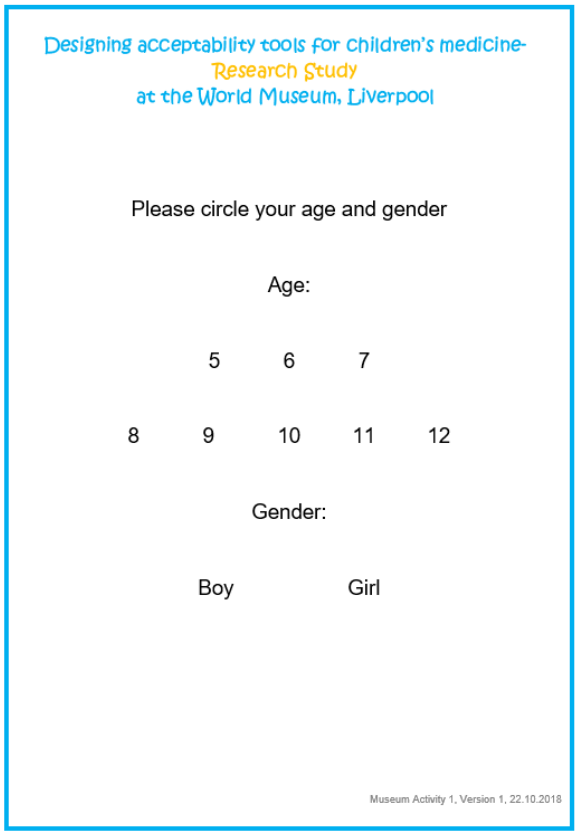
My Marvellous Medicine

- Draw your own Marvellous Medicine- and label the different parts of it!
- Write a letter to Dr. Diamond explaining why you chose the colour, shape, taste, feel, smell, size and name.

Ingredients

Dear Dr. Diamond...

Museum Activity 1, Version 1, 22.10.2018



Designing acceptability tools for children's medicine-
Research Study
at the World Museum, Liverpool

Please circle your age and gender

Age:

5 6 7

8 9 10 11 12

Gender:

Boy Girl

Museum Activity 1, Version 1, 22.10.2018

Appendix 24: Certificate of participation (museum)

CERTIFICATE *Of* PARTICIPATION

Thank you for taking part in the Designing Acceptability Tools for Children's Medicine- Research Study

at World Museum, Liverpool

On 24/11/18

Your participation is greatly appreciated.

Signed: Beth Gibson

Alder Hey Children's NHS Foundation Trust

Edge Hill University

A big thank you from Edge Hill University and Alder Hey Children's Hospital Foundation Trust

Certificate of participation, Version 3. 30/10/18

IRAS ID: 244188

Appendix 25: Recruitment flyer

Edge Hill University

Participate in Children's Medicine Research!

Alder Hey Children's NHS
NHS Foundation Trust

If you would like to help, contact us for more information:

Phone: 01695654314

E-mail: gibsonb@edgehill.ac.uk

Do you live in the North West of England?

Workshops will be running in a number of locations in the North West- use the contact details for more information!

Who?

Children between the ages of 5-12 years old

What?

Participate in fun arts-based activity research workshops to help us to gain a better understanding of children's perceptions of medicine and develop new methods of testing medicine acceptability!

Where?

Here in your local centre!

Why?

We believe that medicine acceptance is really important in children, and want to improve medicine so that it is more child-friendly!

Appendix 26: Thank you and information sheets

Debrief

The purpose of this research workshop was to find out more about what children think of medicine acceptability measures, and to re-design and develop child-friendly ways to assess acceptability of medicine.

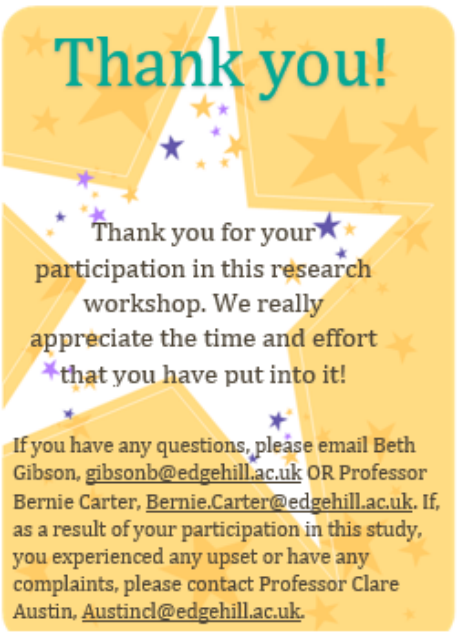
As you know, your participation in the study was voluntary. If you wish, you may withdraw your child's participation after reading this debriefing form. This applies only to any work they may have completed during the workshops and photographs of your child.

If you require any more information, there are some useful websites below:

- http://www.alderhey.nhs.uk
- http://www.eupfi.org

Edge Hill University

Alder Hey Children's NHS



Appendix 27: Certificate of participation (groups)

CERTIFICATE *Of* PARTICIPATION

This certificate is awarded to

_____

Thank you for your participation in the Research Workshop

and for giving your time, effort, ideas and knowledge.

Alder Hey Children's NHS Foundation Trust

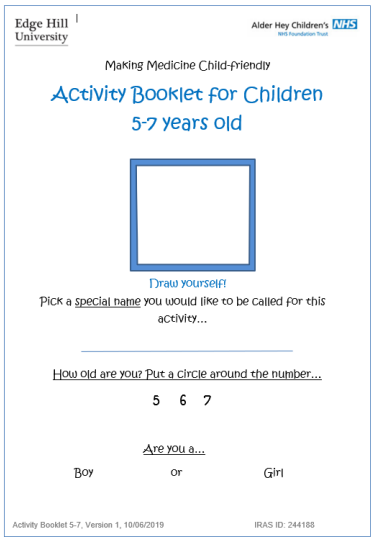
Edge Hill University

Signed: _____

A big thank-you from Edge Hill University and Alder Hey Children's Hospital Foundation Trust 2018

Certificate of participation, Version 1, 15/02/2018

Appendix 28: Activity booklet (5-7yrs)



Edge Hill University

Alder Hey Children's NHS

Making Medicine Child-Friendly

Activity Booklet for Children 5-7 years old

Draw yourself!

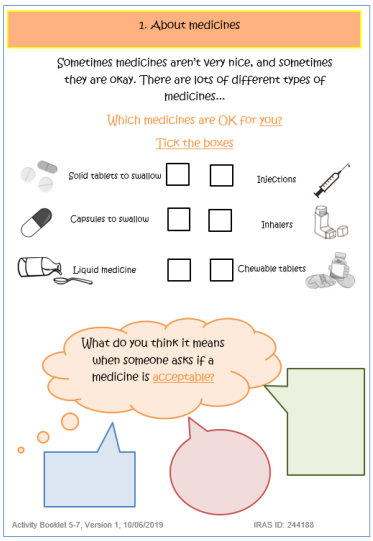
Pick a special name you would like to be called for this activity...

How old are you? Put a circle around the number...

5 6 7

Are you a...

Boy or Girl



1. About medicines

Sometimes medicines aren't very nice, and sometimes they are okay. There are lots of different types of medicines...

Which medicines are OK for you?

Tick the boxes

Solid tablets to swallow

Injections

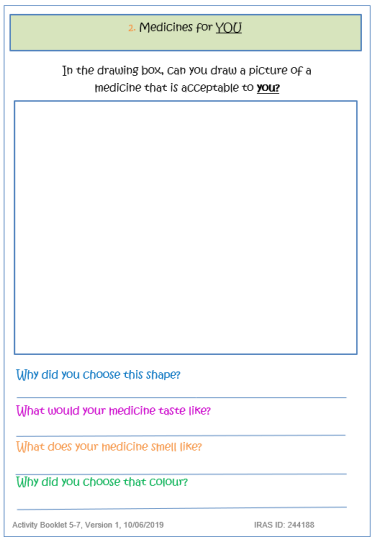
Capsules to swallow

Inhalers

Liquid medicine

Chewable tablets

What do you think it means when someone asks if a medicine is acceptable?



2. Medicines for YOU

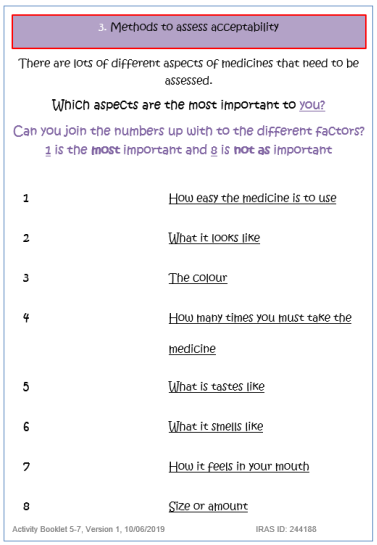
In the drawing box, can you draw a picture of a medicine that is acceptable to **YOU**?

Why did you choose this shape?

What would your medicine taste like?

What does your medicine smell like?

Why did you choose that colour?



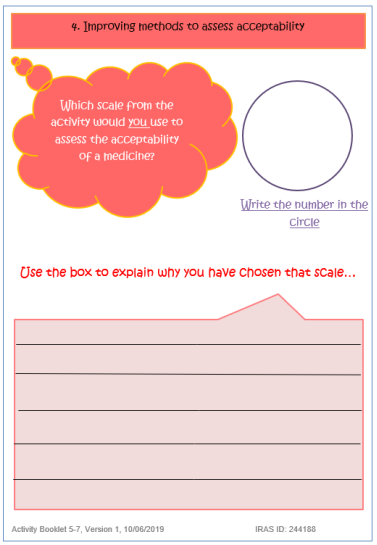
3. Methods to assess acceptability

There are lots of different aspects of medicines that need to be assessed.

Which aspects are the most important to you?

Can you join the numbers up with to the different factors? 1 is the **most** important and 8 is **not as** important

1	How easy the medicine is to use
2	What it looks like
3	The colour
4	How many times you must take the medicine
5	What is tastes like
6	What it smells like
7	How it feels in your mouth
8	Size or amount

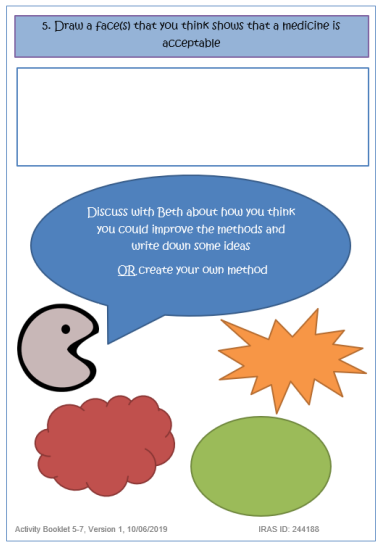


4. Improving methods to assess acceptability

Which scale from the activity would you use to assess the acceptability of a medicine?

Write the number in the circle

Use the box to explain why you have chosen that scale...

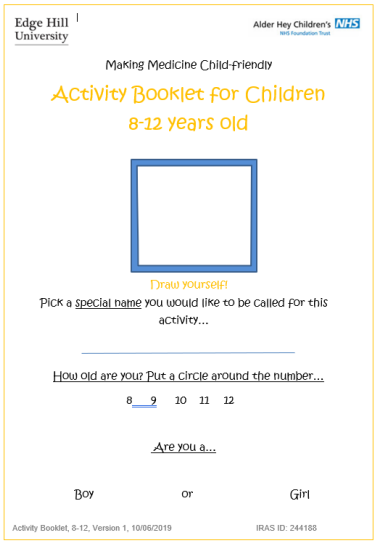


5. Draw a face(s) that you think shows that a medicine is acceptable

Discuss with Beth about how you think you could improve the methods and write down some ideas

OR create your own method

Appendix 29: Activity booklet (8-12yrs)



Edge Hill University

Alder Hey Children's NHS
NHS Foundation Trust

Making Medicine Child-friendly

Activity Booklet for Children 8-12 years old

Draw yourself!

Pick a special name you would like to be called for this activity...

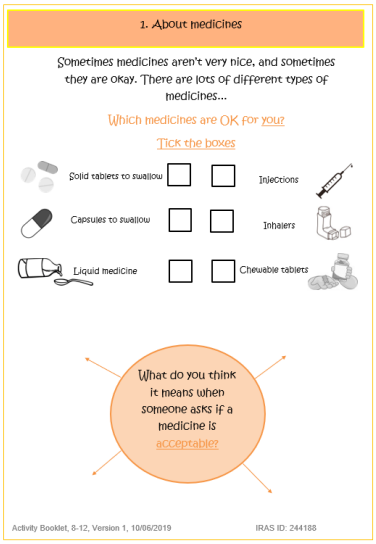
How old are you? Put a circle around the number...

8 9 10 11 12

Are you a...

Boy or Girl

Activity Booklet, 8-12, Version 1, 10/06/2019 IRAS ID: 244188



1. About medicines

Sometimes medicines aren't very nice, and sometimes they are okay. There are lots of different types of medicines...

Which medicines are OK for you?

Tick the boxes

Solid tablets to swallow

Capsules to swallow

Liquid medicine

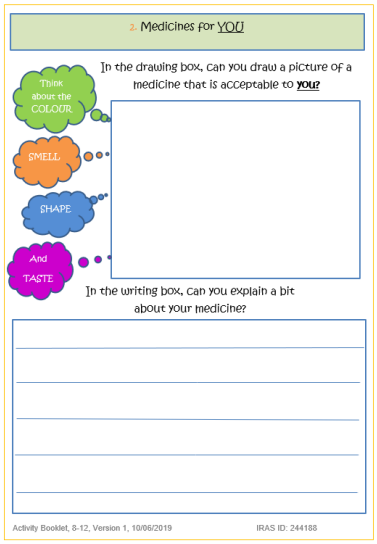
Injections

Inhalers

Chewable tablets

What do you think it means when someone asks if a medicine is acceptable?

Activity Booklet, 8-12, Version 1, 10/06/2019 IRAS ID: 244188



2. Medicines for YOU

Think about the COLOUR

SMELL

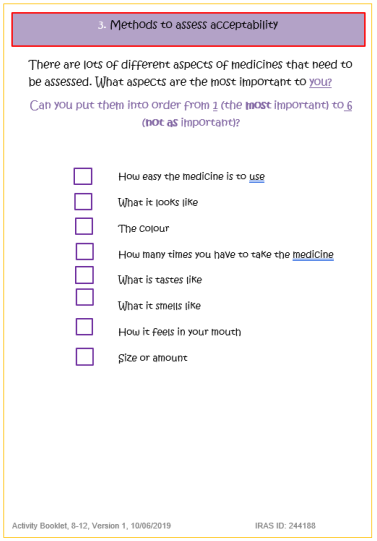
SHAPE

And TASTE

In the drawing box, can you draw a picture of a medicine that is acceptable to **you?**

In the writing box, can you explain a bit about your medicine?

Activity Booklet, 8-12, Version 1, 10/06/2019 IRAS ID: 244188



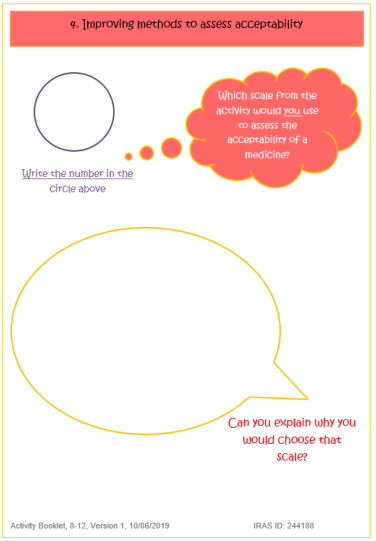
3. Methods to assess acceptability

There are lots of different aspects of medicines that need to be assessed. What aspects are the most important to you?

Can you put them into order from 1 (the **most** important) to 6 (**not as** important)?

- How easy the medicine is to use
- What it looks like
- The colour
- How many times you have to take the medicine
- What is tastes like
- What it smells like
- How it feels in your mouth
- Size or amount

Activity Booklet, 8-12, Version 1, 10/06/2019 IRAS ID: 244188



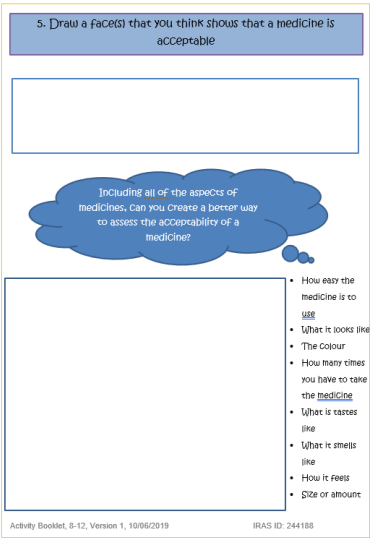
4. Improving methods to assess acceptability

Write the number in the circle above

Which scale from the activity would you use to assess the acceptability of a medicine?

Can you explain why you would choose that scale?

Activity Booklet, 8-12, Version 1, 10/06/2019 IRAS ID: 244188



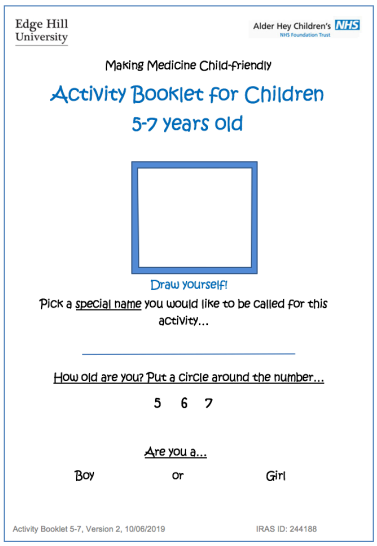
5. Draw a face(s) that you think shows that a medicine is acceptable

Including all of the aspects of medicines, can you create a better way to assess the acceptability of a medicine?

- How easy the medicine is to use
- What it looks like
- The colour
- How many times you have to take the medicine
- What is tastes like
- What it smells like
- How it feels
- Size or amount

Activity Booklet, 8-12, Version 1, 10/06/2019 IRAS ID: 244188

Appendix 30a: Activity booklet (hospital, 5-7yrs)



Edge Hill University

Alder Hey Children's NHS

Making Medicine Child-friendly

Activity Booklet for Children 5-7 years old

Draw yourself!

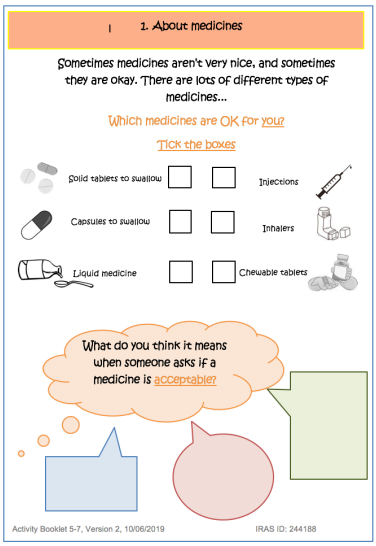
Pick a special name you would like to be called for this activity...

How old are you? Put a circle around the number...

5 6 7

Are you a...

Boy or Girl



1. About medicines

Sometimes medicines aren't very nice, and sometimes they are okay. There are lots of different types of medicines...

Which medicines are OK for you?

Tick the boxes

Solid tablets to swallow

Injections

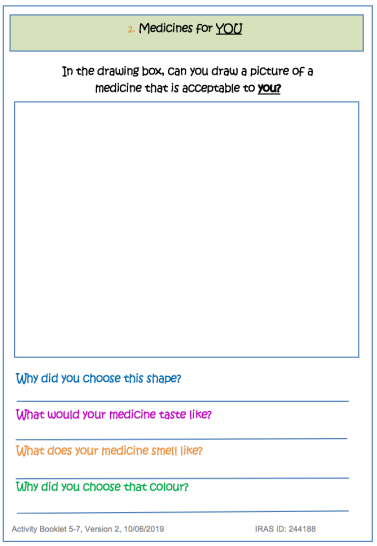
Capsules to swallow

Inhalers

Liquid medicine

Chewable tablets

What do you think it means when someone asks if a medicine is acceptable?



2. Medicines for YOU

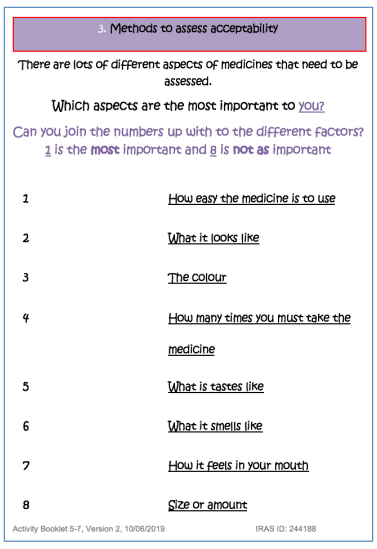
In the drawing box, can you draw a picture of a medicine that is acceptable to **YOU**?

Why did you choose this shape?

What would your medicine taste like?

What does your medicine smell like?

Why did you choose that colour?



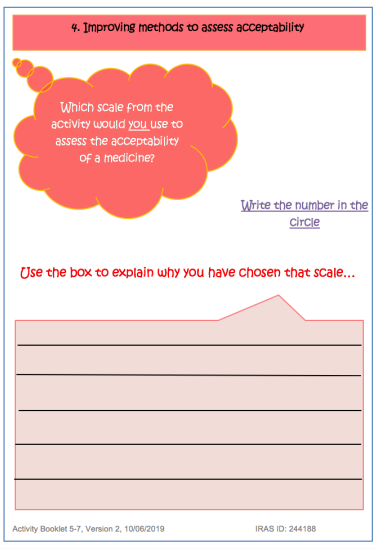
3. Methods to assess acceptability

There are lots of different aspects of medicines that need to be assessed.

Which aspects are the most important to you?

Can you join the numbers up with to the different factors? 1 is the **most** important and 8 is **not as** important

1	How easy the medicine is to use
2	What it looks like
3	The colour
4	How many times you must take the medicine
5	What is tastes like
6	What it smells like
7	How it feels in your mouth
8	Size or amount

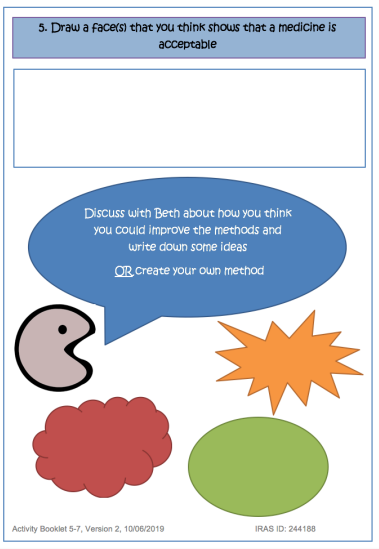


4. Improving methods to assess acceptability

Which scale from the activity would you use to assess the acceptability of a medicine?

Write the number in the circle

Use the box to explain why you have chosen that scale...

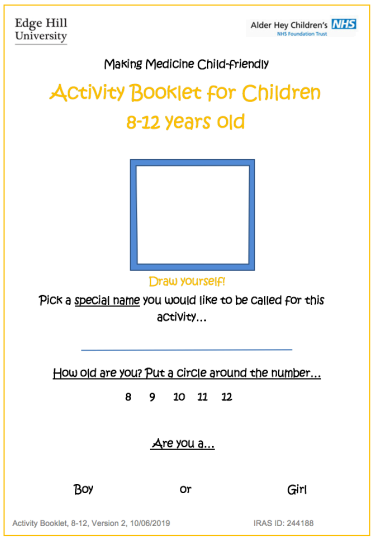


5. Draw a face(s) that you think shows that a medicine is acceptable

Discuss with Beth about how you think you could improve the methods and write down some ideas

OR Create your own method

Appendix 30b: Activity booklet (hospital, 8-12yrs)



Edge Hill University

Alder Hey Children's NHS

Making Medicine Child-Friendly

Activity Booklet for Children 8-12 years old

Draw yourself!

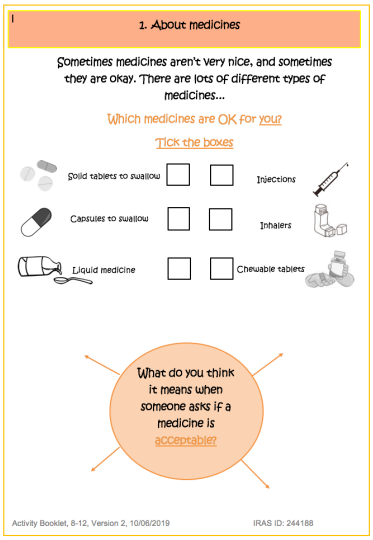
Pick a special name you would like to be called for this activity...

How old are you? Put a circle around the number...

8 9 10 11 12

Are you a...

Boy or Girl



1. About medicines

Sometimes medicines aren't very nice, and sometimes they are okay. There are lots of different types of medicines...

Which medicines are OK for you?

Tick the boxes

Solid tablets to swallow

Injections

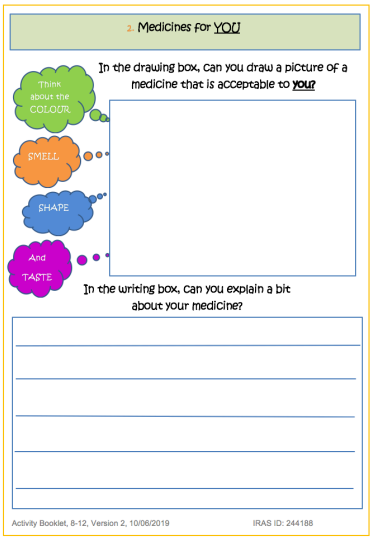
Capsules to swallow

Inhalers

Liquid medicine

Chewable tablets

What do you think it means when someone asks if a medicine is acceptable?



2. Medicines for YOU

In the drawing box, can you draw a picture of a medicine that is acceptable to **you**?

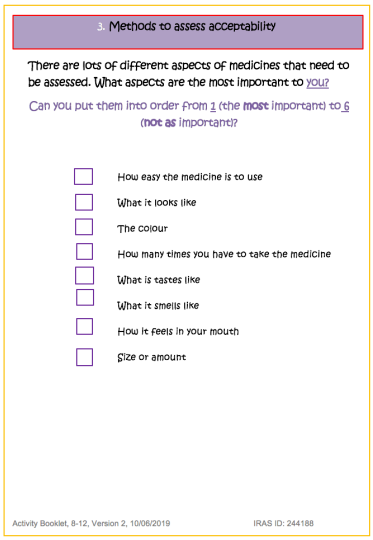
Think about the COLOUR

SMELL

SHAPE

And TASTE

In the writing box, can you explain a bit about your medicine?

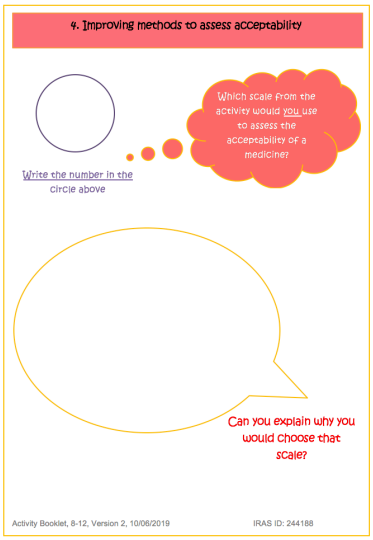


3. Methods to assess acceptability

There are lots of different aspects of medicines that need to be assessed. What aspects are the most important to you?

Can you put them into order from 1 (the **most** important) to 6 (**not as** important)?

- How easy the medicine is to use
- What it looks like
- The colour
- How many times you have to take the medicine
- What is tastes like
- What it smells like
- How it feels in your mouth
- Size or amount

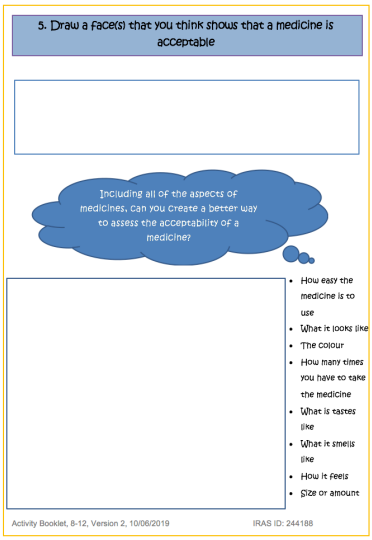


4. Improving methods to assess acceptability

Write the number in the circle above

Which scale from the activity would you use to assess the acceptability of a medicine?

Can you explain why you would choose that scale?



5. Draw a face(s) that you think shows that a medicine is acceptable

Including all of the aspects of medicines, can you create a better way to assess the acceptability of a medicine?

- How easy the medicine is to use
- What it looks like
- The colour
- How many times you have to take the medicine
- What is tastes like
- What it smells like
- How it feels
- Size or amount

Appendix 31: Certificate of participation (hospital)

CERTIFICATE *Of* PARTICIPATION

Thank you for taking part in the Designing Acceptability Tools for Children's Medicine Research Study

at Alder Hey Children's Hospital.

Name: _____

Signed: Beth Gibson

Alder Hey Children's NHS Foundation Trust | Edge Hill University

A big thank you from Edge Hill University and Alder Hey Children's Hospital Foundation Trust

Certificate of participation, Version 3. 13/03/2019

IRAS ID: 244188

Appendix 32: Semi-structured interview guide

Semi-structured workshop guide- Children 5-12 years

Phase 1 a) workshops- Pre-amble: Thank you all for joining me today to take part in the workshop. This workshop will be about understanding your thoughts and feelings towards medicine that you might sometimes take. We are going to do a few different activities using the worksheet and booklet to help us, and then we will try and arrange our drawings in an order so that we can see what things we like the best about our medicine and what things we like the least.

Opening questions (generate understanding and perceptions children have of medicine):

1) Start with a 5 minute intro discussion, 'We are going to have a little chat about different medicines that we might know of or have taken. Does anybody know what medicine is used for? Has anybody been given medicine before? What types of medicine have you had/do you know of?
2) (Using toy doctor doll) 'This is Dr.Diamond who needs out help in making some new medicine better for children, we are going to pass Dr.Diamond around the circle and when it gets to you, can we tell Dr.Diamond what we think about medicine, what is nice and what is not nice? Good and bad?'
   Prompts: What about the smell/taste/feel/sound?
   What kind of medicine helps us to feel better?
   (Researcher will do quick transcription of ideas/thoughts/answers on board/paper).

Main body questions and activities (20 minutes):

Activity 1- Creating own medicine:

1) Now we are all going to make our own marvellous medicine so Dr. Diamond can see all your great ideas, using the activity sheets to help can you draw a picture of a good medicine or a bad medicine? (Using scented pens/pencils, shape stencils, stamps to incorporate as many aspects of medicine as possible- 15 minutes)
2) Circle/group discussion (5-7 years) - child will present their medicine to group one by one.
   Researcher will prompt explanation about things missed out- why that colour? Smell? Shape/type of medicine? Name? What does the medicine do? What does it taste like?
3) Extra writing time (8-12 years) – older children will have the option of writing their explanations or talking with the group/researcher about their drawing.

Activity 2- Ranking aspects of medicine:

1) Dr.Diamond needs to know which parts of your medicine are the most important, we are going to use some flash cards that have different things on them and put them in order. (Smell cards/Taste cards/Shape or form card packs- plus any additional aspects the children come up with within the sessions will be put onto a flashcard). The children will then interact with typical and novel scales/games and have the opportunity to discuss in the group what they like and dislike about each scale.
   - Typical ranking scale (hedonic/bar chart)- emoji's/stickers

Activity 2: Critiquing existing acceptability scales:

1) Children will be provided with a Hedonic Scale and VAS and asked to use one of the medicines to complete each scale. Each child will interact with both scales and then a short group discussion about what they each liked and disliked about each scale will take place. This aims to offer the children an opportunity to evaluate and compare scales, and also leads into the re-development of the scales by giving the children to opportunity to offer ways that they could be improved, or alternate ways to test acceptability.
2) The children will then be given a short time (10 minutes) to create their own ways to test acceptability, either through the use of a typical paper scale- or other options (previously discussed in the first workshops) will be re-introduced for them to interact with. Pictures of outputs from the initial workshops will be available for the children to look at and take ideas from and they will be provided with a number of tools to help them in their development:
   - Check-lists
   - Post-it notes
   - Stickers
   - Sticky paper
   - Emoji markers
   - Lego

Closing Questions (10 minutes)

1) Children will be asked to provide an explanation for why they chose the method/tool-
   - Why did you use that form/game/layout?
   - Can you explain why you chose the colours/pictures?
   - Who is this for? Girl/boy/young/older child?
   - What makes this better than the methods/scales we have already looked at?
2) Ask them to use group evaluation via stickers/hand raising/manzano scale to see whether the other children like/dislike/think the scale is ok.
3) Any questions?

Thank you all so much for all of your help, you have been great. If you want to take your scales/measurements/games home you can, but can I take a picture of them first? If you don't want to take them then you can leave them here and I will take them back to Dr.Diamond. (Children will be rewarded with a small thank you gesture- such as a certificate and small badge/sticker).

The audio/video recorder will remain on until the children have left the room.

Phase 2- workshops- Pre-amble: thank you for all joining me today to take part in the workshop.
Testing methods with children: The most promising methods and measures that have been developed/re-developed in Phase 1 will be given to groups/workshops of children to evaluate them. In this workshop children will be able to offer their advice on the scales and a designer may be on hand to help and support the final design changes.

- Floor scales- footprints/ladder, Hula hoop game
- Wall charts- Velcro/Pegs
- Manzano scales

Closing Questions

1) Is there anything else you want to tell Dr.Diamond about medicine before we go?
2) Which ranking games/scales did you enjoy most? Why? (depending on time)
3) Do you have any questions for me?

Thank you all so much for all of your help, you have been great. If you want to take your pictures/letters home you can, but can I take a picture of them first? If you don't want to take them then you can leave them here and I will take them back to Dr.Diamond. (Children will be rewarded with a small thank you gesture- such as a certificate and small badge/sticker).

The audio/video recorder will remain on until the children have left the room.

Phase 1b) workshops- Pre-amble: thank you for all joining me today to take part in the workshop. In this workshop we will look at some of the existing ways that we can test the acceptability of medicine and try to redevelop them using games, pens, stickers etc.

Opening questions- focus on the consultation, evaluation, assessment and re-development of methods used to test paediatric acceptability:

1) Begin with a short introduction to medicine- discuss the different types of medicine/what it is used for. 'We are going to have a little chat about different medicines that we might know of or have taken. Does anybody know what medicine is used for? Has anybody been given medicine before? What types of medicine have you had/do you know of?

Main body questions and activities (30 mins):

Activity 1- Acceptability triggers:

1) There are some different packages of medication out on the tables, they are all empty and don't have anything in them that could be harmful. I would like you to have a look, touch, feel of the different medicine packages and think about what you like or dislike about them, what makes them 'good' or just 'okay' or even 'bad'. Think about if you have ever used any of them and what you can remember about them.
   - (Children will be provided with prompts such as: post-it notes, sentence starters, 'wishes', word-choice prompts and unfinished stories to help them to engage with the evaluation of the items.)
2) The children will then be shown some novel forms of medicine- such as 'medicine straws', 'lego jellies', plaster patches, animal inhalers etc. and asked to verbally evaluate and compare these with the 'normal' medication (through discussion).

Testing methods with adult stakeholders: Clinicians, pharmacists, researchers, parents, teachers etc. will all be involved in phase 2 of the study, to evaluate the acceptability of the measures/methods that have been designed. It is important that these groups are consulted so that all users of the measures/methods have input to their development and design.

Appendix 33: Semi-structured activity guide (hospital)

Semi-structured activity guide- Alder Hey Children 5-12 years old

Pre-amble: Thank you for agreeing to take part in the study with me today. The activities that you will do are about understanding your thoughts and feelings towards medicine that you might sometimes take. We are going to do a few different activities using the booklet to help us.

Opening questions: (generate understanding and perceptions children have of medicine)

1) Start with a 5 minute intro discussion, 'If it is ok with you we are going to have a little chat about different medicines that we might know of or have taken. Do you know what medicine is used for? Have you been given medicine before? What types of medicine have you had/do you know of?
2) Can you tell me a little bit about what you think about medicine, what is nice and what is not nice? Good and bad?'
   Prompts: What about the smell/taste/feel/sound?
   What kind of medicine helps us to feel better?
   (Researcher will do quick transcription of ideas/thoughts/answers on board/paper).

Main body questions and activities (20 minutes):

Activity 1: Activity workbook

1) Here I have a little workbook for you to fill in. There are lots of different activities on each page, the first one is about drawing and designing your very own medicine that you think would be acceptable for children like you. (Using scented pens/pencils, shape stencils, stamps to incorporate as many aspects of medicine as possible). Researcher will discuss drawing with child and will prompt explanations about things missed out- why that colour? Smell? Shape/type of medicine? Name? What does the medicine do? What does it taste like?
2) The second activity is about your opinion on the medicines we use to make us better. Can you tick the boxes next to the medicines that you are OK with? Researcher will discuss what acceptable means with the child and will help them to write some ideas down.
3) The researcher will explain a little bit about activity 3, that pharmacists and researchers need to know what children think about medicine in order to make it better for them. Researcher will ask the children to put the aspects of medicine into order using numbers.
4) Activity 4: the researcher will provide the children with some examples of currently used methods and scales that evaluate the acceptability of medicine with children. The children will be asked to choose their favourite scale and explain why using the speech bubbles.
5) The researcher will then ask the children how the scales could be made better, and by using page 5 in the activity workbook the children can design their own 'faces' or scales to show or test acceptability.

Closing questions

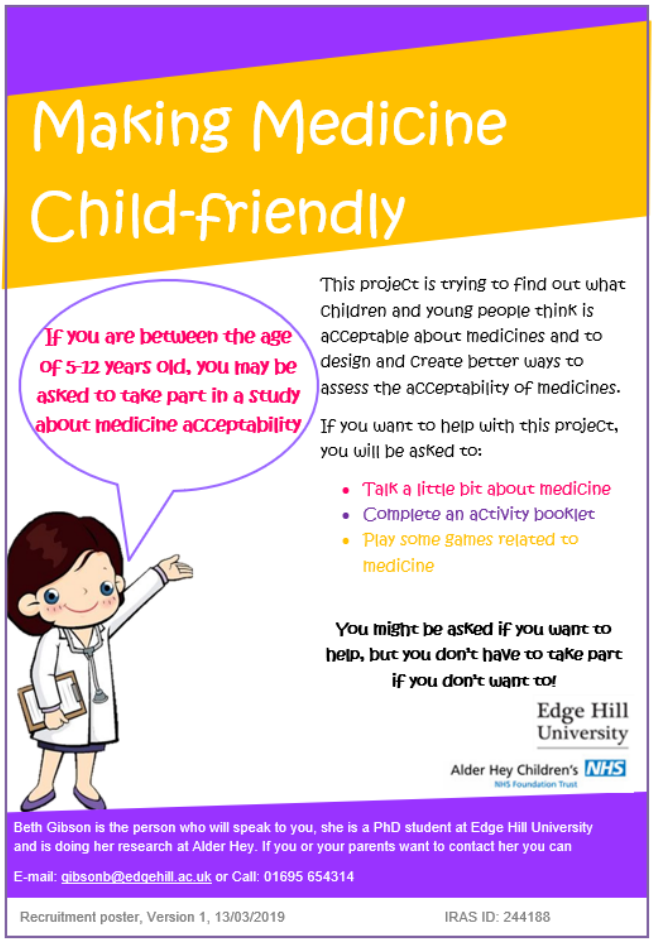
1) Is there anything else you want to tell me about medicine before we go?
2) Do you have any questions for me?

Thank you so much for all of your help, you have been great. If you want to take your activity booklet home you can, but can I take a picture of them first? If you don't want to take them then you can leave them here and I will keep them safe with me. (Children will be rewarded with a small thank you gesture- such as a certificate and small badge/sticker).

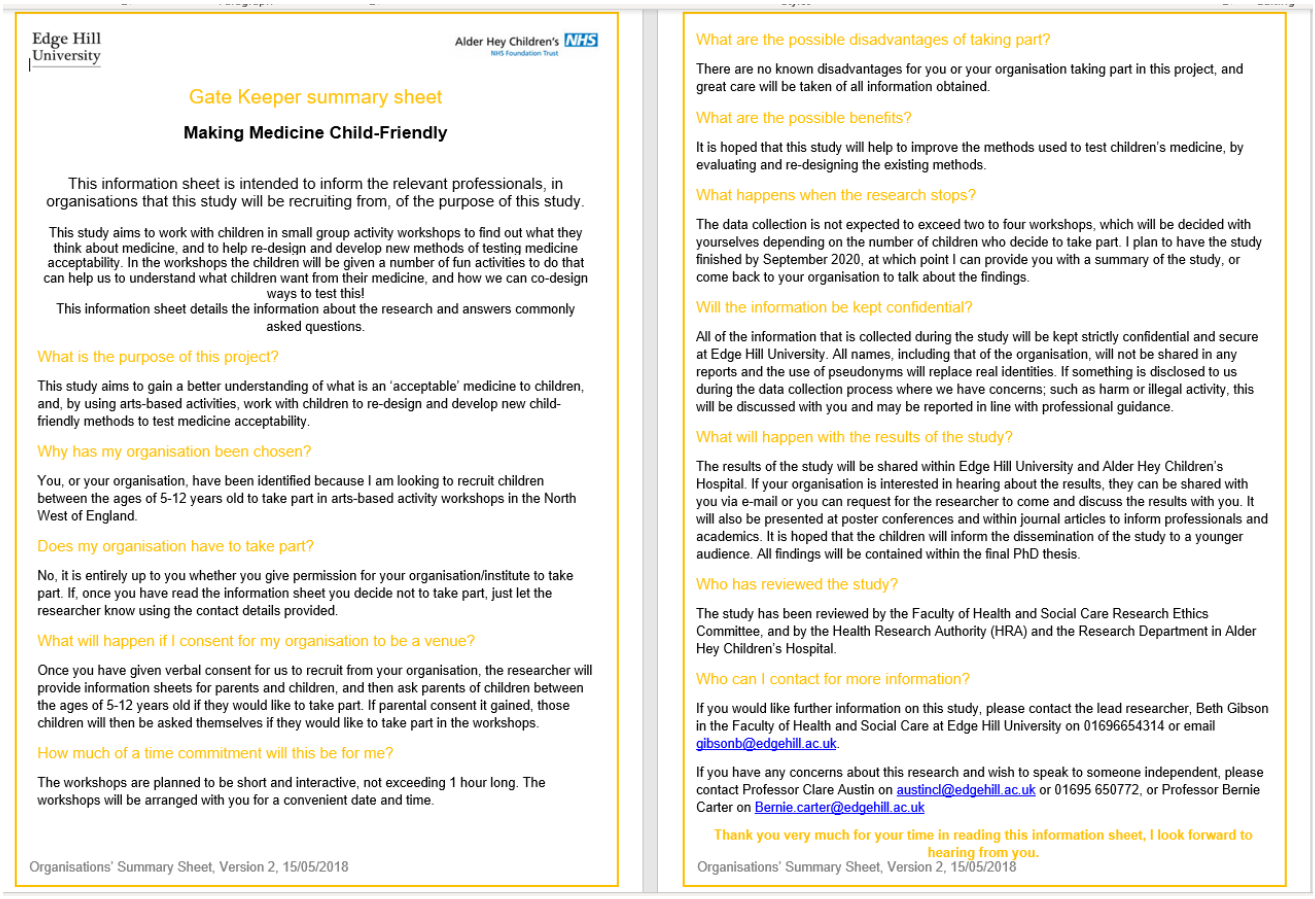
The audio/video recorder will remain on until the children have left the room.

AH Workshop Guide, Version 2, 20/03/2019 IRAS ID: 244188

Appendix 34: Recruitment poster (hospital)



Appendix 35: Gate keeper summary sheet



Edge Hill University

Alder Hey Children's NHS
NHS Foundation Trust

Gate Keeper summary sheet

Making Medicine Child-Friendly

This information sheet is intended to inform the relevant professionals, in organisations that this study will be recruiting from, of the purpose of this study.

This study aims to work with children in small group activity workshops to find out what they think about medicine, and to help re-design and develop new methods of testing medicine acceptability. In the workshops the children will be given a number of fun activities to do that can help us to understand what children want from their medicine, and how we can co-design ways to test this!
This information sheet details the information about the research and answers commonly asked questions.

What is the purpose of this project?

This study aims to gain a better understanding of what is an 'acceptable' medicine to children, and, by using arts-based activities, work with children to re-design and develop new child-friendly methods to test medicine acceptability.

Why has my organisation been chosen?

You, or your organisation, have been identified because I am looking to recruit children between the ages of 5-12 years old to take part in arts-based activity workshops in the North West of England.

Does my organisation have to take part?

No, it is entirely up to you whether you give permission for your organisation/institute to take part. If, once you have read the information sheet you decide not to take part, just let the researcher know using the contact details provided.

What will happen if I consent for my organisation to be a venue?

Once you have given verbal consent for us to recruit from your organisation, the researcher will provide information sheets for parents and children, and then ask parents of children between the ages of 5-12 years old if they would like to take part. If parental consent it gained, those children will then be asked themselves if they would like to take part in the workshops.

How much of a time commitment will this be for me?

The workshops are planned to be short and interactive, not exceeding 1 hour long. The workshops will be arranged with you for a convenient date and time.

What are the possible disadvantages of taking part?

There are no known disadvantages for you or your organisation taking part in this project, and great care will be taken of all information obtained.

What are the possible benefits?

It is hoped that this study will help to improve the methods used to test children's medicine, by evaluating and re-designing the existing methods.

What happens when the research stops?

The data collection is not expected to exceed two to four workshops, which will be decided with yourselves depending on the number of children who decide to take part. I plan to have the study finished by September 2020, at which point I can provide you with a summary of the study, or come back to your organisation to talk about the findings.

Will the information be kept confidential?

All of the information that is collected during the study will be kept strictly confidential and secure at Edge Hill University. All names, including that of the organisation, will not be shared in any reports and the use of pseudonyms will replace real identities. If something is disclosed to us during the data collection process where we have concerns; such as harm or illegal activity, this will be discussed with you and may be reported in line with professional guidance.

What will happen with the results of the study?

The results of the study will be shared within Edge Hill University and Alder Hey Children's Hospital. If your organisation is interested in hearing about the results, they can be shared with you via e-mail or you can request for the researcher to come and discuss the results with you. It will also be presented at poster conferences and within journal articles to inform professionals and academics. It is hoped that the children will inform the dissemination of the study to a younger audience. All findings will be contained within the final PhD thesis.

Who has reviewed the study?

The study has been reviewed by the Faculty of Health and Social Care Research Ethics Committee, and by the Health Research Authority (HRA) and the Research Department in Alder Hey Children's Hospital.

Who can I contact for more information?

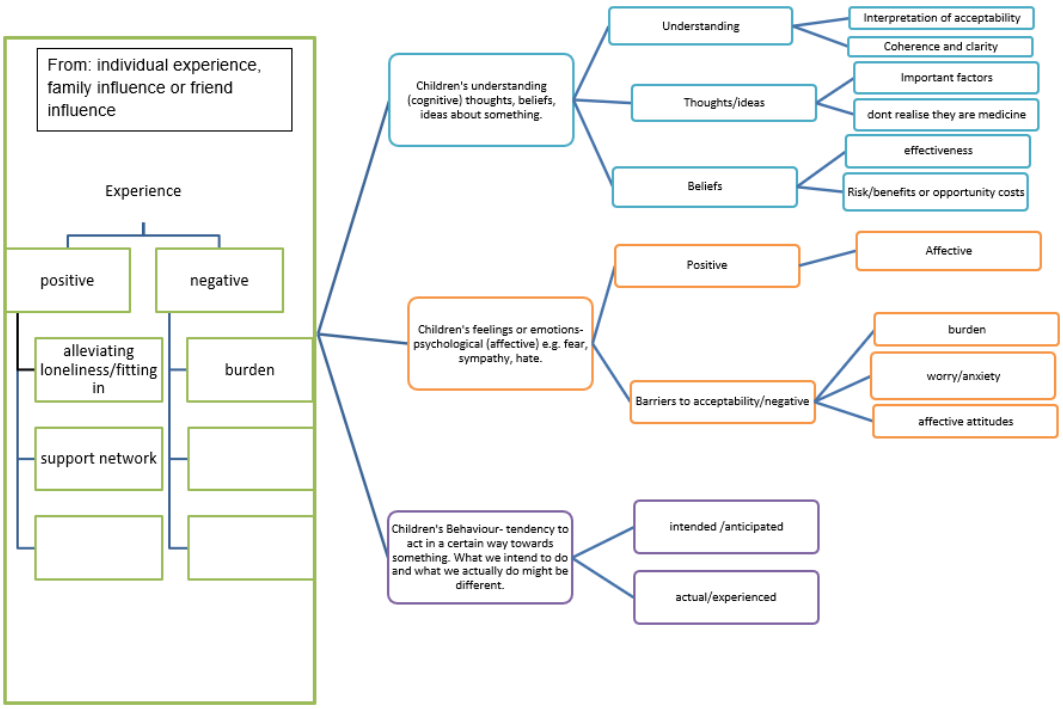
If you would like further information on this study, please contact the lead researcher, Beth Gibson in the Faculty of Health and Social Care at Edge Hill University on 01696654314 or email gibsonb@edgehill.ac.uk.

If you have any concerns about this research and wish to speak to someone independent, please contact Professor Clare Austin on austincl@edgehill.ac.uk or 01695 650772, or Professor Bernie Carter on Bernie.carter@edgehill.ac.uk

Thank you very much for your time in reading this information sheet, I look forward to hearing from you.

Organisations' Summary Sheet, Version 2, 15/05/2018

Appendix 36: Preliminary framework



Appendix 37: Table detailing the number of children who participated in each activity

	Schools			Clubs				Hospital	Museum	Total
Groups	**S1G1**	**S1G2**	**S2G1**	**R1W1**	**R1W2**	**R2**	**B1**	**Ward**	**Museum**	**Total**
Total	3	3	2	7		4	8	3	81	111
Drawing & Discussion	8			19				3	81	111
Activity sheets	5			19				0	81	105
Ranking activities	8			19				0	81	Unknown engagement
Activity booklets	5			11				3	0	19
Audio recorded	Yes, 3 recordings.			Yes, 4 recordings.				Yes, 3 recordings.	No	10