Establishing the burden of polypharmacy on paediatric patients and their parents

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Abstract

Background: Burden of care describes the effects of providing care on carers and treatment burden describes the impact of treatments on patients and caregivers. Polypharmacy is often defined as using ≥2 medicines for paediatric patients. Polypharmacy can increase the risk of health consequences and can lead to a prescribing cascade. Existing studies have assessed the burden of care and treatment burden for various conditions. However, there is a lack of information on polypharmacy related treatment burden in paediatric patients and no known reviews to date about it.

Aims: The overall aim of this study was to determine the impact polypharmacy has on the burden of care for paediatric patients and their parents/caregivers. The systematic review aimed to review the existing literature exploring the domains related to medications that contribute to polypharmacy related treatment burden. The PANDA (Polypharmacy ANd Drug optimisAtion) study aimed to assess the polypharmacy related treatment burden for paediatric patients and their parents.

Methods: A precursor systematic review was conducted by searching for papers on Medline, CINAHL, EMBASE, Web of Science and Cochrane database of systematic reviews to find relevant papers. The review was registered with PROSPERO (PROSPERO registration number: CRD42021285097) and conducted according to PRISMA methodology.

The findings from the systematic review were used to develop a questionnaire for the PANDA study. The questionnaire was validated and altered before recruiting patients. Paediatric patients in inpatient and outpatient settings who were taking ≥5 regular medicines were recruited. Parents completed the questionnaire and responses were analysed in Qualtrics and Excel.

Results: The systematic review identified 6 papers with 8276 participants. The domains most commonly assessed were the perceived effectiveness of medications (4/6 studies), psychosocial impact (3/6 studies) and the impact on work and school (3/6 studies). Other domains included the ease of use of medicines, side effects, adherence to medicines, time requirements, costs, using healthcare resources and support from family/friends/organisations.

36 participants were recruited in the PANDA pilot study. Patients ranged from 3 months old to 16 years and 4 months old and took between 5 and 43 medicines, with the median being 15 medicines. The domains that had a bigger impact on participants were time requirements, side effects, factors affecting adherence to medicines and the psychological impact of medicines.

Conclusions: The systematic review showed that studies assessing the burden of care due to medicines assessed a range of domains related to the impact of medicines on patients and caregivers.

The PANDA pilot study demonstrated the polypharmacy related treatment burden in a group of parents looking after paediatric patients. It also demonstrated the most important domains to consider in future versions of the questionnaire and future studies assessing polypharmacy related treatment burden.

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List of abbreviations

ADHD	Attention-Deficit Hyperactivity Disorder
ADR	Adverse Drug Reaction
AKI	Acute Kidney Injury
ALS	Amyotrophic Lateral Sclerosis
ANM	Axillary Nurse Midwife
ASD	Autism Spectrum Disorder
ASD	Atrial Septal Defect
CarerQoL	Care-related Quality of Life
CDS	Caregivers Difficulties Scale
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CHQ	Child Health Questionnaire
CHQ-PF50	Child Health Questionnaire Parent Form
CKD	Chronic Kidney Disease
CSI	Caregiver Strain Index
CVI	Content Validation Index
HCRW	Health and Care Research Wales
HDAS	Healthcare Databases Advanced Search
HDU	High Dependency Unit
HIV	Human Immunodeficiency Virus
HRA	Health Research Authority
HRQoL	Health Related Quality of Life
I-CVI	Content Validation Index for Items
IFS	Impact on Family Scale
MCSI	Modified Caregiver Strain Index
MPOC-20	Measure of Processes Of Care
MTBQ	Multimorbidity Treatment Burden Questionnaire
NHATS	National Health and Aging Trends Study
NSAID	Non-Steroidal Anti-Inflammatory Drugs
OTC	Over The Counter
PANDA	Polypharmacy ANd Drug optimisAtion
PedsQL	Paediatric Quality of Life Inventory
PedsQLFIM	Pediatric Quality of Life Inventory Family Impact Module
PETS	Patient Experience with Treatment and Self management
PFMS	Parent Fever Management Scale
PIP	Paediatric Inventory for Parents
PIPc	Potentially Inappropriate Prescribing in children
POPI	Paediatrics: Omissions of Prescriptions and Inappropriate Prescriptions
PPI	Proton Pump Inhibitor
QI	Quality Improvement
S-CVI	Content Validation Index for Items
SCVI/Ave	Average Content Validation Index for Items
SF-12	Medical Outcomes 12-item Short Form Health Survey
SF-36	Medical Outcomes 36-item Short Form Health Survey
UA	Universal Agreement

US	Utility Score
VAS	Visual Analogue Scale
VSD	Ventricular Septal Defect
WALT	Willingness to Accept Life-sustaining Treatment
WPAI	Work Productivity and Activity Impairment

Chapter 1: Introduction

1.1 Children's health

This section provides an overview into children's health and the use of healthcare resources. Section 1.1.1 describes the state of children's health overall in the UK and issues that affect it. Section 1.1.2 describes how healthcare resources are used in adult and paediatric populations and the number of medicines that are being prescribed.

1.1.1 Overview of children's health

Children's health in the general population is generally good for most children and adolescents, with 94% of boys and 95% of girls stating that their health was good or very good in the Health Survey for England in 2019 (1). However, the survey showed that 14% of children had longstanding illnesses, which is a reduction from 17%-19% between 2003 and 2009 and 20-23% between 1995 and 2002 (1). Older children were more likely to have longstanding illnesses, with 21% of children aged 13 to 15 years and 2% of children aged under two years old having longstanding illnesses (1). 8% of children had acute illnesses, which was a reduction from 14% in 1995 (1).

Common long term conditions for children in the UK include asthma, diabetes and epilepsy (2). There has been progress with outcomes related to these conditions. More paediatric patients with type 1 diabetes have been able to control their blood glucose levels adequately and more patients are having regular health checks. There have also been fewer hospital admissions due to asthma and epilepsy over the last 10 years (2). However, other conditions such as anxiety and depression are becoming more common in children and adolescents (2).

However, while progress has been shown in certain health related outcomes, there are other areas where either progress has stalled or there has been a deterioration seen in the past few years. The Nuffield Trust reports show that the UK has worse outcomes compared to other developed countries in children aged 0-4 years old in infant and early childhood mortality, childhood obesity and female life expectancy (3). In adolescents, they were shown to do less exercise than adolescents in other countries and there was a higher rate of obesity in the UK (3). The burden of disease due to all medical conditions was high among adolescents in the UK, with higher asthma death rates contributing to it (3). Childhood cancers have also been shown to cause a higher childhood mortality as survival rates for some childhood cancers are low in the UK (4).

Various factors such as poverty (5), education levels and delivery of care to patients in healthcare services (3) have been shown to worsen children's health. Poverty and inequalities in the UK mean that disadvantaged children are more likely to die from illnesses and injuries, suffer from mental health problems and are more likely to have worse overall health in adulthood (5). Additionally, in some cases children and adolescents' health needs are not met by healthcare services, which has a direct negative impact on their health both in the short and long term (3).

1.1.2 Use of healthcare resources

In 2010, more than 920 million items were prescribed in primary care for patients of all age groups in England, with the cost of this being more than £8.8 billion (6). The number of medicines prescribed increased to 1104.1 million in 2016, with an average of 20 medicines being prescribed per person (7).

The Children and Young People's Health Services Monthly Statistics Experimental Statistics showed that in July 2017, 178,327 referrals were received by participating sites for 152,714 paediatric patients, with 65% of these referrals for patients aged ≤5 years and 16% of these referrals for patients aged six to 10 years old. There were also 682,058 telephone and face to face appointments for 407,236 children and young people in this time period (8).

1.2 Polypharmacy

This section explores what polypharmacy is and its clinical relevance. Section 1.2.1 explores the various quantitative and qualitative definitions for polypharmacy in the adult and paediatric populations. Sections 1.2.2 describes the prevalence of polypharmacy in different populations and settings. Section 1.2.3 describes the risk factors for polypharmacy and section 1.2.4 describes the potential consequences of polypharmacy in different age groups. Section 1.2.5 then explores the concept of deprescribing and explains why it is important to prevent polypharmacy.

1.2.1 Definitions of polypharmacy

Polypharmacy is often qualitatively defined as the use of multiple medications at one time (9, 10) for both adult and paediatric patients.

In adults, polypharmacy is typically defined as taking five or more medications (10). A review that aimed to define polypharmacy in adults showed that there were variations in the numerical thresholds and time periods used in definitions of polypharmacy. The most common numerical threshold for polypharmacy in adult patients is five or more medications, but the numerical thresholds ranged from two or more medications to 21 or more medications. The time periods used to define polypharmacy ranged from one or more days to 240 or more days, with the most frequently used time period being 90 or more days (10).

The numerical threshold for polypharmacy is often lower in paediatric patients. Polypharmacy is typically defined as taking two or more medications but like in adults, various definitions are used for polypharmacy in children in both research and clinical practice. A scoping review that aimed to find the most frequently quantitative definition used for polypharmacy in paediatric patients also concluded that two medications was the most common threshold used for paediatric polypharmacy. However, the review also found that the time frames used to define polypharmacy varied in different studies. Some studies do not state a specific duration for paediatric polypharmacy whereas other studies defined polypharmacy as taking two or more medications for ≥1 day or ≥30 days (10). Polypharmacy was defined as ≥2 medicines for my systematic review and ≥5 medicines for the PANDA (Polypharmacy ANd Drug optimisAtion) pilot cohort study.

Other factors that cause variations in definitions for paediatric polypharmacy include medication classes, the suitability of the medications prescribed, the medical conditions medications are prescribed for and clinical settings (10).

Polypharmacy has also been grouped into different types and certain terms are also used to describe polypharmacy. Types of polypharmacy include “overlapping” or “concomitant”; “sequential” meaning; “long-term”; “excessive”, “inappropriate” or “irrational”; and “fixed-dose combinations” (10). For example, WHO’s definition refers to polypharmacy as the use of “an excessive number of drugs” (9).

The threshold for polypharmacy can be referred to as the “depth” or “therapeutic load”. The term “cumulative exposure” has been used to describe the number of medications that were prescribed during hospitalisation, and “daily exposure” refers to the number of medications prescribed during hospitalisation per day. “Duplication” has been used to refer to medications that have been prescribed by different clinicians (10).

In certain circumstances, polypharmacy can be described as being ‘problematic’. This would be the case when medicines are prescribed to patients when they are not appropriate for them, the risks of the medicines outweigh the benefits, taking certain medicines together can cause harm to patients or when taking the medicines is no longer manageable for patients (7).

Polypharmacy can also lead to a “prescribing cascade”. This is when another medicine is prescribed to address adverse effects from other medicines. This can subsequently lead to an increased risk of further adverse effects due to taking more medicines. A common example of this in adult medicine is prescribing levodopa to patients with parkinsonian symptoms caused by taking metoclopramide (7). An example in paediatrics is prescribing laxatives for babies or children using Gaviscon or other feed thickeners for gastro-oesophageal reflux.

1.2.2 Prevalence of polypharmacy

The prevalence of polypharmacy varies in adult and elderly patients. A study assessing the prevalence of polypharmacy in the Scottish general population showed that 16.9% of adult patients were prescribed four to nine medications and that 4.6% were prescribed 10 or more medications in primary care (11). Polypharmacy is more prevalent in older patients as the number of medications prescribed increases with age. A study on polypharmacy in adults showed that 28.6% of patients aged 60-69 years and 51.8% of patients aged ≥80 years were prescribed four to nine medications. Additionally, 7.4% of patients aged 60-69 years and 18.6% of patients aged ≥80 years were prescribed ≥10 medications. In contrast, a much smaller proportion, 2.2%, of patients aged 20-29 were prescribed ≥4 medications (11). Published statistics also showed that one third of people aged over 75 years were taking six or more medicines in England (7).

In children, there is significant variation in the prevalence of polypharmacy recorded in paediatric patients. In one review, the prevalence of polypharmacy in children varied from 0.9% of patients accessing financial assistance for their treatment to 98.4% of ill children who accessed healthcare services, with a median of 39.7% (12). Another review showed that the prevalence of paediatric polypharmacy varied from 18% to 100% across three studies (10). It is also known that polypharmacy is common in hospitalised children, with children in intensive care taking 10 medications a day on

average during their hospitalisation and being prescribed 20 medications when they have been discharged (13).

1.2.3 Risks factors for polypharmacy

Several factors have been shown to increase the risk of polypharmacy. Patients' overall health status, frailty in older patients and patients' underlying diagnoses can all increase the risk of polypharmacy. Prescribing patterns can also increase the risk of polypharmacy. Prescribing more medications instead of deprescribing unnecessary and potentially harmful medications to address or prevent adverse effects increases the number of medications patients are taking at one time. Patients taking unprescribed medications such as over the counter (OTC) medications and supplements adds to the number of medications they take and therefore risk of polypharmacy (14). In some cases, medications are prescribed inappropriately, which also adds to the number of medications patients are taking at one time (9).

Demographic factors such as age, sex and education levels have also been shown to affect the risk of polypharmacy (9). Increasing age can increase the risk of having long term conditions, in one study 58% of people over 60 years and 14% of people less than 40 years old had long term conditions (7). Socioeconomic status can also affect the risk of having long term conditions. People from the lowest social class are 60% more likely to have long-term conditions than people in the richest social class (7). Patients with multiple medical conditions have been shown to be more likely to experience polypharmacy. A study showed that 20.8% of adult patients with two medical conditions and 47.7% of adults with ≥6 medical conditions were prescribed four to nine medications. 41.7% of patients with ≥6 medical conditions were prescribed ≥10 medications. Patients with no medical conditions were less likely to be prescribed multiple medications, with only 0.3% of these patients being prescribed ≥4 medications (11).

Healthcare environments have been shown to affect polypharmacy, with a higher prevalence of polypharmacy in hospital environments compared to the community. Polypharmacy has been shown to be more prevalent in hospital and ambulatory settings compared to community settings. A review on the prevalence of polypharmacy in different settings showed that 36 - 37.1% of elderly patients from the ages 75 to 85 in ambulatory settings and 58.6% of patients in hospital settings were experiencing polypharmacy, which was defined as taking five or more medications. However, two studies by Dwyer and Bronskill included in this review showed that 39.7% and 15.5% respectively were experiencing polypharmacy, which here was defined as taking nine or more medications (14).

Unlicensed medications are more commonly prescribed in children as there is less guidance on prescribing for children in some conditions, and it is another factor that increases the risk of polypharmacy (13).

In children, polypharmacy has also been shown to be more common in children with conditions such as attention-deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) (13). In adults, individual cardiovascular diseases such as heart failure, ischaemic heart disease and atrial fibrillation are associated with higher rates of polypharmacy (11).

1.2.4 Consequences of polypharmacy

Polypharmacy is necessary in some cases as the recommended management of medical conditions such as diabetes mellitus involve the use of multiple medications. As patients with multiple medical conditions need medications to address these conditions to prevent their health from deteriorating (15).

Whilst polypharmacy has shown to be beneficial in certain ways discussed above, polypharmacy can also increase the risk of consequences that affect patients' health and healthcare systems.

Polypharmacy has been shown to negatively impact patients' health through an increased risk of drug interactions and other side effects including adverse drug reactions (ADR), hospital admissions, reduced adherence to medications due to an excessive number of medications and mortality (10). One study showed that 6.5% of hospital admissions were due to ADRs, 70% of which were preventable (7). Taking several medications, including unlicensed medications prescribed for some conditions, has been shown to increase the risk of adverse drug reactions (13). Another study also demonstrated this and reported that for each extra medicine that was prescribed the risk of ADRs increased by 1.25 (16). Unlicensed medicines and off-label medicines have also been shown to be more likely to cause ADRs than other prescribed medicines (17).

Polypharmacy can also affect healthcare systems as prescribing lots of medications increases the money spent on medications and resources by hospitals and other healthcare services (10). It also increases the burden placed on healthcare services and staff due to patients needing more appointments, prescriptions for medications as well as the space and resources required for hospital admissions. Hospital admissions are more likely in people taking lots of medicines, with patients taking 10 or more medicines being three times at risk of being hospitalised (7).

It can also increase the burden of care for patients and their families if patients are dependent on their family to provide care for them. This is likely to be the case for more vulnerable and less independent patients such as children, patients with impairments and elderly patients (10), but has not been explored previously.

1.2.5 Deprescribing

Deprescribing refers to stopping medications for which the potential risks outweigh their benefits. It is an important step to consider when reviewing patients' medications along with ensuring patients are adhering to their medications, and considering potential drug interactions and adverse drug effects. This becomes more crucial when patients are taking several medications to prevent the potential consequences discussed earlier (15).

Rational prescribing refers to prescribing medicines that are clinically appropriate for patients at the correct doses and for the correct time period in a cost-effective manner. Some tools, such as the Paediatrics: Omissions of Prescriptions and Inappropriate Prescriptions (POPI) tool, the modified POPI tool used in the UK and the Potentially Inappropriate Prescribing in children (PIPc) tool were developed to ensure rational prescribing before attempts were made to encourage deprescribing in

paediatrics. These tools included several aspects of inappropriate prescribing including overprescribing medicines (18).

Deprescribing can be a challenge for clinicians for several reasons. A doctor may prescribe medications for a child but as different clinicians are involved at various points of children's care, it is often the case that a different doctor makes decisions about changing the child's medications. Doctors involved in changing children's medications may prefer to add medications instead of removing medications to address potential adverse effects and because they may not want to go against the original prescriber's decision (13). Another reason why clinicians are worried about deprescribing medications is because stopping a medication could cause the patient's family to worry about the patient's health. A lack of knowledge about the medication and not having guidelines on stopping certain medications also prevented clinicians from deprescribing medications that were no longer necessary. Time constraints were also another factor that prevented clinicians from stopping medications (19).

1.3 Burden of care and treatment burden

Burden of care is a term that describes the effects of providing care on a carer's own health and wellbeing. This includes the physical, emotional, social and financial consequences of caregiving (20) as well as other constraints due to the added responsibilities (21) from caring for people with acute or chronic diseases. Burden of care can be affected by various factors such as social and economic status and social support for caregivers (22). Other aspects that have been assessed in studies on the burden of care in specific conditions include caregivers' coping skills (23), the way time is allocated to different aspects of care (24), the effects of chronic conditions on patients' lifestyles and education for paediatric patients (25).

Burden of treatment refers to the impact of healthcare and treatment for medical conditions on patients' and caregivers' functioning and wellbeing (26). This includes the efforts made by caregivers to administer treatment, ensure the patient is adhering to it and organising care for the patient (27, 28). Factors such as the frequency of administration and side effects of medications can negatively affect the burden of treatment for patients, which may lead to non-adherence to treatment as well as clinical consequences (29).

Existing studies on burden of care have shown that medical conditions themselves can impact patients' and parents' quality of life. Studies assessing the treatment burden for medical conditions have also explored the ways various treatments can affect patients' and families' lives but these studies do not always specifically assess the impact of medicines on patients and families. As polypharmacy has been shown to cause certain consequences, the studies presented in this thesis aim to determine the impact of medicines on patients and families and explore how this has been assessed in existing studies.

This section explores the methods in which burden of care and treatment burden have been assessed in existing studies. Section 1.3.1.1 explores existing tools that have been used in studies that assessed the burden of care for caregivers of both adult and paediatric patients. Section 1.3.1.2 explores the quantitative tools and questionnaires that have been used to assess the overall quality of life in caregivers and patients with certain medical conditions. 1.3.1.3 discusses the questions that have been asked in quantitative studies assessing the burden of care for caregivers. Section 1.3.2 explores the methods used to assess treatment burden for patients and caregivers. Section 1.3.3 discusses the

common findings in existing studies that have assessed the burden of care or treatment burden for patients and/or caregivers.

1.3.1 Methods of assessing burden of care

1.3.1.1 Assessing caregiver burden in quantitative studies

Several instruments have been used in quantitative studies assessing the burden of care for caregivers of paediatric and adult patients with various conditions. In some cases, multiple instruments have been used to assess the burden of care and collect other relevant information, such as demographic information about the caregivers and patients (23, 30-38). Some of these instruments are developed to assess burden of care experienced by caregivers and some tools assess the burden of care for patients themselves.

One instrument that is commonly used in studies assessing the burden of care for caregivers of paediatric patients is the Zarit Caregiver Burden Scale (30). It aims to quantify the effects of caring for family members on various aspects of caregivers' lives. This includes their mental health, physical health, emotional and social functioning, financial situation and relationships with their families and other people. It can be administered as a questionnaire or through face to face interviews (30), and is therefore referred to as the Zarit Burden Interview (39-42) or the Zarit Burden questionnaire (35) in some studies. It is also commonly used in studies assessing the burden of care for caregivers of adult patients, with one systematic review assessing methods of assessing burden of care for caregivers of adult patients receiving dialysis showing that the Zarit Burden Interview was the most frequently used tool (39). The questions in the Zarit Caregiver Burden Scale assess the impact of caregiving on various aspects of caregivers' lives but none of the questions are not linked to the impact of medicines (30).

The Burden of Care tool is another instrument that assess caregiver burden for caregivers. It consists of 22 items assessing caregiver burden in five categories. It assessed caregiver burden through questions on the pressures caregivers experience, perceived loneliness, concerns they have with their finances and physical health, emotional problems such as anger and embarrassment, and their ability to deal with problems they encounter with patient care. This tool assesses caregiver burden by determining how difficult certain aspects of caregivers' lives are due to caregiving but none of these are linked to medicines or polypharmacy (43).

The Caregiver Burden Inventory is a survey consisting of 24 items that are categorised into five subscales. These items assess the effects of caregiving on their time, physical health, social functioning and emotional functioning. Items are rated on a 5-point scale and higher scores mean that the burden caregivers are experiencing is high. The items in the Caregiver Burden Index aimed to determine the overall impact of caregiving on caregivers' quality of life rather than the impact of medicines on their quality of life, and none of the questions were related to the impact of medicines or polypharmacy. The items assess the impact of managing children's medical conditions on caregivers but none of the items ask about the impact of medicines (44).

The Caregiving Burden Scale was also developed and validated for caregivers looking after children with cancer. It assessed the effect of caregiving on caregivers' physical health, emotional functioning, social functioning and finances. The questions in this tool were related to the consequences of caregiving but they were not related to the patients' medicines or polypharmacy (45).

The Paediatric Renal Caregiver Scale is a 51 item scale that was developed to assess caregiver burden for caregivers of paediatric patients with chronic kidney disease (CKD). It addresses how the child's CKD affects caregivers physically, financially, socially and emotionally. It also addresses how caring for children with CKD affects their families, problems related to the treatment for CKD and caregivers' responsibilities that are related to it, problems due to healthcare services and other effects of being a caregiver. Even though the difficulties caregivers may experience with healthcare services and managing the patient's condition are addressed through this scale, questions related to treatment burden include other forms of treatment such as dialysis. As most of this scale was not specifically related to polypharmacy related treatment burden, this scale was not ideal to use for the cohort study presented in this thesis (46).

The Caregiver Difficulties Scale (CDS) consists of four subscales that this scale aims to address. These include the worries caregivers have about their child's health and themselves, the negative effects of caregiving on their finances and social functioning, and the support they received. None of these scales covered the impact of medicines, therefore this tool was not suitable for this project (47).

The Caregiver Strain Index (CSI) is a tool that specifically aims to assess caregiver strain (23, 48, 49). It contains 13 yes or no items that aim to assess caregivers' finances, physical and social functioning and the way caregivers use their time for caregiving and other aspects of their lives (23). The Modified Caregiver Strain Index (MCSI), which contains 12 items instead of 13, has also been used in some studies (42). As none of the questions in these tools were related to the impact of medicines, these tools were not suitable to use in the cohort study (23, 42).

Another tool that assesses parental stress for parents caring for paediatric patients is the Pediatric Inventory for Parents (PIP). It consists of 42 items that assess the effects of caregiving on various aspects of life such as communicating with their child, family and medical staff; emotional functioning; sleep; medical care and treatment; and any limitations to their daily activities due to caregiving. The scores from each item are added up to give a total score ranging from 42 to 210, with higher scores indicating higher parental stress and difficulty. Even though parents' experiences with healthcare services was assessed through this tool, it did not specifically assess the impact of medicines and was therefore unsuitable for the cohort study (50).

Some studies also use instruments that were specifically developed to assess the effects of caregiving on specific parts of caregivers' lives.

The Impact on Family Scale (IFS) has been used to assess the effect of caregiving on the patients' and caregivers' family in some studies (31, 32). It assesses the strain caregiving puts on caregivers and other members of the family, the effect of caregiving on the family's finances, how the family cope with the situation and the overall effect of caregiving but none of these were related to the impact of medicines. It consists of 33 items that are rated on a 4-point Likert scale, with higher scores meaning that families experienced a higher burden of care (32).

The Measure of Processes Of Care (MPOC-20) aims to assess parents' opinions on their experiences with healthcare services. It consists of 20 items that are rated on a 7-point Likert scale, with higher scores indicating that they felt their child received better care. The domains assessed are related to the information provided by healthcare staff, the quality of the care their child received and the parents' and healthcare staff's involvement in their child's care (32) This tool was not used for the cohort study even though the questions assessed patients' and parents' experiences with receiving treatment as the questions did not ask about their experiences or the burden of medicines (51).

The Work Productivity and Activity Impairment (WPAI) questionnaire has been used in studies for adult patients to assess caregivers' productivity at work, absenteeism and effects of caregiving on other activities. It consists of six items and higher scores on this questionnaire indicate that caregivers' work and other activities have been more impaired. As this tool did not encompass the impact medicines had on patients or other aspects of carers' lives it was not suitable for the cohort study (37).

Some studies used tools that were specific to the condition they focussed on to assess burden of care. For example, a study assessing the burden of care for families of children with rare genetic diseases used an adapted version of the Checklist For Children With Special Healthcare Needs. The adapted version used in this study assessed caregivers' quality of life, the amount and causes of stress for caregivers and the family, caregivers' experiences and needs for child care, family life and family health, the number of services available to support them and any other support they received (52). The Parent Fever Management Scale (PFMS) is a scale that is specifically used to assess the burden for caregivers looking after a febrile child through discussing parents' practices to manage the condition. It consists of eight items that are rated in a Likert scale (from 0 to 5) (53) Both of these tools were not used in the cohort study as the study aims to assess the polypharmacy related treatment burden in patients with a range of medical conditions rather than specific conditions.

Most of these tools have been used to assess the burden of care in adult and paediatric populations. However, these studies aimed to assess the overall burden of care for specific conditions rather than the effects of any treatment patients received. Most of these studies aimed to determine the burden of care for patients with chronic conditions and a few studies also assessed the burden of care in acute conditions. Even though the consequences of polypharmacy are well-known and medicines are often an important part of managing various medical conditions, none of these tools were used in studies that aimed to assess the impact of medicines or used in conjunction with other tools that focussed more on the impact of medicines.

As none of these tools are suitable for the rationale of this study, which is to assess the polypharmacy related treatment burden for paediatric patients and their families, a new questionnaire was developed for this purpose. The precursor systematic review identified the domains assessed in the existing literature on medication related burden in paediatric patients, which provided a range of questions encompassing a range of domains related to the impact of medicines and polypharmacy.

1.3.1.2 Assessing quality of life in quantitative studies

Some instruments used in studies assessing burden of care also aim to explore caregivers' overall quality of life and health related quality of life (HRQoL), which is defined as the effect of patients' health on different aspects of their life including their physical, psychosocial and financial functioning (54).

One study used the Care-related Quality of Life instrument (CarerQoL) to assess the caregiver burden for parents looking after children with cystic fibrosis. The instrument addresses how caregiving can affect caregivers both positively and negatively. The positive aspects include satisfaction caregivers feel by caring for their children and the support they get from their family and other people. The negative aspects assessed by this instrument include problems caregivers experience with their relationships, mental health, managing daily activities and caring for their child, finances and their physical health. The results from this questionnaire can then be used to calculate a Utility Score (US), with higher scores meaning that caregivers experience less burden overall. The Visual Analogue Scale

(VAS) was also used in this study, which assesses overall happiness and wellbeing on a scale of 0 to 10, with scores of 0 meaning participants do not feel happy at all and 10 meaning that they feel completely happy (33).

The Medical Outcomes 36-item Short Form Health Survey (SF-36) consists of eight scales with multiple items in each scale. It assesses caregivers' quality of life by exploring the effects of caregiving on caregivers' physical health, pain, social life, emotional functioning, mental health and the limitations they have to their physical and emotional functioning due to caregiving. It also asks about their health at the time of the study compared to their health one year ago. The results from this survey are added up to form a score between 0 and 100, with higher scores meaning that the participants' health and wellbeing are better (55). The SF-36 has also been used in studies assessing caregiver burden for caregivers of adult patients and a systematic review showed that it was one of the most frequently used tools to assess quality of life for caregivers of adult patients receiving dialysis (39). Another version of the SF-36 survey is the SF-12 survey, which was used in a study assessing the effect of caregiving on the HRQoL of parents looking after children who are chronically ill or disabled. It contains items that assess parents' physical and mental health. The parents' physical health was assessed through questions on their physical and overall health, pain, and limitations due to their physical health. The parents' mental health was assessed through questions on the effects of caregiving socially, limitations due to their emotional functioning, and overall mental health (31).

Some studies also assessed the burden of care for paediatric patients through instruments that ask about the child's health and quality of life. The Child Health Questionnaire (CHQ) is a 50 item questionnaire that aims to assess children's health and its effect on parents. It mainly focusses on children's physical health and psychosocial functioning. The domains included in the questionnaire to assess children's health also include pain, the effects of their condition(s) on school and activities, mental health, behavioural difficulties and their opinions about different aspects related to their health. The version of the questionnaire given to parents addresses the effect of their child's health on their time, family activities and family relationships. The original version consisted of 98 items but it was shortened to 50 items that would be completed by parents (CHQ-PF50). The questions are rated using a Likert scale, with higher scores meaning that the child or parent has better health and wellbeing (56).

The Pediatric Quality of Life Inventory (PedsQL) is commonly used measure to assess children's HRQoL. Variations of this tool have also been used for specific conditions and in different languages (54). One version of this tool, the PedsQLTM Scale version 4.0, was used in a study assessing the HRQoL in caregivers of children with CKD and consisted of 23 items. (57)

Studies that assessed the HRQoL of patients and parents focussed on participants' overall health and wellbeing and the ways this has been affected by their medical condition or providing care. However, the impact of medicines was not a significant part of these studies even though they would directly impact patients' health and also affect caregivers' lives and the tools used in these studies did not have specific items that assessed the impact of medicines.

1.3.1.3 Assessing burden of care in qualitative studies

Some studies use qualitative approaches to assess burden of care (27, 58-60) or use qualitative tools for assessing burden of care in conjunction with quantitative tools (31, 32). These studies often assess

burden of care by asking questions on certain domains related to caregivers' and patients' burden of care and quality of life through questionnaires or interviews.

Interviews were conducted in a study that assessed the burden of care for parents when children are hospitalised. The questions asked aimed to assess the concerns parents had, their role in their child's care when they are admitted to hospital, and what they felt they needed to aid with their child's health (32). In another study assessing the burden of care for parents of children with congenital heart disease, open questions were asked to establish parents' opinions about caregiving and to gain a better insight into their experience of providing care for their child. Further questions were asked based on the parents' previous answers to obtain more details (58).

One study on the effect of caregiving for parents of children with non-communicable diseases assessed the burden of care through a questionnaire that was administered face to face. Questions were asked on the impact of the patients' condition on the patient and family, care the patient received from healthcare services and factors preventing them from accessing it, parents' knowledge about the patient's health, what providing care for the patient involves for the parents, and any practices they do to improve the patients' health (59).

An online questionnaire was used in a study that assessed the effect of caregiving for parents of children who have chronic conditions or disabilities. It contained questions on the care received by the patient and the parents' opinion on it, the patient's medical condition and any restrictions the patient had due to their condition, the parents' HRQoL and the effect of the patients' condition and caregiving on the family (31).

1.3.2 Methods of assessing treatment burden for disease

A review on the assessment of treatment burden in adult patients showed that studies assessing treatment burden in this population mainly focused on chronic conditions. Most papers included in this review (34 out of 48 papers) were focussed on the treatment burden in a specific condition. The rest of them assessed the treatment burden in more than one condition (61).

Some papers used quantitative methods with scoring systems to assess treatment burden in their target groups. Other papers used quantitative methods to assess treatment burden. Most of the tools used to assess treatment burden in quantitative studies were specific to the medical condition the study population had. These tools often assessed treatment burden as well as other factors that can affect patients' and/or caregivers' overall quality of life (61).

Certain tools that were also used in studies assessing multiple conditions. The most frequently used tool used in these studies was the Treatment Burden Questionnaire, which has 15 items related to treatment burden that are rated on a 0-10 scale. Another tool used in these studies was the Multimorbidity Treatment Burden Questionnaire (MTBQ), which contains questions about any issues with patients' medications and the associated lifestyle changes for patients with multiple conditions. Even though it addressed problems patients may have with their medicines, it was not tailored to paediatric populations and was designed to be used specifically in patients with multiple conditions rather than any medical condition (61). The Willingness to Accept Life-Sustaining Treatment (WALT) assesses the effect of treatment burden on the ways patients want to manage their conditions (61). One study used the Patient Experience with Treatment and Self management (PETS) measure, which consists of 78 items that address various factors that can affect treatment burden. These include the

difficulties patients experience with learning about their medical conditions, administering medications, attending their appointments and accessing healthcare services, lifestyle changes. It also addresses the effect of their treatment on their relationships and tiredness (61). Even though it included questions about patients' experiences with taking medicines, side effects and the impact of medicines on patients' daily lives, the PETS tool was designed to be used in adults and also contains some questions that are not related to the impact of medicines (62). The Living with Medicines Questionnaire explores medication burden through 41 questions rated on a Likert scale. This tool however has only been used in studies assessing the burden of care in adult patients, and therefore there is a need to develop a similar tool to be used in paediatric populations. Other tools that were used to assess the effects of different aspects of management included the Exercise Therapy Burden Questionnaire and the Health Care Task Difficulty scale. The National Health and Aging Trends Study (NHATS) also addressed different ways patients were managing their medical conditions and maintain their health, which included their medications and various lifestyle changes. The Exercise Therapy Burden Questionnaire, Health Care Task Difficulty Scale and the tool used in the NHATS were unsuitable for this project as they assessed the treatment burden for other forms of treatment rather than the impact of medicines specifically (61).

Another systematic review that explored the treatment burden due to medications by reviewing existing qualitative studies demonstrated certain themes and areas in which medications affect patients. This review also focused on the treatment burden in adults and paediatric patients were excluded from this review. Most of the studies included in this review assessed the treatment burden through interviews, which were in-depth or semistructured and were administered in person or by telephone. Focus groups were another common method of assessing treatment burden in this review. One study used a questionnaire and another study included in this review used patient diaries to assess treatment burden (29).

Most reviews on treatment burden included studies that were conducted on adult patients only. Some reviews included studies with adult and paediatric populations. However, there are no known reviews that have explored treatment burden specifically in paediatric populations. Most of these reviews also include more studies on treatment burden in chronic conditions than acute conditions.

Paediatric patients encompass a wide age range, from 0 years old to their 18th birthday, and as their bodies are growing and developing during this stage, the doses and delivery of medicines need to be adjusted based on factors such as their age and weight (63). The formulation of medicines also needs to be considered when prescribing medicines for children as some dosage forms may be more preferable for patients. The heterogenous nature of this age group means that determining optimal doses and treatment regimens for medical conditions can be difficult and therefore unlicensed medicines are often prescribed in clinical practice, which can subsequently cause problems for paediatric patients and their families (64). Further research is therefore needed to explore the polypharmacy related treatment burden specifically for paediatric patients with a larger range of medical conditions. Reviews are also needed on the treatment burden in paediatric patients to identify common issues patients and their families experience with their treatment for a range of medical conditions. Exploring parents' experiences with medicines is important as they are often involved in making decisions about medicines and administering medicines for paediatric patients, especially younger patients.

1.3.3 Themes/domains assessed in studies assessing burden of care

1.3.3.1 Physical impact

Several studies assessing the burden of care have shown that caregiving often negatively impacts caregivers' physical health (36, 38). Caregivers' physical health can be affected in a number of ways including sleep (65), and tiredness. Elderly carers are also more likely to worry about distressing physical symptoms and health problems (34).

The complexity and severity of patients' conditions can contribute to the effect of caregiving on caregivers' physical health. A study assessing the burden of care and HRQoL of parents and caregivers looking after chronically ill and disabled children showed that caring for patients with more complex care needs was associated with lower SF-12 scores for the physical health score, and therefore that it has a stronger negative impact on parents' and caregivers' physical health (31).

Poorer caregiver health and caregivers experiencing physical symptoms themselves have also been shown to have worse physical strain and experience a higher burden of care overall (49).

In some cases, the proportion of parents and caregivers stating that caregiving negatively impacts their physical health can vary. In a cohort of parents looking after children with cystic fibrosis, only 38% of mothers and 70% of fathers agreed that caregiving negatively impacted their physical health (33).

1.3.3.2 Psychological impact

Caring for relatives or patients with medical conditions have also been shown to affect caregivers emotionally in various ways. Several studies show that caring for relatives and patients negatively affects caregivers' mental health and HRQoL, and this effect is more significant when care is required in the long-term for patients with chronic conditions (31). Furthermore, the burden of care increases for caregivers when patients' HRQoL are lower (32) and when patients are experiencing emotional difficulties (49).

Parents and caregivers often worry about various aspects of patients' health when they are ill and need to be looked after. A study on the burden of care in families with children who have rare genetic diseases, caregivers stated they were worried about the child's future and health (52). Another study on the burden of care for parents of children who are hospitalised showed that parents were concerned about the risks of being in hospital, such as pain and infection, and the child's overall safety and health while they are in hospital. Deterioration in the child's condition caused an increased emotional burden for parents (32).

Some demographic factors that affect the emotional burden experienced by parents and caregivers. Education levels and the age of the parent or caregiver have been shown to be related to emotional burden, with younger and less educated parents experiencing a higher emotional burden (43). The gender of the parent or caregiver can also affect the emotional burden, with mothers in a study on children with type 1 diabetes experiencing more communication and emotional difficulties than fathers initially. After a one year period, this pattern changed, with fathers subsequently experiencing more emotional difficulties than mothers (50).

1.3.3.3 Social impact

In addition to the effects caregiving can have psychologically, it can also affect caregivers' social functioning and their relationships, particularly the relationships they have with other family members (38) and their spouses (23). A study assessing the burden of care for caregivers looking after patients with schizophrenia showed that caregiving and the patients' condition negatively affected family activities and interactions between family members (38). Furthermore, changing personal plans and making adjustments within the family was a cause of increased burden for caregivers of patients with cerebral palsy (65). Several studies have also shown that the social impact of caregiving can contribute to caregivers' mental health as well as the burden of care they experience (31).

In some cases, it can also lead to missing out on opportunities that caregivers' peers without caring responsibilities and caregivers themselves would be expected to get at their stage in life. This can affect their social standing and can affect how others view them, which can subsequently affect the burden caregivers experience (34).

1.3.3.4 Financial impact

Financial problems due to caregiving were also commonly reported in studies assessing burden of care (31, 32, 38, 52, 65). Some of the direct costs due to the patients' condition included paying for their treatment, medical appointments (59) and any equipment required to manage the patients' condition outside healthcare facilities (31). Covering these costs as well as their costs of living and travel to receive medical care further increases the financial burden caregivers experienced (59), especially if they also experience financial difficulties due to reduced work productivity and a lack of financial support.

The financial burden experienced by caregivers has been shown to be increased in certain circumstances. For example, in one study older caregivers whose children lived at home with them experienced a higher financial burden (34). Financial difficulties were also increased when caregivers' health declined (49).

1.3.3.5 Caregiver responsibilities

Difficulties arising from caring for ill patients have been shown to contribute to an increased burden of care (65). Providing care for children and relatives with medical conditions involves various responsibilities including assisting patients with personal care, monitoring the patient at home and in other settings outside of healthcare settings, and accompanying the patient to access healthcare services and treatment. Assisting with personal care includes tasks such as helping the patient get dressed, helping them with their hygiene and feeding them (24).

Caring for patients who need more assistance with daily activities and patients who are admitted to hospital more often can also contribute to an increased caregiver burden (49). Hospitalisation in particular can cause difficulties for caregivers as they would be more worried about the patients' wellbeing. When patients' wellbeing was not improving or was worsening, this caused caregivers to

felt less in control and more tired (32). Additionally, managing their other responsibilities as well as caregiving can be difficult for some caregivers (58), especially parents and caregivers of young children or patients with more complex needs.

1.3.3.6 Time allocation to providing care

As caring for a child or relative with a medical condition involves a lot of responsibilities, often a lot of time is spent on fulfilling these. A review on the time various aspects of caregiving take for caregivers of children with complex needs showed that caregivers spend from 63 minutes to 726 minutes a day on their caregiving responsibilities (24). A study on caregivers for adults with amyotrophic lateral sclerosis (ALS) showed that they spent around two to ≥6 hours a day depending on the patients' needs (36).

The time spent on different aspects of caregiving vary, with some responsibilities taking up more time than others depending on the patients' medical conditions and impairments. Assisting with patients' personal care can take over half of the total time caregivers spend caring for patients on a daily basis. Monitoring patients is another aspect of caregiving that takes up a significant amount of time, with the longest time for this reported in a review being 6.5 hours in a day. It can be particularly time consuming and difficult for caregivers of paediatric patients as caregivers felt they could not leave children alone for more than five minutes (24).

Tasks directly related to patients' treatment also take up a significant amount of time regularly. Administering medications to patients has been shown to take 29 minutes and 38 minutes a day in two groups of paediatric patients with HIV (Human Immunodeficiency Virus). Medical appointments have been estimated to take approximately 30 hours to 104 hours/year depending on the setting and type of appointment. Travelling to appointments has been estimated to take approximately 60minutes/day (364 hours/year) when the length of the appointments themselves were excluded (24).

Factors that increased the amount of time needed to provide care included the day of the week, age of the patient and the severity of the patients' medical conditions and impairments. More time was spent on providing care on weekends than weekdays, with one hour more being spent on average on weekends compared to weekdays. More time was also spent on caregiving for younger patients and those with more severe conditions or impairments (24).

Parents and caregivers therefore felt that the way they are able to use their time concerned them. A study conducted on parents and caregivers of patients with rare genetic diseases showed that 54.3% were concerned about not having time for themselves and 49.5% were concerned about their schedule being busy. 47.6% of caregivers were concerned about not having enough time to look after the child and for their partner and 40% were concerned about not having enough time to look after other children in the family (52).

1.3.3.7 School and work productivity

Caregiving can sometimes impact areas of caregivers' lives outside of their caregiving responsibilities. Caregiving has been shown to affect caregivers' productivity at work and working patterns, with

absenteeism (40) and making adjustments to their jobs (65) causing an increased burden for caregivers. This also depends on the condition the patient has as some conditions can have a bigger impact on caregivers' jobs than other conditions. For example, one study showed that caregivers of patients with unipolar depression were absent from work more often and experienced more impairment to their jobs and productivity compared to caregivers of patients with other chronic conditions. Caregivers looking after patients with other chronic conditions also experienced more absenteeism and reduced productivity at work compared to people who were not carers (37).

Managing jobs and caregiving responsibilities has been shown to increase the overall burden of care and cause more difficulty for caregivers (49). Another study also showed that the child's condition affected their school attendance as well as exploring the burden of care for parents (59).

1.3.3.8 Support from family, friends, healthcare staff and organisations

The support caregivers received from family, friends and other organisations for providing care has been shown to affect the overall burden of care caregivers experienced. Several studies showed that caregivers who received less support experienced a higher overall burden of care (40, 43, 49).

The proportion of caregivers receiving support from different sources and purposes varies depending on the patients and caregivers' circumstances. In one study assessing the burden of care for parents of children with rare genetic diseases, 49.5% of them received financial support from organisations, 36.2% had personal support, 26.7% had support from organisations related to devices needed to look after the patient and 7.6% received support for other purposes. Family members, friends and voluntary organisations were also able to assist caregivers for various reasons including their finances, providing care for the patient and emotional support (52).

The support primary caregivers received from their partners was also an important factor that affected caregivers' overall burden of care. Studies have shown that inadequate assistance with providing care and other household tasks from spouses increased the burden of care for primary caregivers (31, 58).

Support from healthcare staff was also important to caregivers to reduce their burden and to help with patients' health. Caregivers felt that it was important for healthcare staff to provide information that can be understand and process easily to enable caregivers to be more involved with making decisions about the patients' care. Consistency with the healthcare services and staff delivering the patients' medical care can also help reduce the burden of care. In some cases, caregivers also stated that help from specialised staff for more complicated healthcare tasks was helpful in the hospital setting (32).

1.3.4 Themes/domains assessed in studies assessing treatment burden

1.3.4.1 Burden due to treatment characteristics and routines

Some characteristics of medications such as the form of the medication, inconvenient packaging, the lack of clear comprehensible instructions can increase the treatment burden. Certain factors related to the form of medications such as the taste of liquid medications, and the size and shape of tablets can make it harder for patients to take their medications. Changing the brand of medications for

generic versions can make patients feel less confident about the efficacy of their medications and can also cause confusion due to the different characteristics of the medications and packaging. Some patients became more worried if the number of medications they had to take increased as they thought it indicated their health was deteriorating (29).

Patients have different strategies to ensure they are adherent to their medications, however these routines can cause an increased burden for them. This could be due to relying on others for support and because treatment routines can be challenging for patients. Managing their own treatment is also a time-consuming process as patients have to understand how the medication works and should be administered, and they have to spend time, often on a daily basis, to administer their medications. This can cause patients' lives to be restricted, which can lead to a reduced adherence to medications (29).

1.3.4.2 Adverse effects from treatments

Patients are commonly concerned about adverse effects when they are taking medications. Their own or other people's experiences of adverse effects can deter patients from taking medications. The possibility of adverse effects, regardless of patients' previous experience of adverse effects, can also deter patients from taking medications in case they experience it in the future. Patients were also concerned about unwanted effects on their body and sexual function due to their medications. All of this can make patients feel more anxious and can influence the way patients think about certain medications, which can then influence their medication-taking practices. For example, patients adjusted the doses of the medications or stopped the medications to prevent adverse effects (29).

1.3.4.3 Healthcare burden due to treatments

Several aspects related to accessing healthcare services for patients' treatment caused an increased treatment burden for patients and caregivers. Getting medications and equipment for treatment from healthcare services caused an increased burden for caregivers and patients due to the time and effort required. In one study, 76% of patients and their relatives experienced problems with getting their medication (60). Travelling for appointments, to collect their medications or for other purposes related to patients' health was a hassle for both patients and caregivers due to the time it takes, costs, parking and other practical issues (29, 61). These burdens were worsened by the waiting times and travelling to different places to access healthcare and medications (29).

A lack of clear information about patients' medications, inadequate communication about the patients' care from healthcare staff and a lack of involvement from patients and caregivers when decisions are made about the patients' care all reduced the trust patients and caregivers had in healthcare staff and therefore increased their overall treatment burden (29). Healthcare staff not considering patients' circumstances when they are planning their treatment also increases the treatment burden for patients and caregivers (29, 60).

1.3.4.4 Impact of treatments on daily life

Patients' treatments have been shown to affect various areas of patients' and caregivers' lives. In one study, 87% of patients reported that their treatments affected their work and it affected their education for 77% of participants. Treatments also affected their relationships with other people, with 69% of patients reporting that treatments affected their relationship with their partner and 75% reported that their friendships were affected. Approximately 80% of patients also reported that their treatments affected their ability to socialise and participate in sports and hobbies (60). Receiving support from family and friends for their treatments reduced the treatment burden patients experienced (29).

Caregivers also expressed financial concerns due to patients' treatment. Managing the cost of treatment and other essential expenses caused emotional distress to caregivers (61). It can also restrict patients' and caregivers' social lives and family activities due to a lack of money, which can cause them to have negative feelings about treatments (29).

1.4 Project rationale

Many existing studies have assessed the burden of care in adult and paediatric patients but a lot of these are focussed on specific conditions, particularly on chronic conditions rather than acute conditions, and specific issues related to them. A lot of the reviews on burden of care aimed to determine either the impact of certain conditions or aimed to assess the quality of different tools used to assess burden of care.

Even though the impact of polypharmacy is considered in clinical practice for both adult and paediatric patients (10), most of the existing literature has focussed on the impact of polypharmacy on adult patients, especially elderly patients as polypharmacy is more prevalent in this age group. Despite the fact that the rate of paediatric polypharmacy has been shown to be high in certain settings, fewer studies have addressed the impact of polypharmacy on paediatric patients (13).

The effects of medications are considered in some studies assessing burden of care. Some reviews have explored the impact of medications on burden of care in the adult population only as paediatric patients were excluded from these reviews (29, 61). However, to date there are no known studies that explore polypharmacy related treatment burden specifically on the paediatric population. Understanding the problems paediatric patients and their families face due to their medicines is important to optimise their medicines and improve the management of their medical conditions. Should considerable medication related burden of care related to medicines be identified, then it will also support efforts to implement deprescribing practices in paediatrics.

1.5 Aims and objectives

The overall aim of this study is to determine the impact polypharmacy has on the burden of care for paediatric patients and their parents/caregivers. The aims of the project are to:

1. Conduct a systematic review to identify the domains related to medicines and polypharmacy in existing studies.
2. Identify the methods used to assess polypharmacy related treatment burden in existing primary studies.

3. Develop a questionnaire for the PANDA (Polypharmacy ANd Drug optimisAtion) cohort study using the domains and questions obtained from the systematic review.
4. Validate the questionnaire and alter it based on each question's content validity index before recruiting patients.
5. Determine the effect of polypharmacy on paediatric patients and their parents, and identify the domains that cause a bigger impact on their lives through the cohort study.

1.6 Summary

Burden of care and treatment burden refer to the effects of medical conditions or treatment on paediatric patients and their families (20, 26). Medications are a common form of treatment and are the commonest form of treatment for some medical conditions (29). As medications are used widely in medical care, polypharmacy, which refers to the use of multiple medications (9), is becoming increasingly more prevalent. More medications are being prescribed (6) as the average life expectancy increases due to an increase in chronic conditions and comorbidities, which along with other factors can contribute to polypharmacy (9).

The impact of paediatric polypharmacy on children's health is well known and is considered in clinical practice. However, the research on polypharmacy has mainly been on adult patients (13). Additionally, an increasing number of studies have assessed the burden of care in specific conditions however more research is needed on the impact of polypharmacy on patients and their families.

To address this gap, this research aims to identify the different areas in which polypharmacy impact patients' and their families by reviewing existing studies, which will then be used to create a questionnaire that can be used to determine the impact of polypharmacy.

This study comprises two parts, a systematic review and a cohort study, to identify the burden of care of polypharmacy on paediatric patients and their families.

This thesis explores the domains commonly asked about in studies assessing burden of care and treatment burden in paediatric patients through the systematic review. This chapter discussed the background of this study and the existing knowledge about burden of care and polypharmacy. The other chapters in the thesis will discuss the rationale, aims and objectives of this study. It also discusses the methodology of the cohort questionnaire study, which includes the procedure of developing and validating the questionnaire, how patients are recruited and the method in which the questionnaires are conducted, and the results of the cohort study.

Chapter 2: What domains related to medicines were measured in studies of burden of care for paediatric patients: a systematic review

2.1 Background

As discussed in the previous chapter, there are numerous studies on the burden of care for parents and caregivers of children with specific conditions, and on the effects of polypharmacy but there is a lack of information related to medicine related treatment burden in children. A systematic review has explored the medicine related burden and how it affects patients' experience in adults, however paediatric patients and other measures of burden of care were excluded. As patients were included in the study regardless of the number of medicines they were taking, polypharmacy was not explored in the study (29). Therefore, exploring the existing literature specifically on the impact of medication for paediatric patients and their parents or caregivers would help to address this gap.

2.2 Aims and objectives

This systematic review aimed to systematically review the literature on the domains and common themes explored in studies about burden of care for parents, caregivers and paediatric patients themselves experiencing polypharmacy. It focussed on the domains related to medicines that were measured in studies of paediatric burden of care, but also explored the way in which these domains were reported in these studies.

The primary outcome for this review was the domains related to medicines that contribute to burden of care. The secondary outcome for this review was any additional domains captured in paediatric burden of care studies.

2.3 Methods

A protocol was written for this systematic review and it outlines the methodology planned for this systematic review. A protocol for this systematic review has also been published on PROSPERO (PROSPERO number: CRD42021285097), which can be accessed here: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021285097. It is also available in Appendix 1: Systematic review protocol submitted to PROSPERO.

This systematic review was completed according to PRISMA guidelines as shown in Figure 1.

Figure 1 - PRISMA checklist

Section and Topic	Item #	Checklist item	Section where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	2.2
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	2.1
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	2.2
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	2.3.2
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	2.3.1
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	2.3.1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	2.3.3
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	2.3.4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	2.4.4
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	2.4.4
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	2.3.5
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	N/A
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	2.3.6

Section and Topic	Item #	Checklist item	Section where item is reported
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	2.3.6
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	2.3.6
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	2.3.6
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	N/A
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	2.3.5
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	2.3.5
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	2.4.1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	2.4.1
Study characteristics	17	Cite each included study and present its characteristics.	2.4.3
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	2.4.2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	N/A
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	2.4.4
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	N/A
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	2.4.2
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	2.4.2

Section and Topic	Item #	Checklist item	Section where item is reported
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	2.5
	23b	Discuss any limitations of the evidence included in the review.	2.5.2
	23c	Discuss any limitations of the review processes used.	2.5.2
	23d	Discuss implications of the results for practice, policy, and future research.	2.5.1
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	2.3
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	2.3
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	N/A
Competing interests	26	Declare any competing interests of review authors.	N/A
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	N/A

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

2.3.1 Search strategy

Scoping searches were conducted to establish the knowledge in the existing literature and the volume of studies on this topic using Google Scholar. Some of the common domains discussed in papers assessing burden of care for patients and caregivers were identified.

The databases chosen for this systematic review were Medline, CINAHL, EMBASE, web of science and Cochrane database of systematic reviews.

Search terms and limits were decided based on the inclusion and exclusion criteria, and synonyms of the key search terms were considered.

The search strategy used for this systematic review is shown below:

MEDLINE, CINAHL and EMBASE:

1. (burden of care).ti,ab
2. (care burden).ti,ab
3. (caregiver burden).ti,ab
4. (care giving burden).ti,ab)
5. (burden of care).ti,ab OR (care burden).ti,ab OR (caregiver burden).ti,ab OR (care giving burden).ti,ab
6. (child*).ti,ab
7. (paediatric*).ti,ab
8. (neonat*).ti,ab
9. (infant*).ti,ab
10. (teen*).ti,ab
11. (adolescent*).ti,ab)
12. (child*).ti,ab OR (paediatric*).ti,ab OR (neonat*).ti,ab OR (infant*).ti,ab OR (teen*).ti,ab OR (adolescent*).ti,ab
13. (polypharmacy).ti,ab
14. (multiple medicines).ti,ab
15. (multiple medication*).ti,ab
16. (multiple drugs).ti,ab
17. (polymedication).ti,ab
18. (multidrug therapy).ti,ab
19. (multiple drug therapy).ti,ab)
20. (polypharmacy).ti,ab OR (multiple medicines).ti,ab OR (multiple medication*).ti,ab OR (multiple drugs).ti,ab OR (polymedication).ti,ab OR (multidrug therapy).ti,ab OR (multiple drug therapy).ti,ab
21. #5 AND #12 AND #20

Cochrane Database of Systematic Reviews:

1. ((burden of care) OR (care burden) OR (caregiver burden) OR (care giving burden)) [Title, Abstract and Keyword]
2. ((child*) OR (paediatric*) OR (neonat*) OR (infant*) OR (teen*) OR (adolescent*)) [Title, Abstract and Keyword]

3. ((polypharmacy) OR (multiple medicines) OR (multiple medication*) OR (multiple drugs) OR (polymedication) OR (multidrug therapy) OR (multiple drug therapy)) [Title, Abstract and Keyword]
4. #1 AND #2 AND #3

Web of Science:

1. (burden of care) OR (care burden) OR (caregiver burden) OR (care giving burden)
2. (ALL=child*) OR (ALL=paediatric*) OR (ALL=neonat*) OR (ALL=infant*) OR (ALL=teen*) OR (ALL=adolescent*)
3. (ALL=polypharmacy) OR (ALL=multiple medicines) OR (ALL=multiple medication*) OR (ALL=multiple drugs) OR (ALL=polymedication) OR (ALL=multidrug therapy) OR (ALL=multiple drug therapy)
4. #1 AND #2 AND #3

Filters and Limits:

- Human studies, patients aged 0-18 years old.
- No date or language restrictions were used in these searches.

Once the search terms were decided, the databases MEDLINE, Web of Science, CINAHL, Embase and Cochrane Database of Systematic Reviews were searched for papers on the chosen topic on 19th October 2021. MEDLINE, CINAHL and Embase were searched simultaneously on HDAS (Healthcare Databases Advanced Search), and Web of Science and Cochrane database of systematic reviews were searched separately on their websites. Details of the papers found were extracted and saved into Excel spreadsheets for screening. The spreadsheets included the following details of the papers found: author, title and publication date or year. The results from this search were also imported onto Endnote for reference management.

2.3.2 Eligibility criteria

Table 1 shows the inclusion and exclusion criteria for the systematic review.

Table 1 - Inclusion and exclusion criteria for the systematic review

	Inclusion Criteria	**Exclusion Criteria**
Population	● Paediatric patients ● Parents/caregivers of these patients ● Inpatient/outpatient in any geographical setting ● Any medical condition	● Adult patients ● Parents/caregivers of patients recruited are not involved in the study ● Non-patient participants
Intervention	● Studies examining burden of care in the population	● Studies that do not explore burden of care/treatment
Comparison	● N/A	● N/A
Outcomes	● Domains related to medicines that contribute to burden of care ● Additional domains captured in paediatric burden of care studies	● Domains not related to medicines that contribute to burden of care
Type of study	● Primary studies, including cohort studies and case studies ● All languages ● All dates	● Systematic reviews ● Literature reviews ● Other review articles

Systematic reviews, literature reviews and other review articles were excluded in this review. However, they were checked for relevance and the reference lists of relevant reviews were searched for eligible records. Any papers that signposted the methodology elsewhere also had those references examined. Reference lists of systematic reviews were last examined on 21st November 2021 to search for relevant papers.

2.3.3 Study selection

Two reviewers independently (TT and JM) screened the titles for all records found from the databases. Any titles that both reviewers excluded were subsequently excluded from this review. Any titles included by either reviewer had their abstracts screened independently by both reviewers. Abstracts that were excluded by both reviewers were excluded at this stage, and any abstracts included by either reviewer then had their full text reports screened. Only full text papers that were included by both reviewers were included in this review. Any disagreements between the reviewers were resolved by a third reviewer (DH), who read the full text reports the reviewers disagreed on and made a final decision.

2.3.4 Data extraction

A data extraction form was created in an Excel spreadsheet. A data extraction form was trialled with some of papers that were included in this systematic review after completing the screening process for all papers. Headings were altered as required depending on the data available in the papers.

In the final version of the data extraction form (Appendix 2), the headings included details of the research papers: authors, title, year of publication, citation, type of publication, country, study aims and objectives, the study's inclusion and exclusion criteria, recruitment procedures used and the study setting. The following data was extracted about the studies' participants: number of participants, age groups for the patients, study population, domains related to burden of care, and the medical conditions(s) the studies focused on. The method of assessing burden of care and the score(s) used to assess the participants' responses were also extracted.

Data were missing for some papers as the questions asked in these studies were not explicitly stated in the papers. The questions for some studies were found from supplementary materials (66), papers referenced by the authors (67, 68) or other sources (69). For one paper, it was clear that the burden of care from medications use was assessed but the questions asked in this study were not explicitly stated in the paper (70). The authors were therefore contacted and the questions from this study's survey were provided by the authors.

One reviewer (TT) extracted the data from the papers included in the screening process and another reviewer (JM) independently checked the data that was extracted from these papers in the data extraction form.

2.3.5 Quality assessment

The Newcastle-Ottawa Scale was used to assess the quality and risk of bias for cohort studies. Two reviewers (TT and JM) independently assessed the quality of the studies included in this systematic review using the appropriate tool. Any disagreements about quality assessment between the reviewers were resolved through discussion with a third reviewer (DH). The Newcastle Ottawa Scale is available in Appendix 3: Newcastle-Ottawa scale for cohort studies.

2.3.6 Data synthesis

The domains measured in the studies included in this review were grouped into themes and recorded in the data extraction tool. The methods used to assess these domains were also included in the data extraction form. A thematic synthesis approach (Thomas and Harden 2008) was used for data synthesis as this study aims to identify and group the domains. Meta-analysis and statistical models were not used at this stage as the data obtained was qualitative. At least two papers were required for data synthesis, and as this requirement was met data synthesis was conducted as described here.

2.4 Results

2.4.1 Study selection

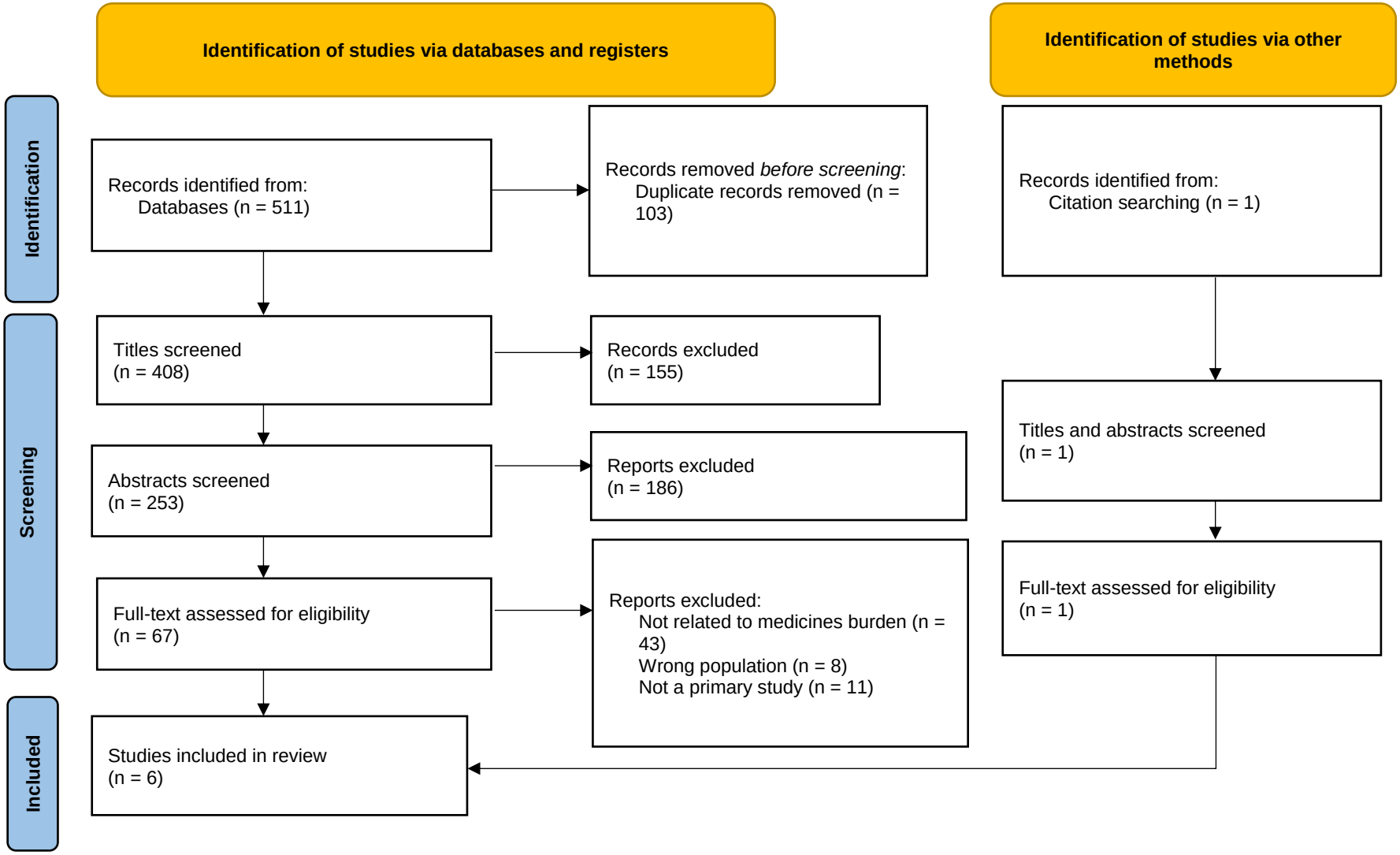
511 reports were found after searching the databases for relevant studies. 103 duplicate reports were removed and after removing these duplicates, the titles of 408 reports were screened. 253 abstracts were then screened, 67 of which were relevant. The full text reports of these papers were then screened.

43 full text reports were excluded as they did not assess treatment burden or were not related to medicines. Eight papers were excluded as the age group or population they assessed did not fit the inclusion criteria. 11 papers were excluded as they were not primary studies, with one of them being a review. Five full text reports (66, 70-73) were included in this review along with one full text report (74) that was identified through citation searching.

Some papers appeared to meet the inclusion criteria but were subsequently excluded after screening the full text reports as they were not related to the burden of medicines on patients or parents (75-81). Some studies addressed some of the issues patients and parents had about medicines but they were not directly related to the burden of care caused by the medicines (75, 77, 79-81). Other studies focussed on the impact of medical conditions but they did not address the impact of medicines (76, 78).

The PRISMA diagram (Figure 2) below summarises the selection of studies for this systematic review.

Figure 2 - PRISMA diagram summarising the study selection process



2.4.2 Quality assessment of included studies

The quality of the studies included in this review were assessed using the Newcastle Ottawa Scale (82). The criteria for each category can be seen in Appendix 3: Newcastle-Ottawa Scale for cohort studies.

The number of stars show the number of factors in each category that demonstrated a low risk of bias. The stars given for the selection category were related to the representativeness of the study's cohort and the method used to determine exposure. Up to two stars could be given for the comparability category depending on the number of factors that were accounted for in the study's analysis. Studies that accounted for one factor were given one star and studies that accounted for two or more factors were given two stars in this category. The number of stars given in the outcome category were related to the method of assessing the outcome and the length of the follow up period. A maximum of four stars could be given for the selection category, two stars for the comparability category and three stars for the outcome category.

Table 2 summarises the overall quality of these studies:

Table 2 - Risk of bias in cohort studies

Study	Selection	Comparability	Outcome	Overall quality
Andersen AM et al., 2020 (70)	✵✵	✵	✵✵	Fair
Fridman M et al., 2017 (72)	✵✵	✵✵	✵✵	Fair
Cheung M et al., 2021 (71)	✵			Poor
Taminskiene V et al., 2019 (73)	✵			Poor
Yotsu RR et al., 2012 (66)	✵✵			Poor
Quittner AL et al., 2011 (74)	✵✵			Poor

Selection: the representativeness of the study cohort and selection of the cohort. Comparability: other factors that were accounted for in the study's analysis. Outcome: assessment of outcome and follow-up of the cohort.

The cohorts in all studies were "truly representative" or "somewhat representative" of children with the condition studied in these studies. Most studies also established the exposure, which was defined as starting medication in this study, through checking patients' medical records (66, 74) or as part of their interview process (70, 72), which made their selection process less biased.

However, there were some issues with these studies which increased their risk of bias. No studies had a non-exposed cohort and most studies did not follow up with the cohort after the initial questionnaires or interviews were completed. Two studies were retrospective and therefore had an adequate follow up period from the time patients started taking medications to the completion of the questionnaire or interview (70, 72). One study asked about the effects of medicines on parents

looking after paediatric patients with ADHD within the last six months (72). Another study asked about the effects of medications for ASD within the last two years (70).

Only two studies accounted for other factors in their statistical analysis (70, 72). Both studies accounted for patients' comorbidities, and one study also accounted for the subtypes of the medical condition (72).

2.4.3 Study characteristics

Table 3 summarises the characteristics of the studies included in this review. This includes the studies' design and methodology, the studies' main focus, the location the studies were conducted in and the medical conditions covered in these studies. All studies included in this review were cross-sectional cohort studies. Some studies had similar methods of assessing medication burden. Taminskiene V et al. (73) and Quittner AL et al. (74) used questionnaires with overlapping questions.

Table 3 - Summary of study characteristics

Study	Country	Medical condition	Method of assessing burden of care/ treatment burden	Sample size	Study's main focus
Taminskiene V et al., 2019 (73)	Lithuania	Asthma	Questionnaire	527	Medication burden
Quittner AL et al., 2011 (74)	USA	Cystic fibrosis	Questionnaire	4796	Medication burden
Andersen AM et al., 2020 (70)	USA	Autism spectrum disorder (ASD)	Questionnaire	526	Medication burden
Fridman M et al., 2017 (72)	Denmark, Finland, France, Germany, Italy, the Netherlands, Norway, Spain, Sweden, UK	ADHD	Survey	2,326	Medication burden
Cheung M et al., 2021 (71)	USA	X-Linked Hypophosphatemia	Survey	86	Medication burden and treatment experiences

Yotsu RR et al., 2012 (66)	India	Acute flaccid paralysis	Interview	26	Treatment experiences

2.4.4 Domains related to burden of medicines

2.4.4.1 Summary of results

This review identified studies that were conducted across various countries, with five studies based in a single country and one study based in 10 European countries. 8276 children and parents were included overall. Studies were carried out between 2003 and 2016 in USA (n = 3) and with one publication in Denmark, Finland, France, Germany, India, Italy, Lithuania, the Netherlands, Norway, Spain, Sweden and the UK. Patients with a range of medical conditions were recruited in these studies: Autism Spectrum Disorder (ASD), ADHD, X-Linked hypophosphatemia, asthma, acute flaccid paralysis and cystic fibrosis.

Although several existing studies assessing the burden of care and treatment burden in paediatric patients used a range of tools to do so, most of these studies devised their own questions to assess the impact of patients' medicines. A few studies used tools that were specific to the condition patients had.

Table 4 summarises the domains that were assessed in the studies included in this review. This includes the studies that assessed these domains and the questions that were asked in these studies for each domain.

Table 4 - Summary of results from studies found

Domain assessed	Andersen AM et al., 2020 (70)	Fridman M et al., 2017 (67, 72)	Cheung M et al., 2021 (71)	Taminskiene V et al., 2019 (68, 73)	Yotsu RR et al., 2012 (66)	Quittner AL et al., 2011 (69, 74)
Perceived effectiveness of medications	Yes - "For the following medication, please indicate how effective it has been in reducing elopement"	No	Yes	No	Yes - "How is your child now?"	Yes - "How do you think your child's health is now?"
Ease of use/convenience	No	No	Yes	No	No	Yes - "How difficult is it for your child to do his/her treatments (including medications) each day?", "Doing your treatments bothered you"
Adherence to medicines	No	Yes	No	No	No	Yes - "You were able to do all your treatments"
Medication side effects	Yes - "For the following medication, please indicate how severe the side effects or adverse effects it caused have been"	No	Yes	No	No	No
Physical impact on everyday life	No	No	No	No	No	No
Psychosocial impact on everyday life	No	Yes - "Over the past 6 months, how much time did you spend worrying or stressing about your child?", How often did you plan your day around your child?", "How	No	Yes - Worrying about child's treatment and side effects	No	Yes - "My child's treatments get in the way of his/her activities", "You had to stop fun activities to do your treatments"

		often did you avoid social activities when with your child?", "How often did you worry about other people's perceptions of you as a parent?" while on and off ADHD medication				
Time requirements	No	No	Yes - timing/frequency of medication	No	No	Yes - "My child spends a lot of time on his/her treatments everyday"
Caregiver responsibilities	No	No	No	No	No	No
Direct costs	No	No	Yes - cost of treatment	No	Yes - "What did/do you feel about the cost of treatment?", "How is the treatment cost affecting your family?"	No
Indirect costs	No	No	Yes - costs due to illness, travel, insurance	No	No	No
Use of healthcare resources	No	No	Yes - "access to appropriate treatment"	No	Yes - "Where are you getting treatment/support /care for your child? If Not getting any, then why?",	No

					"What kind of treatment/support /care?", "What were your difficulties getting treatment, support, and care at the time of onset of polio?", "What are your difficulties now getting treatment, support, and care for your child?"	
Work/school productivity/absenteeism	No	Yes - "Have you had to change your job, cut back your work hours, work schedule, or quit work altogether due to your child's ADHD?", "In the past 4 weeks, how many total hours of work did you miss due to your child's ADHD?" while on and off ADHD medication	Yes – impact on education and work	No	No	Yes - "How often your child was absent or late for school or other activities because of his/her illness or treatments"
Effect of medicines on relationships	No	Yes - "How much strain did your child's ADHD put on your relationship with your partner?",	No	No	No	No

		"How much strain did your child's ADHD put on your relationship with your other children?" while on and off ADHD medication				
Other domains	Overall burden of interventions			Frequency of rescue medication use	Treatment provided by doctors/ANMs - "What kind of treatment, support, or care did you get after the stool test from the people visiting you at your house [ANMs, doctors]?". Information provided by doctors about treatment - "what information did they provide you regarding treatment, support, and care of the disease [polio]?".	

2.4.4.2 Perceived effectiveness of medications

This was addressed in most of the studies included in this systematic review (four out of six studies) (66, 70, 71, 74). In one study, participants were asked about their perceived effectiveness of individual medications to manage their child's ASD (70). Two studies addressed this by asking about their perception of their child's health (66, 74).

2.4.4.3 Ease of use/convenience

Two studies addressed this (71, 74), with one of them asking multiple questions about it. Quittner AL et al. assessed the difficulties parents and children had related to administering the child's medicines by asking how difficult this was and to rate how much administering the medicines bothered them (74).

2.4.4.4 Adherence to medicines

Adherence to medicines was assessed in two studies (72, 74). One study asked participants whether they were able to take all of their medicines by asking them to rate a statement based on how much they agreed or disagreed with it/with a scale from strongly agree to strongly disagree (74).

2.4.4.5 Medication side effects

Two studies addressed this (70, 71). One study did this by asking participants to rate the severity of side effects their child experienced from individual medications (70).

2.4.4.6 Psychosocial impact on everyday life

Three studies assessed the impact of medications on participants' social and emotional functioning (72-74). One study asked parents about the amount of time they were worried about their child, the adjustments they had to make to activities and their concerns on other people's opinions of them as parents while their child is taking their medications (72). Another study addressed this domain by asking participants about the impact of medications on the child's activities (74). The third study assessed participants' worries regarding their child's treatment and potential side effects (73).

2.4.4.7 Time requirements

Two studies addressed this domain (71, 74). One study assessed this through assessing the timing and frequency of the child's medications. The other study asked parents whether their child spent a lot of time taking their medicines on a daily basis (74).

2.4.4.8 Direct costs

Two studies asked about the cost of their medicines and treatment (66, 71). One study also asked participants about their opinions about these costs and the effect of these costs on their family (66).

2.4.4.9 Indirect costs

One study assessed this domain by addressing the costs of accessing medications and lost income due to the child's medical condition. This included costs due to the child's illness, travelling to access the child's medications and health insurance (71). Studies in this review also addressed the psychological impact of direct costs on caregivers and their families.

2.4.4.10 Use of healthcare resources

Two studies assessed this domain (66, 71). One study did this by assessing whether parents felt they had access to adequate treatment for their child (71). Another study asked questions on the services they are accessing for their child's treatment and for additional support, the treatment their child was receiving, and the difficulties parents encountered with accessing treatment for their child when their child was diagnosed with the condition and at the time the interviews were conducted (66).

2.4.4.11 Work/school productivity/absenteeism

This domain was assessed in three studies (71, 72, 74). One study asked questions on the impact of their child's medications on their job. This included questions on whether they quit their jobs or adjusted their work hours and the total time they missed in their jobs due to their child's condition and medications (72). Another study assessed the impact of medications on the child's education by asking participants how often the child was late or absent to school because of their medications (74).

2.4.4.12 Effect of medicines on relationships

One study assessed this through asking questions on the negative impact of the child's medications on participants' relationships with their partners and their other children (72).

2.4.4.13 Other domains

Other domains assessed in these studies that did not belong in the other categories included an overall assessment of the burden of treatments (70), how often medications were used to treat exacerbations (73), the type of treatment and support children were provided by doctors and other healthcare staff,

and the information participants were provided about their child's medical condition and medications (66).

No studies assessed the physical impact of medications or the impact of medications on parents'/caregivers' responsibilities. Most of the studies included in this review addressed the physical impact on participants but this was related to the medical condition rather than medicines.

2.5 Discussion

Six relevant studies were identified in this systematic review. All of them covered at least one domain but no studies addressed all domains. All of these studies contained questions that specifically assessed the impact of medicines on patients and their families. All studies included in this review aimed to determine the medication related burden patients and their families experienced, and to explore their experiences with medicines.

The most commonly assessed domain in these studies was parents' and patients' perceived effectiveness of their medications. The next commonest domain assessed was the psychosocial impact of the medications. A lot of these studies aimed to assess the burden of treatment and the factors that affected it as well as patient's and parents' experiences of managing their child's condition using medicines. As medicines are often a part of treatment for most conditions, finding out whether medicines are effective would help to determine whether patients and parents are likely to have a higher or lower burden. Another review on treatment burden in adults identified studies that also addressed this domain through asking about patients' views and satisfaction with their medicines and the way the perceived effectiveness of their medicines and other factors influenced the way they managed their medicines (29).

The psychosocial impact of medicines was also an important factor to explore in these studies as managing the child's medicines can significantly alter the parent or caregiver's daily routine as well as causing potential stress due to various difficulties with this (28), which are linked to the other domains in this review. In other studies assessing burden of care, the psychosocial impact was linked to the impact of balancing caregivers' responsibilities (28), the difficulties patients experienced with their medicines and accessing healthcare services, and the stigma associated with their medical conditions and medicines (29).

However, none of the studies included in this review assessed the physical impact or the impact of medicines on caregivers' additional responsibilities. In studies included in this review, the questions about side effects encompassed the physical impact of medications and this is also the case for other studies in the existing literature. This included questions about the severity of the side effects, when they occurred, and the number of side effects patients experienced (28). Another review identified studies that asked about the worries patients had about side effect and the impact side effects had on the way patients managed their medicines (29).

Caregivers' responsibilities were mainly related to managing the child's medicines, jobs and other relationships, which were all covered in other domains. Other reviews addressed the psychological effect of looking after the child and other family members, managing the child's medical condition outside medical settings and keeping up with other personal tasks caregivers had (28).

The convenience of medicines and adherence to medicines were also explored in this review through questions that directly asked about these domains. In other studies, the convenience of using medicines was addressed through asking about tasks associated with patients' treatment that disrupted their daily activities (28); methods of managing their medicines and the difficulties patients experienced with this; and issues patients had with the medicines' timings, packaging and formulation (29). Adherence was also addressed in other studies through questions about patients' choices when they are taking their medication. This included stopping a medicine completely, intentionally or accidentally missing doses of their medicines and taking other medicines or other therapies instead of their prescribed medicines (29).

The impact of the time requirements on patients and parents were assessed differently in studies included in this review compared to other studies. Other reviews on treatment burden identified studies that asked about the time patients and their families spent travelling to appointments, getting used to the medicines, dealing with side effects that occurred (28) and the time taken to access medicines from a pharmacy or other healthcare setting (29).

In the existing literature, other reviews also identified studies that addressed the costs of medicines and transport (28, 29), which is similar to the findings in this review. Financial concerns were commonly found in other studies due to the impact managing patients' medicines had on caregivers' jobs (28) (29).

The impact of medicines on participants' relationships with others was addressed in other studies by asking about the support they received from their families and the ways their families and friends affected the way they managed their medicines (29).

Most studies used their own questions to assess these domains. Only two studies used questionnaires that were already developed to assess burden of care. These were the Cystic Fibrosis Questionnaire-Revised (CFQ-R) (74) and Pediatric Quality of Life Inventory Family Impact Module (PedsQLFIM) (73).

Variations in healthcare systems in these countries and patients' socioeconomic factors were accounted for in these studies. Questions related to them were therefore asked to participants to establish the impact of these factors on the burden of medicines. Yotsu (2012) was set in a district in Uttar Pradesh, where over 30% of its population experiencing poverty. As the cost of medicines and accessing healthcare was likely to cause a significant burden for participants in the study, more emphasis was put on the support they received from various sources, any concerns they had about the costs of treatment and other difficulties they had with accessing healthcare (66).

2.5.1 Implications of this review

This systematic review has demonstrated the domains assessed and the ways in which researchers have asked about these domains in different studies. It also showed that even though there is a large volume of papers assessing the burden of care of specific conditions for both paediatric patients and their families, there is a lack of studies that address the effects of medicines on paediatric patients' and their families' lives. There are also variations in the domains assessed in these studies and some studies have more emphasis on the effect of medicines than others. This review and the questionnaire that will be developed for the PANDA study will help to address this gap as the questions asked will specifically address the polypharmacy related treatment burden rather than the impact of specific medical conditions or treatments as a whole. The questions asked to address each domain in these

studies will be used to guide the development of the questionnaire for the PANDA study, with additional questions being added as necessary.

Even though tools that assess the effect of medicines have been developed for adult populations, there are no known tools that have been developed to this for paediatric patients. A new paediatric tool is needed to assess the effects of medicines specifically rather than the effect of the condition as a whole in paediatric patients. As children who are hospitalised or treated in the community often experience polypharmacy, understanding the impact of polypharmacy on patients' and their families' lives can help clinicians to tailor their care to ease their burden and prevent the problems arising from polypharmacy.

2.5.2 Limitations of this review

One study (71) did not ask explicit questions to assess the impact of medicines. However, two open ended questions were asked in this study instead. One question asked about the symptoms and complications that negatively affected the patient's lives. The other question asked participants about anything they felt the research team needed to know about their condition. Several themes, some of which were addressed in this review, were derived from the responses (71).

The lack of non-exposed cohort in all of the studies made their risk of bias higher. However, as this review and these studies aimed to assess parents' and children's opinions, non-exposed cohorts would not be necessary in these studies.

It was also clear from this review that studies assessing the impact of medicines on paediatric patients and their parents assessed the impact of medicines on certain aspects of their lives. However, no studies assessed the impact of medicines on most or all of these aspects, even though they are commonly assessed in studies assessing the overall burden of care in various medical conditions.

Some relevant articles may have been missed in this review process. Even though various combinations search terms that covered the paediatric population, burden of care and medicines were trialled and a range of databases were searched without any time or language restrictions.

2.6 Conclusion

This systematic review has shown that a broad range of domains assessing the impact of medicines on various aspects of patients' and parents' lives were assessed across these studies, but no single study has captured them all.

Moreover, existing studies focused more on the overall impact of specific medical conditions, the symptoms and complications it causes etc. rather than the impact of treatment even though treatment and medicines can be a large part of managing their conditions. There is therefore a need to carry out further research into the effects of medicines in individual medical conditions. The PANDA study aims to address this gap in the literature through developing a questionnaire that assesses the impact of medicines on parents of children experiencing polypharmacy and recruiting parents to gather their views.

2.7 Support for this review

No financial support was required to conduct this systematic review. Additional support was not required from anyone other than the authors of this systematic review.

2.8 Competing interests

The authors of this systematic review had no competing interests.

Chapter 3: Polypharmacy ANd Drug optimisAtion (PANDA) study – methodology

3.1 Introduction

The systematic review, which was discussed in Chapter 2, showed that various domains related to different aspects of patients' and their parents' lives were assessed in studies on burden of care. The questions and domains assessed in the studies included in the systematic review were collated to create a questionnaire that specifically assessed the effect of medicines on the chosen population (66-74). Various questionnaires and tools exist to assess the treatment burden due to medicines in adults but there are no known questionnaires that have been used to assess the polypharmacy related treatment burden for paediatric patients.

3.2 Aims and objectives

This study aimed to develop and pilot a questionnaire that can be used to determine the impact of polypharmacy on paediatric patients and their parents. A questionnaire was therefore developed and evaluated before recruiting patients to complete the questionnaire in a pilot study.

3.3 Methods

3.3.1 Research team

The Chief Investigator for this study was Dr Daniel Hawcutt. The co-investigators were Dr Louise Bracken, Matthew Ryan and Tharshiya Thatparan.

3.3.2 Study sponsorship and ethical approval

This study was sponsored by Alder Hey Children's Hospital.

This study obtained ethical approval (IRAS number: 304972) from HRA (Health Research Authority) and HCRW (Health and Care Research Wales) in February 2022. The letter from HRA and HCRW can be seen in Appendix 7: PANDA study – Ethical approval.

Ethical approval was not given until the final questionnaire was provided.

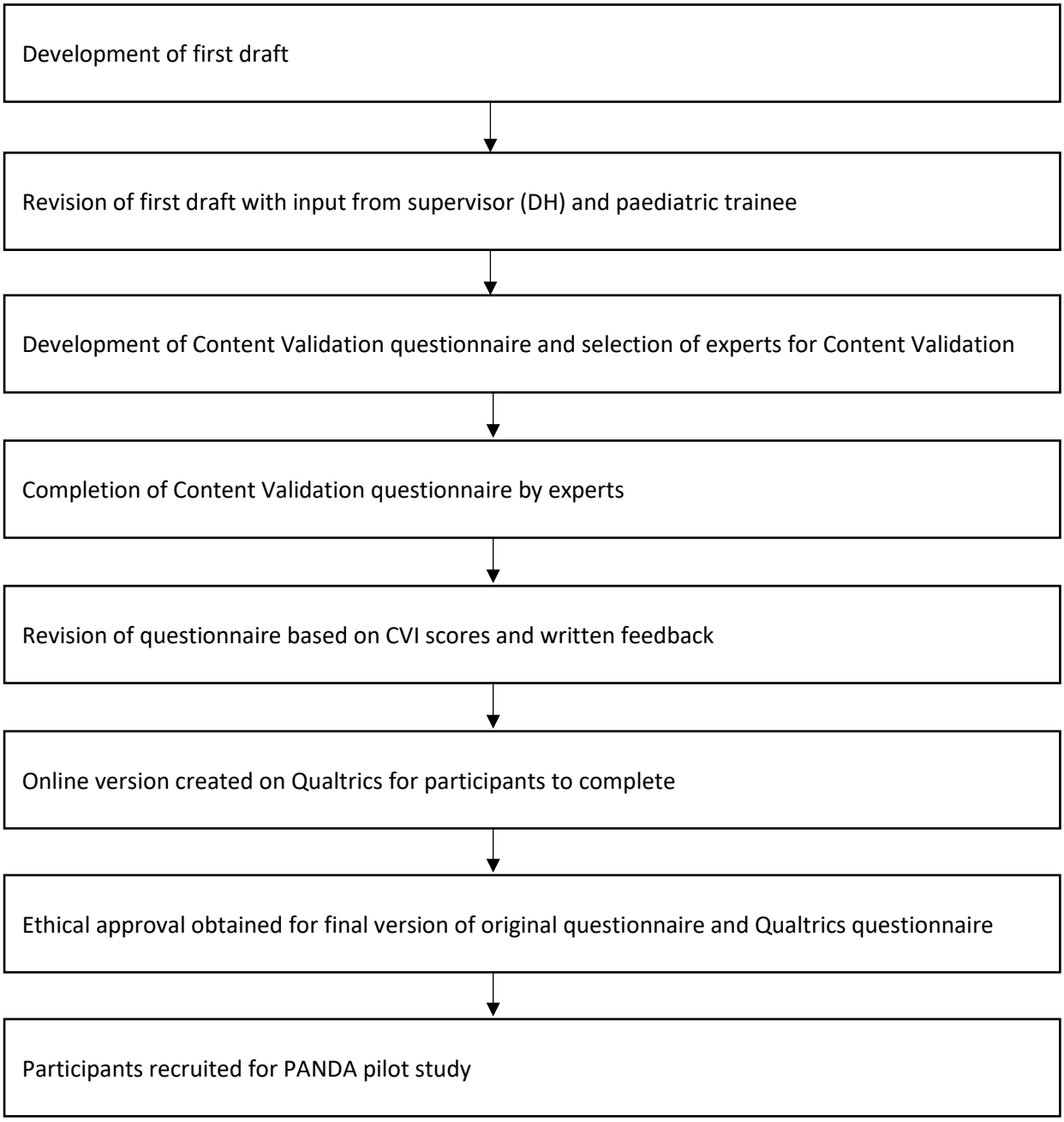
3.3.3 Study design

This study was a prospective questionnaire cohort study. It was conducted according to the protocol, which can be seen in Appendix 4: PANDA study protocol.

3.3.4 Developing the questionnaire

Figure 3 provides an overview of the process of developing and validating the questionnaire for the PANDA study.

Figure 3 - Flowchart of developing the questionnaire



Some questions were collated from the questions identified in papers included in the systematic review. Further questions and sections were added to the questionnaire after the questionnaire was reviewed by my supervisor and other members of the research team.

A section on patient demographics, which included questions about the patient's age and gender as well as questions on factors that can increase the risk of polypharmacy such as prematurity.

Another section was added to ask parents about the number of medicines their child is taking and details about these medicines.

Once the first version of this questionnaire obtained ethical approval, the questionnaire was developed online on Qualtrics. One questionnaire was created for parents to complete and another questionnaire was created to validate the questionnaire. As some questions were linked to each other, the questionnaire for parents was set up on Qualtrics so that some questions only appeared when a certain answer was chosen for another question. The first and final versions of the questionnaire for parents can be found in Appendix 5: PANDA Study parent questionnaire v1.0 and Figure 4 - PANDA Parent Questionnaire - Final version.

3.3.5 Questionnaire validation

A content evaluation questionnaire was created on Qualtrics to validate this questionnaire. The questionnaire included introductory questions to establish the assessor's role and experience working with children. The roles and experience working with children for the assessors are shown in Table 5:

Table 5 - Assessors' roles and experience working with children

Role	Experience working with children
Pharmacist (Research)	10 years
ST8 Paediatric Pharmacology GRID trainee	3 years
Research co-ordinator	3 years
Pharmacist	12 years
Honorary Consultant in Paediatric Clinical Pharmacology	2 years
Clinical Pharmacist	30 years

A Likert table was created for assessors to rate the relevance, essentialness and clarity for each question of the original questionnaire. Free text questions were also created for each question for assessors to include their suggestions to improve the questions. The Likert table questions were compulsory. Free text questions were optional unless a low score was given for any of the components (relevance, essentialness, clarity) for a question. The content evaluation questionnaire can be seen in Appendix 6: Content Evaluation Questionnaire.

Potential assessors were contacted prior to distributing the questionnaire by email. We aimed to recruit six to eight assessors. Six staff members from Alder Hey Children's Hospital agreed to validate this questionnaire. An anonymised link to the content evaluation questionnaire was sent to them to validate this questionnaire. A summary of their responses is shown below in Table 6:

Table 6 - Summary of ratings given by experts for each question

Question	Category	Number of experts who gave this rating			
		Not…	Somewhat…	Quite…	Very…
Q1	Relevance	0	0	0	6
	Essentialness	0	0	1	5
	Clarity	0	2	1	3
Q2	Relevance	0	1	2	3
	Essentialness	0	1	2	3
	Clarity	0	0	1	5
Q3	Relevance	0	0	0	6
	Essentialness	0	0	0	6
	Clarity	0	1	2	3
Q4	Relevance	0	0	1	5
	Essentialness	0	0	1	5
	Clarity	0	3	0	3
Q5	Relevance	0	0	6	0
	Essentialness	0	1	5	0
	Clarity	0	0	1	5
Q6	Relevance	0	1	4	1
	Essentialness	0	1	4	1
	Clarity	1	2	1	2
Q7	Relevance	1	2	1	2
	Essentialness	2	1	2	1
	Clarity	1	0	2	3
Q8	Relevance	1	3	1	1
	Essentialness	2	2	2	0
	Clarity	0	2	2	2
Q9	Relevance	0	0	0	6
	Essentialness	0	0	0	6
	Clarity	0	1	1	4
Q10	Relevance	0	0	0	6
	Essentialness	0	0	0	6
	Clarity	1	1	2	2
Q11	Relevance	0	0	0	6
	Essentialness	0	0	0	6
	Clarity	1	2	1	2
Q12	Relevance	0	0	1	5
	Essentialness	0	0	1	5
	Clarity	1	0	2	3
Q13	Relevance	0	0	0	6
	Essentialness	0	0	0	6
	Clarity	1	0	1	4
Q14	Relevance	0	0	1	5
	Essentialness	0	0	1	5
	Clarity	1	0	1	4
Q15	Relevance	0	0	1	5

	Essentialness	0	0	1	5
	Clarity	0	0	2	4
Q16	Relevance	0	1	1	4
	Essentialness	0	1	1	4
	Clarity	0	1	1	4
Q17	Relevance	0	0	0	6
	Essentialness	0	0	0	6
	Clarity	0	0	2	4
Q18	Relevance	0	0	0	6
	Essentialness	0	0	0	6
	Clarity	0	0	2	4
Q19	Relevance	0	1	2	3
	Essentialness	0	1	2	3
	Clarity	0	1	1	4
Q20	Relevance	0	0	2	4
	Essentialness	0	0	2	4
	Clarity	0	1	3	2
Q21	Relevance	0	0	1	5
	Essentialness	0	0	1	5
	Clarity	0	2	0	4
Q22	Relevance	0	0	2	4
	Essentialness	0	0	2	4
	Clarity	0	1	2	3
Q23	Relevance	0	0	2	4
	Essentialness	0	0	2	4
	Clarity	0	1	3	2
Q24	Relevance	0	0	2	4
	Essentialness	0	0	2	4
	Clarity	0	0	4	2
Q25	Relevance	0	0	1	5
	Essentialness	0	0	1	5
	Clarity	0	1	2	3
Q26	Relevance	0	1	1	4
	Essentialness	0	1	1	4
	Clarity	2	2	2	0
Q27	Relevance	0	2	1	3
	Essentialness	0	1	2	3
	Clarity	0	2	2	2
Q28	Relevance	0	0	3	3
	Essentialness	0	0	4	2
	Clarity	0	0	1	5
Q29	Relevance	0	0	2	4
	Essentialness	0	0	2	4
	Clarity	0	0	1	5
Q30	Relevance	0	0	1	5
	Essentialness	0	0	2	4

	Clarity	0	3	1	2
Q31	Relevance	0	0	2	4
	Essentialness	0	0	3	3
	Clarity	1	1	1	3
Q32	Relevance	0	0	4	2
	Essentialness	0	0	4	2
	Clarity	1	0	3	2
Q33	Relevance	0	1	2	3
	Essentialness	0	1	3	2
	Clarity	0	0	1	5
Q34	Relevance	0	1	2	3
	Essentialness	0	1	2	3
	Clarity	0	3	1	2
Q35	Relevance	0	0	2	4
	Essentialness	0	0	2	4
	Clarity	0	1	2	3
Q36	Relevance	0	0	0	6
	Essentialness	0	0	0	6
	Clarity	0	1	0	5
Q37	Relevance	0	0	0	6
	Essentialness	0	0	0	6
	Clarity	0	0	3	3
Q38	Relevance	0	0	1	5
	Essentialness	0	0	1	5
	Clarity	0	1	1	4
Q39	Relevance	0	1	2	3
	Essentialness	0	1	2	3
	Clarity	0	2	2	2
Q40	Relevance	0	0	3	3
	Essentialness	0	0	3	3
	Clarity	0	1	4	1
Q41	Relevance	0	0	1	5
	Essentialness	0	0	1	5
	Clarity	0	1	3	2
Q42	Relevance	0	0	1	5
	Essentialness	0	0	2	4
	Clarity	0	0	0	6
Q43	Relevance	0	0	1	5
	Essentialness	0	0	1	5
	Clarity	0	0	0	6
Q44	Relevance	0	0	2	4
	Essentialness	0	0	2	4
	Clarity	0	1	3	2
Q45	Relevance	1	0	1	4
	Essentialness	1	0	1	4
	Clarity	0	0	1	5

Q46	Relevance	0	0	2	4
	Essentialness	0	0	2	4
	Clarity	0	1	1	4
Q47	Relevance	0	0	1	5
	Essentialness	0	0	1	5
	Clarity	0	0	2	4
Q48	Relevance	0	0	3	3
	Essentialness	0	0	4	2
	Clarity	0	0	3	3
Q49	Relevance	0	0	1	5
	Essentialness	0	0	1	5
	Clarity	0	0	0	6
Q50	Relevance	0	0	1	5
	Essentialness	0	0	1	5
	Clarity	1	2	2	1
Q51	Relevance	0	0	0	6
	Essentialness	0	0	0	6
	Clarity	0	0	0	6
Q52	Relevance	0	0	1	5
	Essentialness	0	0	1	5
	Clarity	0	2	1	3
Q53	Relevance	0	1	2	3
	Essentialness	1	0	2	3
	Clarity	0	1	3	2
Q54	Relevance	0	1	1	4
	Essentialness	1	0	1	4
	Clarity	0	2	1	3
Q55	Relevance	0	0	1	5
	Essentialness	0	0	1	5
	Clarity	0	1	1	4
Q56	Relevance	0	0	2	4
	Essentialness	0	0	2	4
	Clarity	0	1	2	3
Q57	Relevance	0	2	1	3
	Essentialness	0	2	2	2
	Clarity	2	0	4	0
Q58	Relevance	0	0	1	5
	Essentialness	0	0	1	5
	Clarity	0	0	2	4
Q59	Relevance	0	0	1	5
	Essentialness	0	0	2	4
	Clarity	0	1	0	5
Q60	Relevance	0	0	1	5
	Essentialness	0	0	1	5
	Clarity	0	4	2	0
Q61	Relevance	0	1	1	4

	Essentialness	0	1	1	4
	Clarity	0	0	2	4
Q62	Relevance	0	1	1	4
	Essentialness	0	1	2	3
	Clarity	0	1	4	1

The number of experts who provided each rating (Not, Somewhat, Quite, or Very) for each category (Relevance, Essentialness and Clarity) for each question.

A Content Validation Index (CVI) score was then calculated for each item in the questionnaire based on the feedback from the content evaluation questionnaire. A score of one was given to questions that were rated “Quite relevant” or “Very relevant” by an expert (staff member) and a score of 0 was given to questions that were rated “Somewhat relevant” or “Not relevant”. The same was done for essentialness and clarity. The average score for each question was used to calculate the CVI for items (I-CVI). The Universal agreement (UA) score was calculated as either one or zero, with a score of one being given if all experts agreed that an item was relevant and a score of 0 if not all experts agreed. The average of the I-CVI scores for each question were then used to calculate the CVI for scale (S-CVI). As six experts were involved in evaluating the questionnaire, questions remained in the questionnaire if their I-CVI was at least 0.83 (83). Questions were removed if their I-CVI values were less than 0.83. Table 7 shows the results from the content evaluation process in more detail:

Table 7 - Content Validation Index (CVI) Scores for the questions' relevance

Item	Expert 1	Expert 2	Expert 3	Expert 4	Expert 5	Expert 6		Experts in agreement	I-CVI	UA	Interpretation
Q1	1	1	1	1	1	1		6	1	1	Adjusted
Q2	1	1	1	1	1	0		5	0.833333	0	Adjusted
Q3	1	1	1	1	1	1		6	1	1	Adjusted
Q4	1	1	1	1	1	1		6	1	1	Adjusted
Q5	1	1	1	1	1	1		6	1	1	Remain
Q6	1	1	1	1	0	1		5	0.833333	0	Adjusted
Q7	1	0	0	1	0	1		3	0.5	0	Remove
Q8	1	0	0	1	0	0		2	0.333333	0	Remove
Q9	1	1	1	1	1	1		6	1	1	Adjusted
Q10	1	1	1	1	1	1		6	1	1	Adjusted
Q11	1	1	1	1	1	1		6	1	1	Adjusted
Q12	1	1	1	1	1	1		6	1	1	Remain
Q13	1	1	1	1	1	1		6	1	1	Adjusted
Q14	1	1	1	1	1	1		6	1	1	Adjusted
Q15	1	1	1	1	1	1		6	1	1	Remain
Q16	1	1	1	0	1	1		5	0.833333	0	Remain
Q17	1	1	1	1	1	1		6	1	1	Adjusted
Q18	1	1	1	1	1	1		6	1	1	Adjusted
Q19	1	1	1	1	0	1		5	0.833333	0	Adjusted
Q20	1	1	1	1	1	1		6	1	1	Adjusted
Q21	1	1	1	1	1	1		6	1	1	Adjusted
Q22	1	1	1	1	1	1		6	1	1	Adjusted
Q23	1	1	1	1	1	1		6	1	1	Adjusted
Q24	1	1	1	1	1	1		6	1	1	Adjusted
Q25	1	1	1	1	1	1		6	1	1	Remain
Q26	1	1	1	1	0	1		5	0.833333	0	Adjusted

Q27	1	1	1	0	0	1		4	0.666667	0	Remove
Q28	1	1	1	1	1	1		6	1	1	Adjusted
Q29	1	1	1	1	1	1		6	1	1	Remain
Q30	1	1	1	1	1	1		6	1	1	Adjusted
Q31	1	1	1	1	1	1		6	1	1	Adjusted
Q32	1	1	1	1	1	1		6	1	1	Adjusted
Q33	1	1	1	1	0	1		5	0.833333	0	Remain
Q34	1	1	1	0	1	1		5	0.833333	0	Adjusted
Q35	1	1	1	1	1	1		6	1	1	Adjusted
Q36	1	1	1	1	1	1		6	1	1	Adjusted
Q37	1	1	1	1	1	1		6	1	1	Remain
Q38	1	1	1	1	1	1		6	1	1	Adjusted
Q39	1	1	1	1	0	1		5	0.833333	0	Adjusted
Q40	1	1	1	1	1	1		6	1	1	Adjusted
Q41	1	1	1	1	1	1		6	1	1	Adjusted
Q42	1	1	1	1	1	1		6	1	1	Remain
Q43	1	1	1	1	1	1		6	1	1	Remain
Q44	1	1	1	1	1	1		6	1	1	Adjusted
Q45	1	1	1	0	1	1		5	0.833333	0	Adjusted
Q46	1	1	1	1	1	1		6	1	1	Adjusted
Q47	1	1	1	1	1	1		6	1	1	Adjusted
Q48	1	1	1	1	1	1		6	1	1	Adjusted
Q49	1	1	1	1	1	1		6	1	1	Remain
Q50	1	1	1	1	1	1		6	1	1	Adjusted
Q51	1	1	1	1	1	1		6	1	1	Remain
Q52	1	1	1	1	1	1		6	1	1	Adjusted
Q53	1	1	1	1	0	1		5	0.833333	0	Adjusted
Q54	1	1	1	1	0	1		5	0.833333	0	Adjusted
Q55	1	1	1	1	1	1		6	1	1	Adjusted
Q56	1	1	1	1	1	1		6	1	1	Adjusted

Q57	1	1	1	0	0	1		4	0.666667	0	Remove
Q58	1	1	1	1	1	1		6	1	1	Adjusted
Q59	1	1	1	1	1	1		6	1	1	Adjusted
Q60	1	1	1	1	1	1		6	1	1	Adjusted
Q61	1	1	1	1	0	1		5	0.833333	0	Remain
Q62	1	1	1	0	1	1		5	0.833333	0	Adjusted
Proportion relevance	1	0.967742	0.967742	0.903226	0.806452	0.967742		**S-CVI/Ave**	**0.935484**		
Average proportion of items judged as relevant across 6 experts							**0.9355**	**S-CVI/UA**		**0.7258**	

I-CVI: Content Validity Index for Item; S-CVI: Content Validity Index for Scale; UA: Universal Agreement; S-CVI/Ave: Average S-CVI score for all items; S-CVI/UA: Average of UA scores for all items.

The appropriate changes were made to the questionnaire to improve the clarity of 45 questions. 18 of these questions were made clearer due to low I-CVI scores for clarity and 27 questions were adjusted based on feedback from the experts. Questions 7, 8, 27 and 57, which were related to the mother's pregnancy, administering regular medicines overnight and difficulties accessing their child's medicines were removed from the original questionnaire as their CVI scores were less than 0.83. Despite removing these questions, all of the domains covered in the systematic review are assessed in the new version of the questionnaire. Some questions were reworded to make it clearer for participants. Explanations were also added to some questions to clarify any doubts participants may potentially have. The options were also changed for some of the multiple choice questions. The original questionnaire had 62 items and the new version had 58 questions. This version of the questionnaire can be seen in Figure 4:

Figure 4 - PANDA Parent Questionnaire - Final version

Alder Hey Children's NHS
NHS Foundation Trust

PMRU

University of Liverpool

PANDA Study

Study Questionnaire – Parent/Guardian

➢ General information about your child

What is your child's age in years and months, e.g. 2 years 5 months? If your child is under 1 please give your answer in months.: _____ years and _____ months

What is your child's gender?:

- o Male
- o Female
- o Prefer not to say

Does your child have underlying medical conditions, e.g. asthma? If so, what are they?

_____

_____

Would you be happy if we review clinic letters to gather this information?

- o Yes
- o No

Was your child born prematurely?

- o Yes
- o No

How many weeks gestation was your child born? _____ weeks

➢ Quantity and type of medicines

How many different medicines is your child currently taking?
Please include medicines prescribed by your child's GP or the hospital. This can include all forms of medicines, e.g. tablets, capsules, oral liquids, injections.
Do not include over the counter medicines, i.e. medicines bought at a pharmacy or shop without a prescription.

_____

If your child's medicines are complex or you are not sure of all the details, are you happy if we review their current prescription and/or clinic letter to collect this information?

- Yes
- No

For each medicine, please state the following (e.g. salbutamol 100 micrograms, taken when needed, inhaler; omeprazole 40mg once daily, regular medicine, tablet):

- Drug: _____
- Dose: _____
- Frequency: _____
- Is it a regular medicine or a medicine taken when needed?
  _____
- Formulation: _____

➢ How effective are your child's medicines?

Overall, please indicate how effective your child's medicines are in managing their condition(s):

- Very good
- Good
- Just adequate
- Poor
- Useless
- Don't know/can't tell

It is possible to manage my child's condition(s) with medicines so they are free of symptoms:

- Strongly agree
- Agree
- Disagree
- Strongly disagree
- Don't know/can't tell

It is possible to control my child's condition(s) with medicines so that they can carry out daily activities like other children:

- Strongly agree
- Agree
- Disagree
- Strongly disagree
- Don't know/can't tell

I worry about the effectiveness of my child's medicines:

- Strongly agree
- Agree
- Disagree
- Strongly disagree
- Don't know/can't tell

How do you think your child's health is now?

- Excellent
- Good
- Fair
- Poor
- Don't know/can't tell

Which medicine(s) do you think work well for your child? Please write the names of the medicines below, e.g. omeprazole, Gaviscon, aspirin:

_____

Which medicine(s) do you think do not work well for your child (if any)? Please write the names of the medicines below, e.g. omeprazole, Gaviscon, aspirin:

_____

➢ <u>How easy is it to administer your child's medicines?</u>

Has a doctor or health care professional ever given you instructions on how to administer any of your child's medicines?

- Yes
- No

How easy is it to administer your child's medicines each day (please tick the appropriate score)?

- 0 – very difficult
- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9
- 10 – very easy

Who is involved in administering your child's medicines? Tick all that apply:

- Parent
- Grandparent
- Child
- Carer
- Other: _____

How often does your child take his/her medicines on his/her own?

- Daily
- Weekly
- Monthly
- Never

- Don't know/can't tell

Administering your child's medicines upsets you:

- Strongly agree
- Agree
- Disagree
- Strongly disagree
- Don't know/can't tell

Administering your child's medicines upsets your child:

- Strongly agree
- Agree
- Disagree
- Strongly disagree
- Don't know/can't tell

On average, how many times a day do you have to give your child their regular medicines, i.e. medicines that need to be taken once or more each day?

_____

On average, how many times a day do you have to give your child their as required medicines?

_____

➢ Factors affecting adherence to medicines

Have you ever run out of any of your child's medication(s)?

- Yes
- No

Has your child ever missed a dose of their medication(s)?

- Yes
- No

How often does your child miss doses of their medications?

- Daily
- Several times a week
- Once a week
- More than once a month
- Less than once a month

Who writes the prescriptions for your child medicines? Tick all that apply:

- GP
- General paediatrician
- Specialist paediatrician
- Other: _____

Are all of your child's medicines on one single repeat prescription?

- o Yes
- o No

Do you receive any medicines through a "Homecare" delivery?

- o Yes
- o No

How many medicine(s) does your child require to be issued on repeat prescription each month?

_____

How often do you have problems getting prescriptions dispensed at the pharmacy?

- o Never
- o Once a year
- o Once a month
- o Once a week

➢ Medication side effects

Do you think your child has had any side effects from their current medicines?

- o Yes
- o No

Which medication(s) do you think is causing these side effects?

_____

What side effect(s) does your child's medication(s) cause?

_____

When do these side effects occur?

- o After the dose
- o All the time
- o Daily
- o More than once a week
- o Less than once a week

Who did you inform about the side effects your child has had?

_____

Overall, how severe do you think the side effects are that your child's medicines have caused:

- o Very serious - bad enough to go to hospital
- o Somewhat serious - to see a healthcare professional like a doctor or pharmacist
- o Was bad enough to affect what you do everyday

- Mild or uncomfortable
- Very mild or slightly uncomfortable
- Not serious
- Don't know

I worry about the side effects of my child's medicines:

- Strongly agree
- Agree
- Disagree
- Strongly disagree
- Don't know/can't tell

➢ How do your child's medicines affect your child physically?

My child's medicines stop my child from doing certain activities:

- Strongly agree
- Agree
- Disagree
- Strongly disagree
- Don't know/can't tell

➢ How do your child's medicines affect you psychologically?

How often do you worry or stress about your child while they are on medication?

- Daily
- Weekly
- Monthly
- Not at all

I often feel helpless in managing my child's medicine(s):

- Strongly agree
- Agree
- Disagree
- Strongly disagree
- Don't know/can't tell

➢ How do your child's medicines affect your and your child's social life?

How often do you plan your day around your child's medication(s)?

- Almost all the time (90% or higher)
- Most of the time (75%)
- Some of the time (50%)
- A little of the time (25%)
- Never (0%)

How often do you avoid social activities with your child because of their medication(s)?

- Almost all the time (90% or higher)
- Most of the time (75%)

- Some of the time (50%)
- A little of the time (25%)
- Never (0%)

How often do you worry about other people's perceptions of you as a parent because they are on medication?

- Almost all the time (90% or higher)
- Most of the time (75%)
- Some of the time (50%)
- A little of the time (25%)
- Never (0%)

➢ How much time is needed to administer your child's medicines?

My child spends a lot of time taking their medicines everyday:

- Strongly agree
- Agree
- Disagree
- Strongly disagree
- Don't know/can't tell

In total, how long do you spend preparing and administering your child's medicines each day? Please answer in hours and minutes. _____

➢ How much do your child's medicines cost?

Do you have to pay for any of your child's prescriptions?

- Yes
- No

How much do you spend on medicines each month? £_____

How do you feel about the cost of their medicines?

_____

How does the cost of medicines affect your family?

_____

➢ How much does it cost to access your child's medicines?

How much do you spend picking up medicines each month (e.g. fuel, parking charges, transport, etc.)? £_____

➢ How does administering your child's medicines affect work and school?

Does your child experience any problems taking medicines at school?

- Yes

- No
- Not applicable – doesn't take medicines at school

How often is your child absent or late for school or other activities because of their medicines?

- Every day
- Once a week
- Once a month
- Once a year
- Never
- Not applicable

Have you ever had to change your job, cut back your work hours, work schedule, or quit work altogether due to issues related to your child's medicines (and not for their medical condition)?

- Yes, have to change job
- Yes, have to change work shift
- Yes, have to cut back hours
- Yes, have to quit working
- No
- Not applicable

In the last 4 weeks, how many total hours of work did you miss due to issues related to your child's medicines? _____

➢ <u>How does managing your child's medicines affect your relationships?</u>

Does managing your child's medicines put strain on your relationships, e.g. relationships with your children, spouse, etc.?

- A tremendous amount of strain
- A lot of strain
- A moderate amount of strain
- A little strain
- No strain
- Not applicable

➢ <u>Other difficulties accessing and administering your child's medicines</u>

Do you have any other difficulties with accessing or administering medicines not mentioned above?

- Yes, please state: _____
- No

<u>Thank you for taking the time to complete our questionnaire</u>

3.3.6 Recruitment of participants

3.3.6.1 Inclusion and exclusion criteria

Parents of children aged 0 days to 18 years old who attended Alder Hey as inpatients or outpatients were recruited for this study. As this study aimed to assess the impact of polypharmacy, the participants' children must be on ≥5 medications at the time of recruitment. This threshold was chosen as patients of all ages experiencing polypharmacy would be taking at least five medicines and as numerical definitions of paediatric polypharmacy varied in existing studies. Children taking four medications or less were therefore excluded. All routes of administration were included. Blood products were excluded.

3.3.6.2 Recruitment process

A full-time research student asked clinical and administrative members of the healthcare team if they had suitable participants in selected wards (HDU, Ward 1C, Ward 3C, Ward 4A, Ward 4B and Ward 4C) and outpatient clinics. Participants were then approached by a full-time research student with copies of the appropriate consent/assent forms and patient information sheets. Age appropriate patient information sheets were provided for children and young people. The research student was available to answer any queries participants had during the consent process. The research student returned after a 24 hour period to check if the families approached were interested, address any remaining questions or concerns and take consent and assent (where appropriate) from those who agreed to take part. Participants who provided consent to participate in this study then completed the questionnaire electronically on Qualtrics with the research student or another staff member present.

3.3.7 Statistical analysis

The data was analysed through Qualtrics and Excel. Numbers, percentages and standard deviations for each question were obtained through Qualtrics. Mean and median figures were also calculated where necessary. The data that was collected from the patient information systems on patients' medical conditions and medicines was added to the raw data in an Excel spreadsheet.

For results related to patient's medicines that were unclear, the data collected from patients' medical records was checked to find the appropriate information. If this information could not be found, the responses are presented as reported by participants.

I have previously conducted an audit at the same unit in Alder Hey to determine the scale of polypharmacy and the types of medicines that contributed to it. The data has been published (84) and will be compared with the data from the PANDA pilot study.

To determine the impact of each domain in this pilot study, the numbers and percentages of participants who provided responses that demonstrated an impact for each question were gathered. These figures were then grouped into each domain and was converted to a number by calculating

the average percentage for each domain. These were then used to make a radar diagram that demonstrated the relative impact of each domain on participants in the pilot study.

Chapter 4: Polypharmacy ANd Drug optimisAtion (PANDA) study pilot phase – results

4.1 Results/main findings

The target recruitment for the PANDA study was 100 patients, but due to time constraints of the MPhil and thesis submission, the results for the first 36 patients are presented in this thesis while recruitment is ongoing.

4.1.1 Sample characteristics

36 participants agreed to take part in the study. 63 parents were approached for the study by a full-time research student on chosen wards and clinics as described in Section 3.3.6.2 Recruitment process. Eight parents refused to take part due to various reasons. Seven stated that they had a lot going on and two also refused due to taking part in other research studies. Five participants were lost to discharge and 12 parents could not be contacted after the first approach. One reason for this was because participants seen in outpatient settings did not respond to follow up emails about taking part.

Parents of 36 patients were recruited to pilot the questionnaire. Patients of various ages were recruited and the proportion of male and female patients was nearly even in this cohort. Parents of 20 female patients and 16 male patients completed the questionnaire.

Patients in this cohort ranged from 3 months old to 16 years and 4 months old, with the mean age being approximately eight years old (8.36). 14 patients were 0-6 years old, nine patients were 7-11 years old, 11 patients were 12-15 years old and two patients were 16-18 years old. One patient completed the questionnaire themselves and the parents of the remaining 35 patients completed the questionnaire for this study.

Patients were recruited from various areas in the hospital. One patient was recruited from the High Dependency Unit (HDU). Three patients were recruited from Ward 1C and 12 patients were recruited from Ward 3C. Two patients were recruited from Ward 4A, six patients were recruited from Ward 4B and 12 patients were recruited from Ward 4C.

Prematurity was more common in this cohort than in the general population, with seven out of 36 (19.4%) patients being born prematurely compared to 7.4% of children being born prematurely in the UK in 2020 (85). Their gestation ranged from 28 weeks to 36 weeks.

Patients recruited to this study had a large range of underlying diagnoses. The commonest medical conditions patients had were epilepsy, gastroesophageal reflux, acute kidney injury (AKI), constipation, dystonia, developmental delays and visual impairments. Table 8 shows the commonest medical conditions in this cohort and the prevalence of these medical conditions.

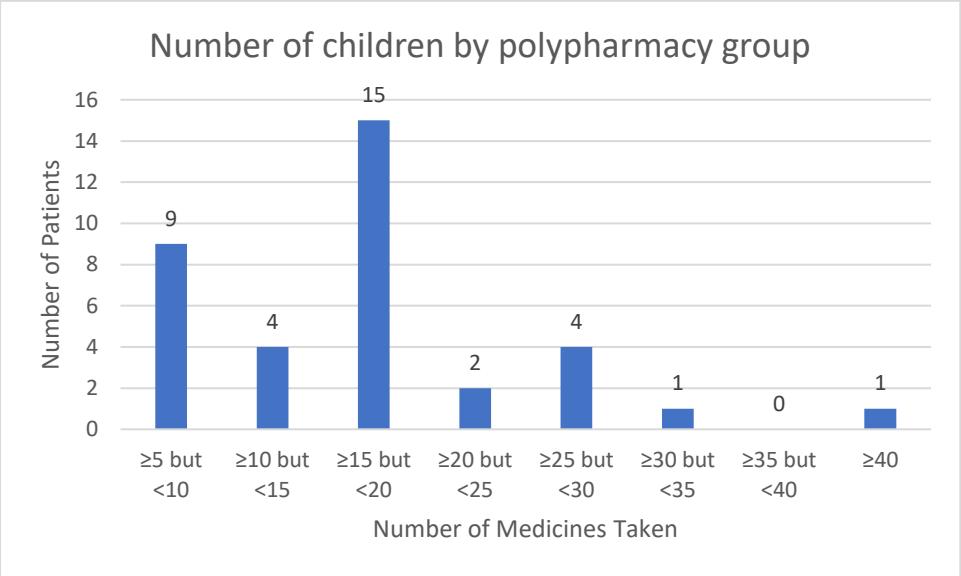
*Table 8 - Top 10 underlying medical conditions**

Medical condition	Number of patients with the condition (n = 36)
Seizures/epilepsy	10
Global developmental delay	7
Gastroesophageal reflux	6
Acute Kidney Injury (AKI)	5
Ventricular septal defect (VSD)	5
Constipation	4
Dystonia	4
Scoliosis	4
Atrial septal defect (ASD)	3
Cerebral palsy	3

**patients may have more than one medical condition*

Patients in this cohort were taking a range of medicines. The number of medicines patients were taking ranged from five to 43, with the mean number of medicines patients in this cohort took being 15.8 and the median being 15 medicines. The number of medicines taken by patients is shown in Figure 5.

Figure 5 - Number of medicines taken by patients grouped by polypharmacy group



Certain medicines were taken by more patients in this study than others. The commonest medicines taken by patients in this cohort are shown in Table 9. There were some similarities between the results of this study and the results of the audit (84). Omeprazole, sodium chloride, dioralyte sachets, heparin/saline ampoules, morphine and paracetamol were among the commonest medicines in both studies (84). Anti-emetics and corticosteroids were also among the commonest medicines in both studies but different medicines in these classes were used more frequently in both cohorts (84).

Table 9 - Top 10 commonest medicines taken by patients

Medicine	Number of times it was prescribed
azithromycin [azithromycin 200mg/5ml suspension]	11
omeprazole [omeprazole 10mg/5ml oral suspension]	11
hydrocortisone [hydrocortisone 5mg/5ml suspension]	10
paracetamol [paracetamol 250mg/5ml (over 6) suspension]	10
sodium chloride [sodium chloride 0.9% 10ml plastic ampoule]	10
domperidone [domperidone 5mg/5ml suspension]	8
octenidine hydrochloride [octenisan antimicrobial hair and body wash]	8
oral rehydration salts [dioralyte sachets]	8
heparin sodium [heparin/saline 10 units/ml 5ml ampoule]	7
levetiracetam [levetiracetam (Keppra) 100mg/ml oral liquid]	7

4.1.2 Medication related burden – results from questionnaires

4.1.2.1 Effectiveness of children's medicines

Most participants felt that their child's medicines were effective overall in managing their child's underlying conditions, with 13 parents reporting that their child's medicines were very effective and 10 parents reported their child's medicines were good. 10 parents felt that their child's medicines were adequate, one parent felt that their child's medicines were not effective and two parents were not sure.

Most parents felt that their child's medicines managed their child's conditions adequately so their child was free of symptoms (22/36) and so that their child could carry out daily activities (24/36). Nearly half of the participants (17/36) were worried about the effectiveness of their child's medicines but 14 parents reported that they were not worried about it.

Table 10 - Managing participants' children's conditions with medicines

Question	Number and % of participants (n = 36)				
	Strongly agree	Agree	Don't know/can't tell	Disagree	Strongly disagree
It is possible to manage my child's condition(s) with medicines so they are free of symptoms:	7 (19.4%)	15 (41.7%)	7 (19.4%)	6 (16.7%)	1 (2.8%)
It is possible to control my child's condition(s) with medicines so that they can carry out daily activities like other children:	9 (25.0%)	15 (41.7%)	5 (13.9%)	4 (11.1%)	3 (8.3%)
I worry about the effectiveness of my child's medicines:	7 (19.4%)	10 (27.8%)	5 (13.9%)	14 (38.9%)	0 (0.0%)

Over half of the participants (17/36) felt that their child's health was 'fair' overall. Half of the remaining participants (9/36) felt that their child's health was good and nine parents felt that their child's health was poor. One parent reported that they were unsure. Patients whose health was perceived to be good and fair or poor had various health conditions, with patients whose health was perceived to be fair or poor having a greater number of underlying diagnoses. Certain chronic conditions were more common in patients whose health was perceived to be fair or poor, such as gastroesophageal reflux and global developmental delays.

Participants reported that certain medicines worked well in managing their child's conditions. Antiepileptics (n = 12) and proton pump inhibitors (PPI) (n = 9) were most commonly reported to work well for patients. The medicines that were most frequently reported to work well are shown in Table 11. Two parents also stated that none of their child's medicines worked well for them and three parents stated that they were unsure which medicines worked well for their child. Another parent also felt that all of their child's medicines were working well for them. Some parents also stated how they felt certain medicines worked well for them. For example, one participant stated that omeprazole helped their child settle when they were feeling sick and another parent stated that their child's nebuliser provided "instantly visible results". Some parents also stated which medicines managed certain conditions well.

Table 11 - Medicines that were reported to work well by more than one participant

Medicine that worked well for patients	Number of participants (n = 36)
Melatonin	6
Omeprazole	5
Domperidone	3
Furosemide	3
Prednisolone	3
Aspirin	2
Carbamazepine	2
Clobazam	2
Clonidine	2
Esomeprazole	2
Gabapentin	2
Lansoprazole	2
Levetiracetam (Keppra)	2
Sodium chloride	2
Trimethoprim	2
Zonisamide	2

Some parents also reported certain medicines that were not effective in managing their child's conditions. A lot of parents felt that all of their child's medicines were effective. Some parents felt that a some of their child's medicines were not effective and two parents felt that none of their child's medicines were effective. In some cases, participants were unsure if certain medicines were necessary and some participants stated that their child still had symptoms or other issues despite taking their medicines. The commonest medicine that parents felt did not work well for their child was omeprazole, with five parents mentioning this. Table 12 shows the medicines that were most frequently reported to be ineffective.

Table 12 - Medicines that were reported to not work well by more than one participant

Medicines that did not work well for patients	Number of participants (n = 36)
None	14
Omeprazole	5
Sodium chloride	3
Azithromycin	2
Paracetamol	2

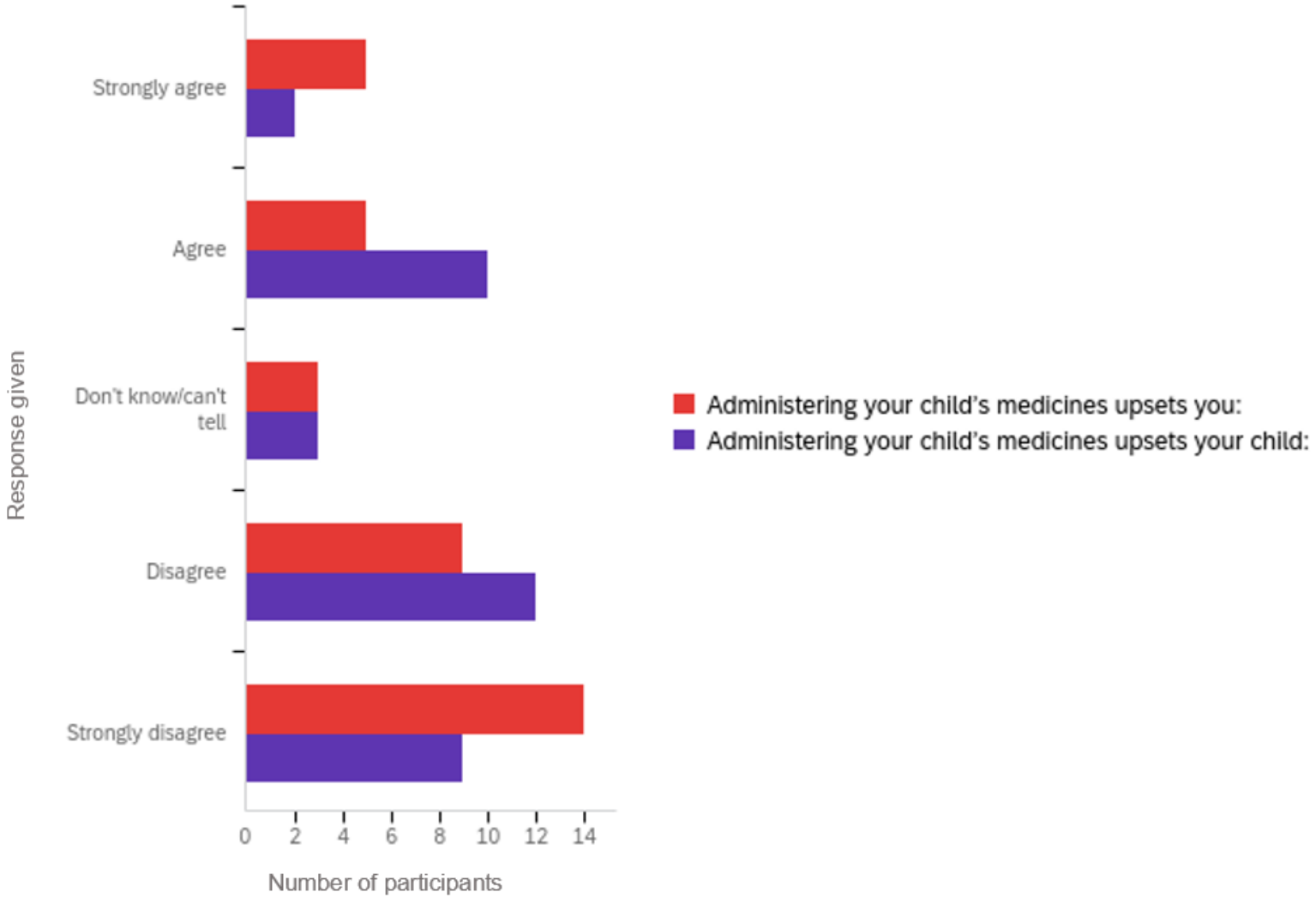
4.1.2.2 Ease of use/convenience

Overall, parents felt that their child's medicines were easy to administer. The vast majority of parents (35/36) were given written instructions on administering their child's medicines by a doctor or other healthcare professional. When parents were asked to rate the ease of administering their child's medicines from 0-10 (with 0 meaning it is it very difficult and 10 meaning it is very easy), most parents rated it as a 10 (19/36). There was some variation in the results for this question, with the standard deviation being 2.67.

All parents were involved in administering their child's medicines. Five patients also administered their own medicines, with all of them being adolescents. Other people who were involved in administering their child's medicines included carers (5/34), nurses (4/34), grandparents (1/34), and teaching assistants in schools (1/34). Another question that asked how often children administered their own medicines showed that 12 children administered their medicines daily and the remaining 22 children never administered their own medicines. It is possible however that this question was misinterpreted by some participants as the findings from this question are inconsistent with the findings from the previous question.

Administering their child's medicines were shown to cause more distress to children than parents, as shown in Figure 6.

Figure 6 - Does administering your child's medicines upset you or your child?



Parents had to administer their child's regular medicines nearly four (3.71) times a day on average and their child's PRN medicines over three (3.07) times a day on average.

4.1.2.3 Adherence to medicines

An even proportion of parents reported running out of their child's medicines, with 18 parents reporting that they have run out of their child's medicines and 18 reporting that they hadn't. A similar pattern was seen when parents were asked whether their child missed any doses of their medications, with slightly more parents saying that their child had never missed a dose of their medicines (20/36). Out of those who have missed doses of their medicines (n = 16), the vast majority of them (14/16) missed doses less than once a month, one child missed doses once a week and only one child missed doses of their medicines several times a week.

A range of medical professionals were involved in prescribing medicines for the paediatric patients in this cohort. GPs prescribed medicines for 21 patients, general paediatricians prescribed medicines for at least 10 patients and specialist paediatricians prescribed medicines for at least 22 patients. Other healthcare staff who were prescribed medicines for patients included nurses and ANPs (advanced nurse practitioners).

Over half of participants (19/36) stated that their prescriptions were not on a single repeat prescription, with the remaining 17 participants reporting that their child's medicines were on a single repeat prescription.

Some parents stated that they received their child's medicines through a homecare delivery (14/36) but most participants did not have their medicines delivered (22/36).

The number of medicines that patients needed to be issued on repeat prescription each month ranged from 0 to 15, with an average of 8.75 medicines being issued on repeat prescriptions each month.

Most participants experienced problems getting medicines dispensed at the pharmacy, with three participants experiencing difficulties weekly, 13 participants experiencing difficulties monthly and seven participants experiencing difficulties annually. 13 participants reported they never had difficulties getting medicines dispensed at the pharmacy.

4.1.2.4 Side effects

Slightly more participants (19/36) reported that their child experienced side effects, compared to 17 participants whose child did not have any side effects. Patients who experienced side effects took between six and 43 medicines, with a mean of 17 medicines and a median of 16 medicines.

Some participants were unsure which medicines were causing their child's side effects. Antiepileptic medicines (n = 6), including levetiracetam (n = 2), carbamazepine (n = 1) and clobazam (n = 1), were suspected to cause side effects more often than others. Table 13 shows the medicines that were suspected to cause side effects in this cohort.

Table 13 - Medicines suspected to cause side effects

Medicines causing side effects	Number of participants (n = 19)
Unsure	3
Antiepileptics – not specified	2
Levetiracetam	2
Atenolol	1
Carbamazepine	1
Clobazam	1
Clonidine	1
Dalivit	1
Diuretics	1
Fluoxetine	1
Hydrocortisone	1
Laxatives	1
Midazolam	1
Movicol	1
Mycophenolate	1
Pizotifen	1
Prednisolone	1
Quetiapine	1

A range of side effects were reported by parents, with the commonest side effects being vomiting and sleepiness or drowsiness. Other side effects mentioned included behavioural changes, low mood, changes to their sleep, changes to their renal function, changes to their blood glucose levels, etc. Antiepileptic medicines were shown to cause a range of side effects including headaches, respiratory problems, sadness, sleepiness, drowsiness and low muscle tone.

Table 14 - Side effects reported participants

Side effect	Number of participants (n = 19)
Drowsiness	2
Sleepy	2
Vomiting	2
Behaviour	1
Bowel changes	1
Choking	1
Hair loss	1
High blood sugar levels	1
Itchy rashes	1
Kidney issues	1
Loose bowels	1
Low muscle tone	1

Nausea	1
Respiratory problems	1
Sad	1
Stops breathing	1
Tummy ache	1
Weight gain	1

Side effects occurred at varying frequencies for participants in this study as shown in Table 15.

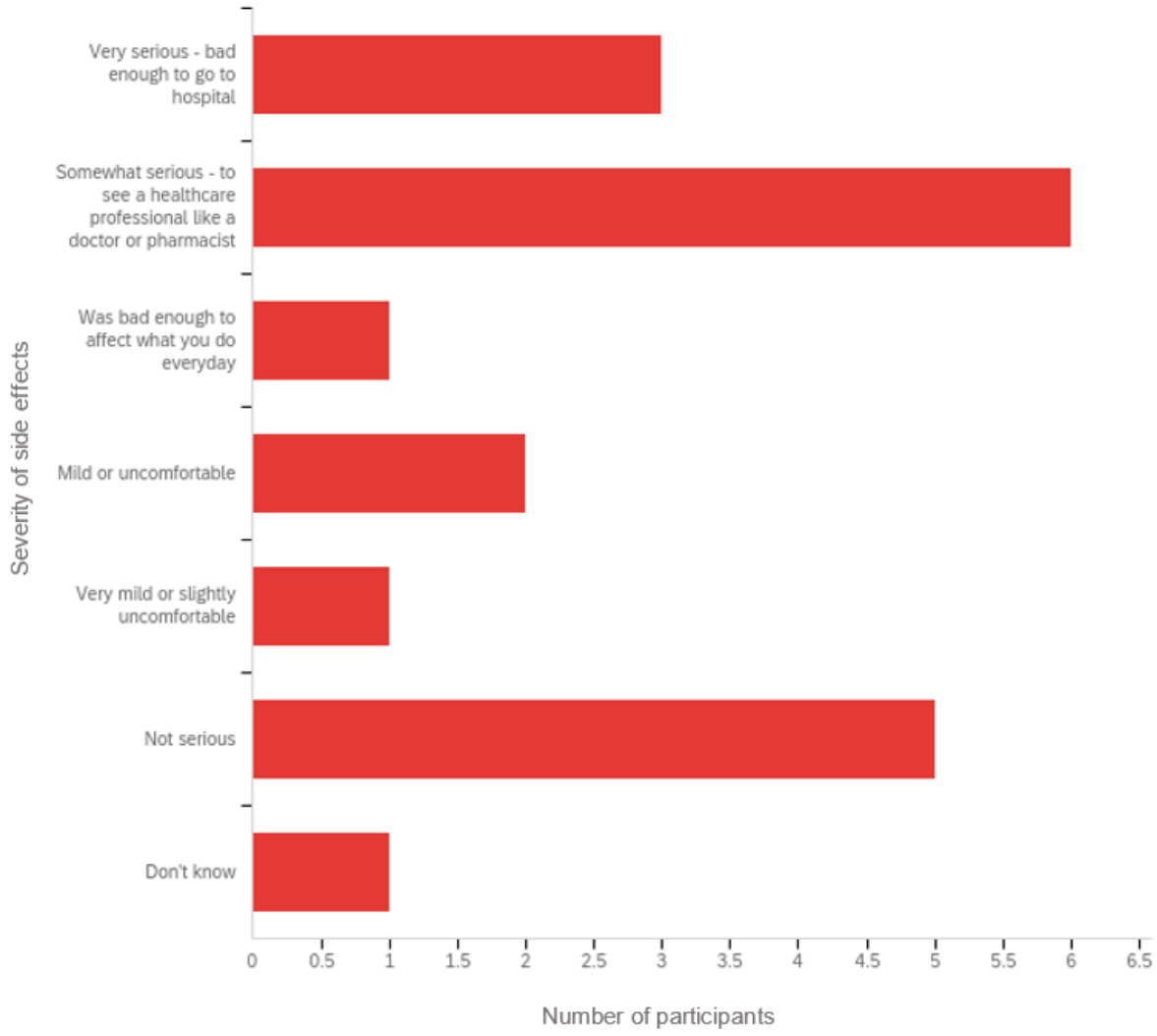
Table 15 - How often patients experienced side effects

When the side effect occurred	Number of participants
After the dose	6
All the time	5
Daily	1
Less than once a week	7

Most parents reported their child's side effects to nurses or their doctor. One participant stated that they did not report their child's side effects to anyone and adjusted the doses of their child's medicines instead. Two parents reported their child's side effects in A&E.

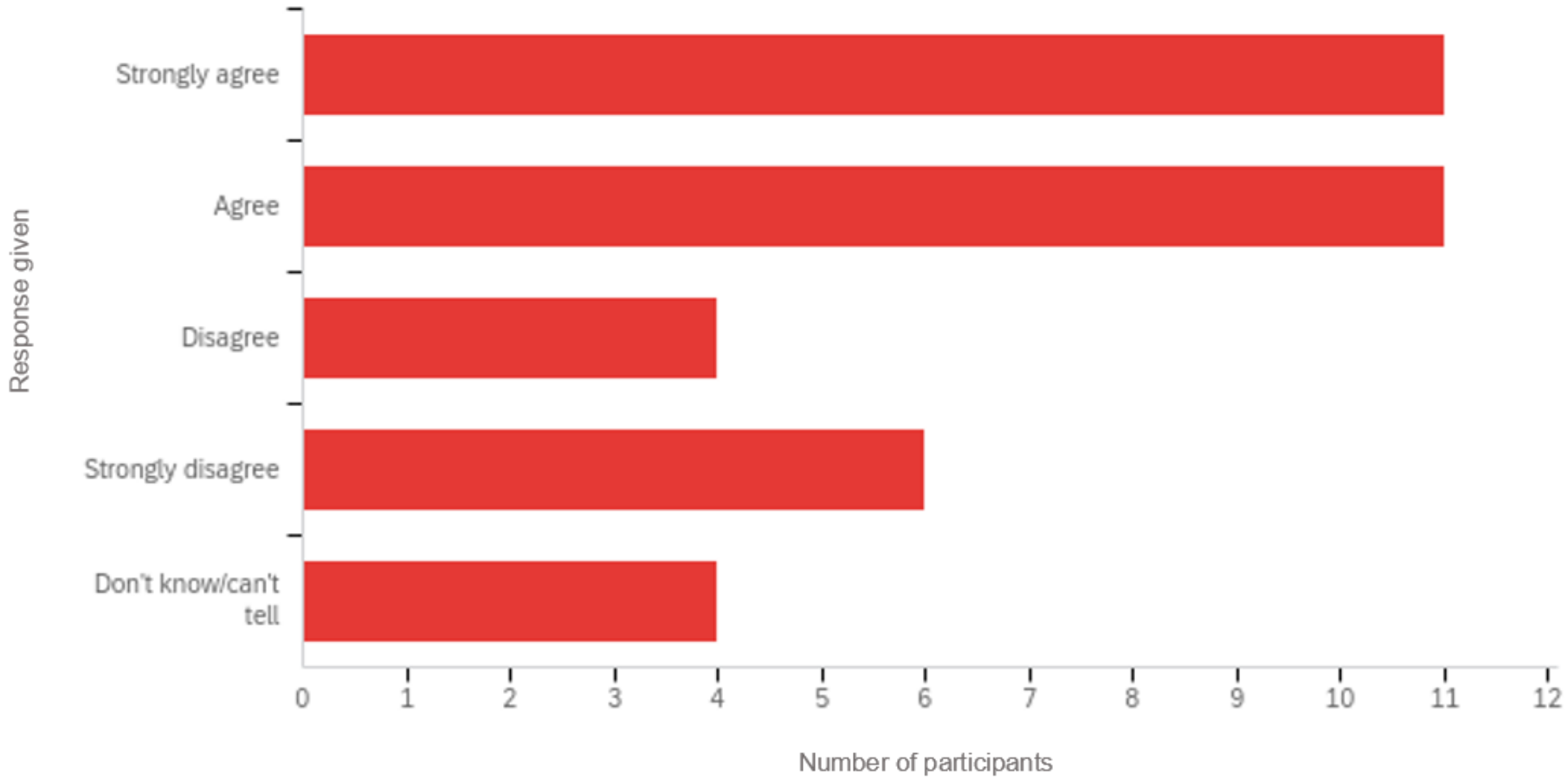
The severity of side effects varied in this cohort, as shown in Figure 7, with most parents reporting that their child's side effects were serious (9/19) enough to see a healthcare professional or to go to hospital. Eight participants also stated that the patients' side effects did not affect their daily activities.

Figure 7 - Severity of side effects



Most participants also reported that they were worried about the side effects of their child's medicines (22/36). 10 participants were not worried about side effects and four participants were unsure. Eight out of the nine participants whose child had somewhat serious or very serious side effects were worried about side effects.

Figure 8 - Worries about side effects of patients' medicines



4.1.2.5 Physical impact of medicines

Most parents reported that their child's medicines prevented their child from doing certain activities (15/36). 12 participants felt that their child's medicines did not prevent their child from doing certain activities and nine participants were unsure. The number of medicines was shown to impact patients' physical functioning, with those who strongly agreed that they were prevented from doing certain activities due to their medicines taking more medicines on average than those who strongly disagreed. Those who strongly agreed took between 11 and 25 medicines and took 19 medicines on average. Those who strongly disagreed took between nine and 21 medicines and took 15 medicines on average. Certain medicines were more common among those who strongly agreed. These medicines included paracetamol, epoetin beta, midazolam, alfacalcidol, levetiracetam, ondansetron and phenytoin sodium.

4.1.2.6 Psychological impact of medicines

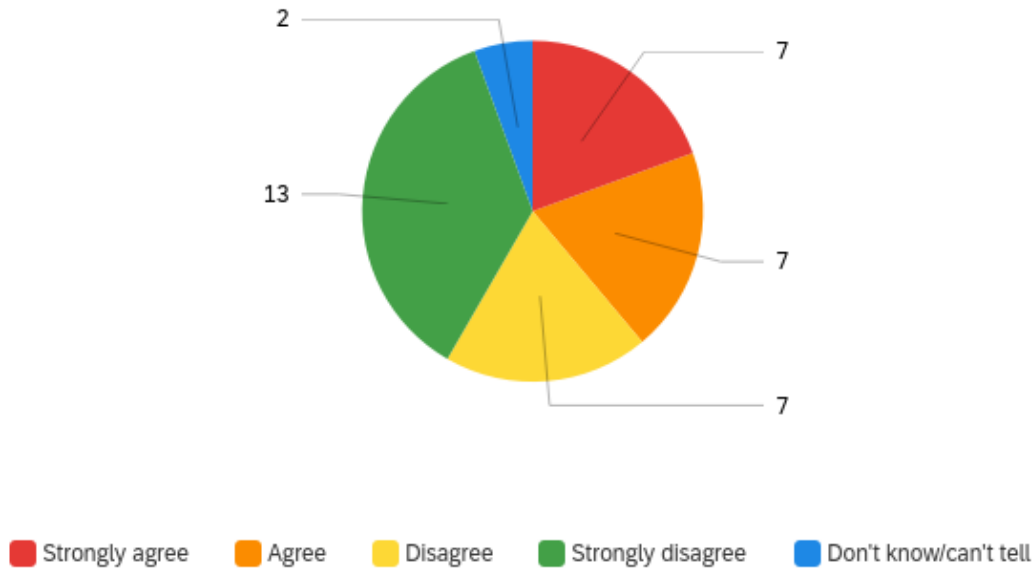
Most participants felt worried or stressed about their child while they were on medication, with 17 participants experiencing this daily and five participants experiencing this weekly. 13 participants also stated that they never felt worried or stressed while their child was on medication. Certain medicines were more commonly prescribed for patients whose parents felt stressed daily. These medicines included omeprazole, paracetamol, hydrocortisone, ondansetron, tacrolimus, chlorphenamine and furosemide. Participants whose child had AKI, hydrocephalus, VSD, ASD, migraines, CKD and scoliosis as underlying diagnoses were also more likely to be stressed about their child's medicines more often. The number of medicines did not differ a lot between parents who experienced some stress and parents who were not stressed at all, as shown in Table 16.

Table 16 - Comparison of the number of medicines taken and participants' stress

Parental stress – frequency	Average number of medicines patients were taking	Median number of medicines patients were taking
Daily (n = 17)	15.29	15
Weekly (n = 5)	21	25
Monthly (n = 1)	43	43
At least monthly (n = 23)	17.74	16
Not at all (n = 13)	12.38	15

Despite the fact that most parents were worried or stressed when their child was on medication, most parents did not feel helpless in managing their child's condition (20/36). 14 participants felt helpless in managing their child's condition and two participants were unsure.

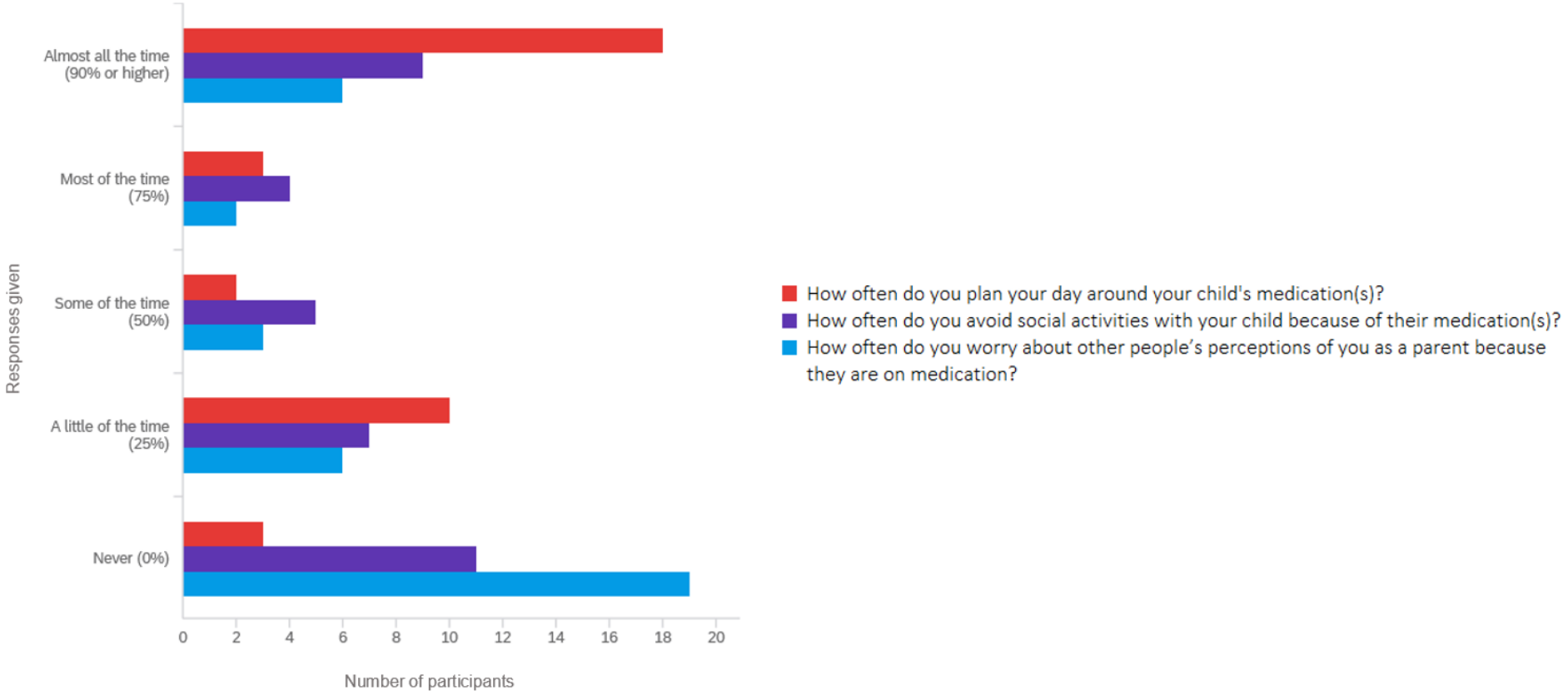
Figure 9 - Helplessness in managing their child's condition



4.1.2.7 Social impact of medicines

Medicines were shown to influence participants' daily routines, with 18 participants stating that they plan their day around their child's medicines almost all of the time and three participants planning their days around their child's medicines most of the time. The proportion of parents who avoided social activities due to their child's medicines varied, with 18 participants reporting that they avoided social events at least 50% of the time and 18 participants avoiding social events with their child less than 50% of the time. Most (19/36) parents were not worried about others' perceptions of them as a parent because of their child's medicines, six parents were only worried about others' perceptions a little of the time and the remaining 11 participants were worried about others' perceptions of them at least 50% of the time.

Figure 10 - Impact of children's medicines on participants' and their children's social life



4.1.2.8 Time requirements

Most participants (20/36) reported that patients spent a lot of time administering their medicines. 15 participants did not feel that patients spent a lot of time administering their medicines and one participant was unsure. Participants spent from five minutes to eight hours, with the average time being nearly 98 minutes (1 hour 38 minutes). The time spent administering medicines also contributed to the social impact of polypharmacy, with 16 out of the 20 participants who felt that they spent a lot of time administering patients' medicines reporting that their daily routines were affected by patients' medicines.

4.1.2.9 Direct costs

Only one parent of an adolescent patient had to pay for their child's prescriptions. They spent £20 a month for their child's medicines. They felt that the cost of their child's medicines was "too much" but did not state the impact this cost had on their family.

4.1.2.10 Indirect costs

Most participants (19/36) stated that they had no indirect costs to access their child's medicines. The mean indirect cost was approximately £14.74 and the median cost was £0, with costs ranging from £0 to £100 per month. Table 17 shows the indirect costs for participants in this study.

Table 17 - Indirect costs

Indirect costs (£)	Number of participants (n = 36)
0	19
5	3
6	1
10	2
20	4
50	2
80	1
100	2
Unsure	2

4.1.2.11 Impact of medicines on work/school

Most patients did not experience problems taking medicines at school as most patients (20/36) did not take their medicines at school. 12 out of the 16 patients who took their medicines in school did not experience any problems taking their medicines in school. Most patients who took their medicines in school (10/16) were not absent or late to school because of their medicines but one patient was absent or late to school once a month and five patients were absent or late to school daily because of their medicines.

Some parents' jobs were affected due to their child's medicines but this was not the case for most participants. 15 participants stated that changes to their jobs due to their child's medicines were not applicable for them and a further 11 participants stated that they did not have to alter their jobs or work schedule due to their child's medicines. 25% of participants' jobs were affected, with six participants stating that they had to quit working, one participant having to reduce the number of hours they worked and three participants having to change their jobs. Most participants (33/36) stated that they did not miss any hours of work due to their child's medicines in the last four weeks, with the remaining three participants missing between one hour and five full days of work.

4.1.2.12 Impact of medicines on personal relationships

Medicines were less likely to affect participants' personal relationships, with 12 participants stating that their medicines caused no strain to their personal relationships and six participants experiencing a little strain to their personal relationships. A third of participants found that their child's medicines caused more strain on their relationships, with four participants experiencing a moderate strain, three participants experiencing a lot of strain and five participants experiencing a tremendous amount of strain.

4.1.2.13 Other difficulties participants experienced

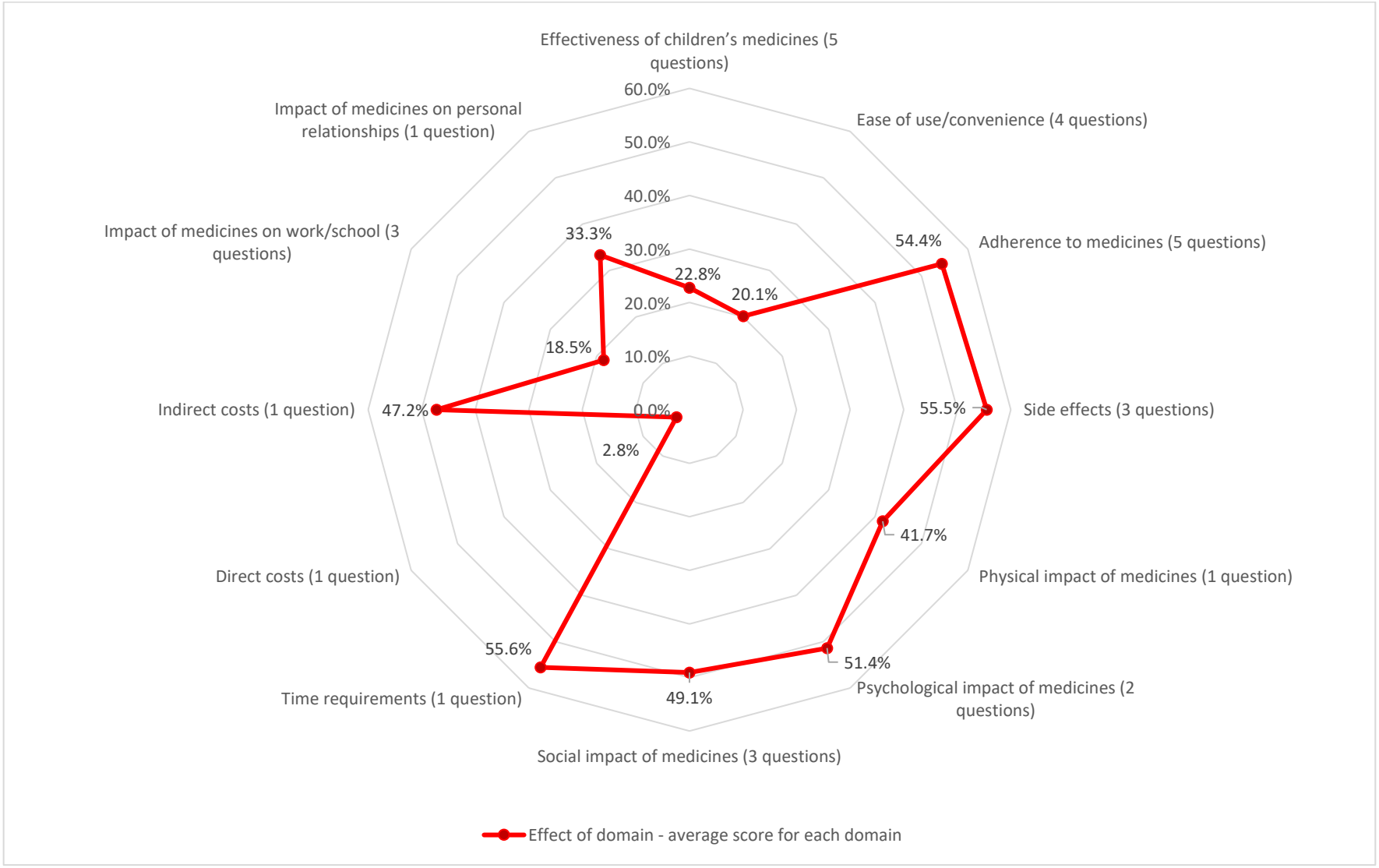
A free text question was added at the end of the questionnaire to give participants the opportunity to state any additional problems they experienced with accessing or administering their child's medicines.

Three participants completed this question. Most of their comments were related to difficulties getting their child's prescriptions. Issues related to their child's prescriptions included the locations, not being able to access their child's medicines in a timely manner due to issues with the pharmacy's stock or other delays, incorrect medicines or prescriptions being sent to parents, and prescriptions going missing.

4.1.2.14 Overall impact of medicines on all domains

Overall, certain domains were shown to have a larger impact on parents and patients than others. Time requirements, side effects, factors affecting adherence to medicines and the psychological impact of medicines were shown to affect participants the most whereas the effectiveness of children's medicines, ease of use/convenience of medicines, the impact of medicines on work/school and the direct costs of medicines had the least impact on participants. The overall impact of each domain is illustrated in Figure 11.

Figure 11 - Relative impact of domains measured in relation to burden of care from paediatric polypharmacy on participants



4.1.3 Missing data

Some information about patients' medicines was missing. Some parents did not know all the details for their child's medicines. However, they also refused to allow access to their child's clinical notes (n = 4), which meant that information on their child's medicines' doses, frequency, etc. could not be obtained.

The impact of direct costs on participants could not be determined from the responses given. One participant stated they had to pay for prescriptions but did not state the impact this cost had on their family.

For certain questions, some participants stated that they were not sure. Table 18 shows the questions where participants provided this response and the number of participants that did so.

Table 18 - Questions where participants stated they were unsure

Question	Number of participants who stated they were unsure
How many different medicines is your child currently taking? Please include medicines prescribed by your child's GP or the hospital. This can include all forms of medicines, e.g. tablets, capsules, oral liquids, injections. Do not include over the counter medicines, i.e. medicines bought at a pharmacy or shop without a prescription.	1
Overall, please indicate how effective your child's medicines are in managing their condition(s):	2
It is possible to manage my child's condition(s) with medicines so they are free of symptoms:	7
It is possible to control my child's condition(s) with medicines so that they can carry out daily activities like other children:	5
I worry about the effectiveness of my child's medicines:	5
How do you think your child's health is now?	1
Which medicine(s) do you think work well for your child? Please write the names of the medicines below, e.g. omeprazole, Gaviscon, aspirin:	3
Which medicine(s) do you think do not work well for your child (if any)? Please write the names of the medicines below, e.g. omeprazole, Gaviscon, aspirin:	1
Administering your child's medicines upsets you:	3
Administering your child's medicines upsets your child:	3
Which medication(s) do you think is causing these side effects?	3
Overall, how severe do you think the side effects are that your child's medicines have caused?	1
I worry about the side effects of my child's medicines:	4
My child's medicines stop my child from doing certain activities:	9
I often feel helpless in managing my child's medicine(s):	2
My child spends a lot of time taking their medicines everyday:	1
How much do you spend picking up medicines each month (e.g. fuel, parking charges, transport, etc.)?	2

The question that asked participants who prescribed their child's medicines caused some confusion for participants. Some parents were unsure whether patients' medicines were prescribed by general paediatricians or specialist paediatricians. Some participants stated that "hospital doctors", "consultants", doctors in particular specialties and the hospital prescribed their child's medicines. As participants were asked to tick all the options that applied to them, it was more difficult to interpret the results for this question.

Chapter 5: Polypharmacy ANd Drug optimisAtion (PANDA) study pilot phase – discussion

5.1 Discussion

This pilot study has demonstrated that the questionnaire developed was able to be completed by families, and collected data on the various domains in which polypharmacy related burden of care affects families. In addition, we have demonstrated that we can compare the relative burden of each domain, enabling future research to focus on the areas of need for parents once the final version of the questionnaire has been undertaken.

Most of the commonest underlying diagnoses were chronic conditions but the commonest medicines taken by patients were not related to these conditions. Some of the commonest medicines were used for acute problems or symptomatic relief. Azithromycin is an antibiotic used to prevent chest infections (86), paracetamol would be used for pain relief, sodium chloride is used as in intravenous fluids (87) and to help clear secretions from the respiratory tract, dioralyte sachets are used in the management of hydration and domperidone can be used to relieve nausea and vomiting, although its use for this purpose in paediatrics has been reduced significantly in recent years (88). However, some of the commonest medicines could be linked to common underlying diagnoses in this cohort as omeprazole and domperidone could be used to manage gastroesophageal reflux (88, 89), and as levetiracetam could be used to manage epilepsy (90).

An audit was previously conducted at Alder Hey to determine the scale of polypharmacy and the medicines contributing to it (84). On comparing the data from this pilot study to the polypharmacy audit, patients in this cohort took more medicines on average than patients recruited in the polypharmacy audit. A smaller proportion of patients in this study took ≥5 but <15 medicines, with 36% of patients in this study (13/36) taking five to 14 medicines compared to 53% (94/179) of children in the audit (84). However, a larger proportion of patients in this study took ≥20 medicines (8/36) compared to children in the audit (8/179, 4%) (84). The mean numbers of medicines taken were 15.81 in this pilot study and seven in the polypharmacy audit (84). The median numbers of medicines taken were 15 in this study and six in the polypharmacy audit (84). This could be because patients in this study had to be taking at least five regular medicines to be eligible for this study, which meant that patients in this study had to take a minimum of five medicines in total. In the polypharmacy audit there was no minimum number of medicines for patients to be included. Therefore, patients taking less than five medicines were included in the audit, which formed a larger proportion of patients in the audit's cohort (84). As a lot of patients admitted to hospital take less than five medicines, the average number of medicines may have been higher in this pilot study. As one patient took 43 medicines, which was an outlier in this cohort, this would have also increased the mean number of medicines patients in this cohort took.

Although the vast majority of participants felt that their child's medicines were at least adequate overall, the impact of patients' medicines on their functioning and overall health varied and effectiveness of patients' medicines was still a cause of concern. This could be due to the subjective nature of the questions as participants may have different definitions of good health and good functioning. Some participants have may compared patients' overall health and functioning to the patients' health previously whereas other participants may have considered these factors in comparison with that of other healthy children. Underlying diagnoses were also shown to affect

participants' perception of patients' health, with chronic diagnoses being linked to a worse state of health. In conditions such as gastroesophageal reflux medicines would be used for symptomatic relief rather than being curative and in patients with global developmental delays medicines and other forms of treatment would be used to manage their clinical manifestations. In these patients, their health may never be good or excellent regardless of their medicines' effectiveness due to the impact of their underlying diagnoses.

Some medicines were more commonly reported to work well for patients than others. Certain drug classes and medicines have more obvious signs that they are effective for patients. For example, anticonvulsants would be deemed to be effective when patients experience fewer seizures, melatonin would be effective when patients' sleep improve, and PPIs would be effective when patients experience heartburn and acid reflux less often. It was also easier for participants to determine when certain medicines were ineffective for patients. For example, azithromycin was reported to be ineffective by a few participants due to persistent infections and paracetamol was reported to be ineffective due to the lack of analgesia.

Factors such as the number of medicines patient took were not shown to affect the prevalence of side effects in this cohort. The type of drug was a factor that affected the prevalence of side effects, with antiepileptics being the commonest drug class participants reported to have caused side effects. The findings in this study were similar to findings in the existing literature. A study that aimed to identify adverse reactions caused by various antiepileptic medicines found that patients had similar side effects to those patients in this cohort experienced with antiepileptics such as levetiracetam, carbamazepine and clobazam (91).

Among patients who participants felt were prevented from doing certain activities, certain medicines were more commonly prescribed. However, the commonest medications these patients took indicated that their underlying medical conditions were more likely to affect their physical functioning rather than the medicines themselves. Paracetamol and ondansetron are used for symptomatic relief to manage pain and vomiting respectively. Epoetin beta is used to manage symptomatic anaemia in patients with renal disease (92) and alfacalcidol is used to prevent vitamin D deficiency in patients with renal disease (93). Other common medicines included midazolam, levetiracetam and phenytoin sodium are antiepileptics, which indicates that frequently occurring seizures prevented these patients from doing certain activities.

A similar pattern was seen when participants' stress due to patients' medicines was explored. Patients whose parents were worried or stressed more frequently while they were on medication had a range of underlying diagnoses. However, a lot of these diagnoses were chronic conditions that would be managed with medicines and other forms of treatment in the long term and having several underlying diagnoses further increased participants' worries about their children's health. The most frequently prescribed medicines for patients whose parents felt more stressed were prescribed to manage symptoms or as long-term treatments for certain medical conditions. The number of medicines however did not differ between patients whose parents felt stressed more often and parents who did not feel stressed at all due to their child's medicines.

For some questions, participants may have felt reluctant to disclose their views honestly. For example, more participants stated that administering patients' medicines caused their child to be distressed more than themselves. In other questions about running out of medicines and patients missing doses of their medicines, the number of patients who were not fully adherent to their medicines and the frequency at which they missed doses could have been underestimated. As the research student was present while participants completed the questionnaire and as it was known

that other healthcare staff were also involved in this study, some participants may have preferred to say what healthcare professionals expect from them.

One aspect of accessing medicines that caused difficulties for most parents was getting medicines dispensed at the pharmacy. As some participants stated at the end of the questionnaire, there are various causes of these difficulties. Other reviews of treatment burden in other studies stated difficulties such as a lack of information about patients' medicines, traveling to access medicines and the costs of medicines (28, 29). As prescriptions are free for patients under 16 years old and 16-18 year old patients who are in full-time education (94), the cost of medicines was not an issue for most participants in this study. This study has identified other issues related to getting medicines such as issues with the stock in pharmacies and errors with patients' prescriptions.

Another factor that caused an increased burden for participants was the impact polypharmacy had on participants' social functioning. The proportion of participants whose daily routines and social activities were affected due to patients' medicines was higher in this study compared to other studies, with 28% of participants' daily routines being affected and 14% of participants' social activities being affected in another study assessing the burden of care in ADHD (72). As a lot of time was spent administering medicines on a daily basis, participants' daily routines had to be adjusted to make time for this. Social events would also have been affected due to the pressure of managing patients' medicines, their jobs and/or other commitments and personal relationships.

One finding that was unexpected in this study was that fewer patients were affected by their medicines at school. Other studies found that children had problems with taking their medicines at school due to social stigma, being unable to participate in all lessons and the impact on their attendance (95). One reason why fewer participants in this study experienced problems taking their medicines in school could be because more patients in this study may have been attending special schools rather than being in mainstream education due to their medical conditions.

The most interesting findings from this pilot study were related to the time it takes to administer medicines and its impact on participants' social functioning. While other studies have demonstrated the overall amount of time required to provide care for patients and the time required to manage all forms of treatment patients received (24), this study has determined the amount of time that managing medicines takes for patients experiencing polypharmacy and their parents. Participants in this cohort reported spending more time managing patients' treatment (mean: 98 minutes per day) compared to other studies (mean: 42 minutes per day) (24). Most participants who felt like they spent a lot of time administering patients' medicines also reported that their social activities and daily routines were affected by this.

5.2 Implications for research

This questionnaire is a tool that has addressed various domains related to polypharmacy related treatment burden. It has helped to address the gap in existing research related to the burden of medicines in paediatric patients and for their families.

The results from the pilot study have demonstrated the domains that impacted parents the most. The domains that scored highly were the time requirements, side effects, adherence to medicines, psychological impact of medicines, social impact of medicines, indirect costs and the physical impact of medicines. The literature could be reviewed to identify existing interventions that have been used

to ease problems related to each domain and polypharmacy. Interventions that are shown to work well could be tested in the paediatric population through controlled trials or Quality Improvement (QI) projects to establish their overall effectiveness in reducing the burden for patients and parents, and to identify ways of improving these interventions.

Potential interventions could aim to encourage deprescribing to ensure patients are adherent to their medicines and to reduce the number of side effects that occur. Financial assistance to help families with the costs of accessing children's medicines could also be trialled to test its feasibility in hospital and community settings. Identifying methods of making medicines easier to carry and administer in different settings could help to ease the social and physical impact of medicines. Various forms of information such as guidelines and leaflets could help to improve healthcare professionals' and the general public's awareness about the impact of polypharmacy on patients and their families.

This pilot study has also provided a useful guide as to which questions are useful to assess the burden of medicines in paediatric patients. The questionnaire will be altered (see below) based on the responses and the verbal feedback from participants while they completed the questionnaire. This updated questionnaire will be used on a larger scale to determine the impact of polypharmacy in different regions and in larger populations. This questionnaire can then be used to assess treatment burden in different medical settings (for example, in the community) and treatment burden in different conditions. The total scores and impact of each domain can then provide a better insight into the difficulties faced by patients and parents in different situations.

5.3 Implications for clinical practice

The main findings from this questionnaire demonstrate which aspects of patients' and parents' lives need to be considered when medicines are prescribed. It also demonstrates problems parents experienced with accessing medicines and the ways in which medicines affect parents' and patients' daily lives. An increased awareness of these issues can encourage healthcare professionals to review patients' medicines and stop any medicines that may be harmful or unnecessary before prescribing new medicines and at regular points in patients' care.

5.4 Strengths and limitations

The questionnaire and the findings covered a wide range of domains, which enabled us to identify the ways in which polypharmacy impacted patients and families in different aspects of their lives. Most parents were willing to participate in the study as they felt that certain aspects of managing patients' medicines were making them distressed. Most questions were answered adequately, which enabled us to collate these findings and identify links between different factors.

However, it was difficult to recruit patients in outpatient settings in this pilot study. It would be useful to liaise with staff in more inpatient and outpatient clinics, both in the hospital and outside of the hospital, to obtain the views of patients and families outside of inpatient settings and compare these results to the results from patients admitted onto wards. It would also be useful to collect

more data on treatment burden in specific conditions to determine whether certain conditions are likely to affect treatment burden more than others.

Some questions were misunderstood by participants and need to be reworded in future versions of the questionnaire. These questions and the reasons they may have been misinterpreted by participants are discussed in section 4.2.3.1. some suggested changes to improve these questions and the rephrased versions of these questions are mentioned in section 4.2.3.2.

5.4.1 Questions that were misunderstood by participants

Some questions were misunderstood by participants, which led to inadequate or incomplete answers. In some cases, it was because participants did not understand the terminology used in a question and in other cases the wording of the questions caused participants to misinterpret the meaning of the question. Some participants sought clarification from the research student regarding any doubts they had about the questions but not all participants did so.

Three participants mistakenly reported that their child was born prematurely as they reported gestations of over 37 weeks. A few participants did not know the cut off for prematurity and asked the research student about this while they completed the questionnaire.

The question asking about the number of medicines patients were currently taking. A few participants listed their child's medicines instead of providing a number. A lot of participants were unsure about the exact number of medicines patients took. Despite this, it was not a major issue as most parents were happy for the patients' medical records to be checked.

The question asking how often patients administered their own medicines was misread by some participants even though the question explicitly asked about their child taking their medicines. The previous question that asked participants to state who was involved in administering their child's medicines showed that five children administered their own medicines. However, the next question showed that 12 patients administered their own medicines daily. This question could have been misinterpreted by some participants as they may have reported how often they administered their child's medicines instead, which might mean that these parents administered their child's medicines daily rather than the patient themselves.

The questions asking about the number of times participants had to administer patients' regular and PRN medicines each day were misunderstood by some participants. Some participants were not sure what was meant by regular medicines and as needed medicines. Some participants also needed clarification about the wording of the question and asked if they needed to count each medicine separately for these questions. Some participants gave non-numerical responses and some participants reported that they administered their child's medicines at more than 15 different times a day. The question that asked participants how much time they spent preparing and administering their child's medicines was also misunderstood by some participants, with a few participants stating that they spent 7-24 hours administering their child's medicines daily.

The terminology was confusing for the questions that mentioned single repeat prescriptions and homecare deliveries. Some participants asked the research student to clarify this when they completed the questionnaire but other participants may have answered these questions based on their interpretation of the questions even though these may have been incorrect.

In some questions, the answer options did not adequately reflect participants' answers and participants had to pick the option that matched their actual answer most closely even though the true answer was in between two options. The question that asked how often participants experienced difficulties getting their child's medicines prescribed at the pharmacy was an example of this. Some participants stated that the time ranges provided were not suitable as their true answer lied in between the frequencies. For example, some parents experienced difficulties more than yearly but less than once a month.

5.4.2 Suggested rewording of questions that were misunderstood

As some questions were misunderstood by participants as discussed in the previous section, Table 19 shows the changes that could be made to improve these questions and reworded versions of these questions. These changes will be made to the current version of the questionnaire before recruiting a larger sample size.

Table 19 - Suggested changes to improve questions that were misunderstood by participants

Original question	Suggested change	Reworded question	Would this change affect the results for this question?
Was your child born prematurely?	Add cut off for prematurity	Was your child born prematurely, i.e. born before 37 weeks?	No – incorrect answers can be removed manually.
How many different medicines is your child currently taking? Please include medicines prescribed by your child's GP or the hospital. This can include all forms of medicines, e.g. tablets, capsules, oral liquids, injections. Do not include over the counter medicines, i.e. medicines bought at a pharmacy or shop without a prescription.	1. Remove the explanation after the question to reduce its length 2. Or add a sentence stating that the answer should be a number.	1. How many different medicines is your child currently taking? 2. How many different medicines is your child currently taking? Please include medicines prescribed by your child's GP or the hospital. This can include all forms of medicines, e.g. tablets, capsules, oral liquids, injections. Do not include over the counter medicines, i.e. medicines bought at a pharmacy or shop without a prescription. Please give your answer as a number.	Yes – the answers obtained from completing the updated version of this questionnaire might be different. However, as most participants are willing to let us access their child's medical records, the number of medicines can be checked there. Non-numerical answers will be excluded from data analysis.
On average, how many times a day do you have to give your child their regular medicines, i.e. medicines that need to be taken once or more each day?	Provide an example so that participants know what is expected of them for this question.	On average, how many times a day do you have to give your child their regular medicines, i.e. medicines that need to be taken once or more each day? E.g. If you administer two medicines in the morning and three medicines in the evening, this counts as administering medicines two times.	Yes – the interpretation of this question by participants in the pilot study and future participants may be different.
On average, how many times a day do you have	Provide an example so that participants know	On average, how many times a day do you have	Yes – the interpretation of

to give your child their as required medicines?	what is expected of them for this question.	to give your child their as required medicines? E.g. If you administer their as required medicines once in the morning and once in the afternoon, this counts as administering medicines two times a day.	this question by participants in the pilot study and future participants may be different.
Are all of your child's medicines on one single repeat prescription?	Reword the question to include what single repeat prescriptions are in the question.	Are all of your child's medicines on one single repeat prescription (i.e. prescriptions on one page)?	Yes – the interpretation of this question by participants in the pilot study and future participants may be different.
Do you receive any medicines through a "Homecare" delivery?	Explain what homecare deliveries are in the question.	Do you receive any medicines through a "Homecare" delivery (i.e. are your child's medicines delivered to their house)?	Yes – the interpretation of this question by participants in the pilot study and future participants may be different.
How often do you have problems getting prescriptions dispensed at the pharmacy? Answer options: • Never • Once a year • Once a month • Once a week	Change the answer options.	How often do you have problems getting prescriptions dispensed at the pharmacy? Answer options: • Never • Once a year • Less than once a month • Once a month • Once a week	Yes – an extra answer option added, which might fit participant's circumstances better.
In total, how long do you spend preparing and administering your child's medicines each day? Please answer in hours and minutes.	Reword the question so that it is shorter and clearer for participants.	How long do you spend giving your child's medicines in total each day? Please answer in hours and minutes.	Yes – the interpretation of this question by participants in the pilot study and future participants may be different.

Some follow up questions could also be helpful to obtain additional information or additional context.

There was no breakdown in costs for indirect costs in this study. A follow up question asking participants to report how much they spend for different costs of accessing their child's medicines such as fuel and transport could give an insight into the costs that increase the financial burden for parents.

A lot of parents stated that changes to their jobs and missing time from work did not apply to them. This could have meant that participants already changed/quit their jobs due to their child's medicines or that they were not working prior to their child starting their medicines. A text box could be added after the "not applicable" option in the question about changes to their jobs so that participants can provide an explanation. Alternatively, this could also be done through a separate follow up question.

Healthcare professionals' views on deprescribing have been explored in existing research studies. A survey completed by healthcare professionals showed that they thought parents don't want their child's medicines to be stopped due to being worried about it (96). As polypharmacy has been shown to affect patients and parents in various ways, it would also be useful to find out whether parents tried to stop any of their child's medicines. This could be added to the existing questionnaire or it could be explored in a separate follow up study about parents' views on deprescribing.

5.5 Conclusions

This pilot study demonstrated the polypharmacy related treatment burden in a group of parents looking after paediatric patients. Certain domains and aspects of managing children's medicines were shown to have a bigger impact on parents and paediatric patients more than others. It demonstrated that we can assess the most important domains to consider in future versions of the questionnaire and future studies assessing polypharmacy related treatment burden. The pilot study has also provided a good insight into the quality of the questionnaire from parents' perspective and has enabled us to find ways to improve the questionnaire before recruiting larger groups of participants.

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Appendices

Appendix 1: Systematic review protocol submitted to PROSPERO

What domains related to medicines were measured in studies of burden of care for paediatric patients? A systematic review

Tharshiya Thatparan, Julien Marro, Daniel Hawcutt

Citation

Tharshiya Thatparan, Julien Marro, Daniel Hawcutt. What domains related to medicines were measured in studies of burden of care for paediatric patients? A systematic review. PROSPERO 2021 CRD42021285097
Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021285097

Review question

What domains related to medicines were measured in studies of burden of care for paediatric patients?

Searches

MEDLINE, Web of Science, CINAHL, Embase and Cochrane Database of Systematic Reviews will be searched and records in all languages and all dates will be included. MEDLINE, CINAHL and Embase will be searched simultaneously on HDAS (Healthcare Databases Advanced Search), and Web of Science and Cochrane database of systematic reviews will be searched separately on their websites. Details of the papers found and the search strategies for each database will be saved. References for the papers found will also be imported to Endnote.
Review articles will be excluded, however the reference lists of relevant reviews will be searched for eligible records. Any papers which signpost the methodology elsewhere will also have that reference examined.

Types of study to be included

Any primary studies (including cohort studies and case control studies) assessing the burden of care from medicines use for paediatric patients and their parents will be included.
Systematic reviews and other reviews will be excluded but any relevant review articles will have their references examined. Eligible studies in these references will then be included in this study.
Any papers which signpost the methodology elsewhere will also have that reference examined.

Condition or domain being studied

Medicine related domains of burden of care in paediatric patients and their parents/caregivers.

Participants/population

Inclusion: Paediatric patients (generally 0-18 years old*) and their parents/caregivers, patients with any medical conditions.
*Papers will also be included if they include data on adult patients and the paediatric data can be extracted from them.

Exclusion: non-human participants, adult patients (generally >18 years old), non-patient participants.

Intervention(s), exposure(s)

Inclusion: studies assessing medicine related domains of burden of care, studies assessing other domains of burden of care that can affect patients'/caregivers' lived experience with medicines.

Exclusion: studies that do not assess any domains of burden of care.

Comparator(s)/control

Not applicable

Context

This is a precursor systematic review for a primary cohort study on polypharmacy and drug optimization that aims to investigate the effects of polypharmacy on patients' and parents' lived experiences. This systematic review therefore aims to determine the domains related to medicines that were assessed in studies on paediatric burden of care. The findings from this study will inform the questions that will be asked in the cohort study to assess the effects of polypharmacy for paediatric patients and their parents/carers.

Main outcome(s)

To identify the domains related to medicines use that were assessed in studies on paediatric burden of care. These domains would include any impact on patients' or parents' health and wellbeing specifically due to the patients' medication. This can include but is not limited to the effects of medicines/treatment on patients' and their parents' quality of life, finances, use of healthcare resources and adverse effects of medications.

The primary outcome: domains that were assessed through questionnaires, surveys or other means in studies included in this review related to burden of care in children with polypharmacy will be extracted and grouped into common themes, which will then help inform the questions for a future cohort study. Several studies have explored the overall burden of care for patients and parents, often in specific conditions, and this review aims to group the findings related to medicines use to explore the impact of medications further.
Understanding medicines related domains for burden of care will help improve the management of polypharmacy for children in the UK. This systematic review intends to identify the most important features to measure relating to burden of care in paediatric polypharmacy and utilise this in a prospective cohort study.

Measures of effect

Not applicable

Additional outcome(s)

To identify other domains related to burden of care.
To identify the methods used to report the domains related to medicines use and burden of care.

Measures of effect

Not applicable

Data extraction (selection and coding)

Searches using chosen search terms will be conducted on the databases and the results will be exported onto a excel spreadsheet. The titles, abstracts and full text papers will be checked for relevance. Two reviewers will independently screen records for inclusion using the eligibility criteria. A third reviewer will check the full text papers if there are disagreements about including full text papers in the systematic review.
The details of the papers found will be recorded on an excel spreadsheet. This will include the reasons for including and excluding papers and the stage at which the papers were excluded.
A data extraction tool will be made and data will be recorded in an Excel spreadsheet. The data extraction table will include the following headings:

- Name of paper
- Author(s)
- Year
- Type of study
- Number of participants in the study
- Age groups
- Medical condition(s)
- Specific domains measured (for example, quality of life, drug related problems, costs, use of healthcare resources)
- Method of assessing burden of care (interview/questionnaire/score/other)
- Score(s) used to assess responses

Additional headings will be used if other relevant information is found in relevant studies. The participants' views on the effects of the medicines related domains measured will not be included.

The extraction table will be made and data will be recorded in an Excel spreadsheet. One reviewer will extract data from included studies into the extraction table and a second reviewer will check the data extracted. A third reviewer will check the data extracted by the two reviewers if there are any disagreements between the two reviewers. Study investigators will be contacted to obtain missing data or additional details. If they cannot be contacted, this will be stated as a limitation of this systematic review.

Risk of bias (quality) assessment

Two reviewers will independently assess the quality of studies using the appropriate tools for different study types. The Newcastle Ottawa scale will be used for cohort studies and case control studies. Other appropriate tools will be used for other study types. Any disagreements between the reviewers regarding the quality assessments will be resolved through discussions with a third reviewer.

Strategy for data synthesis

The domains measured will be recorded in the data extraction tool and will be grouped into themes. The methods used to measure these domains will also be extracted. As this study aims to identify and group themes and domains, a thematic synthesis approach (Thomas and Harden 2008) will be used for data synthesis. No meta-analysis or statistical models will be required as the data will be qualitative. At least two studies are required for data to be synthesised.

Analysis of subgroups or subsets

Not applicable

Contact details for further information

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Dr Daniel Hawcutt. Alder Hey Children's Hospital, The University of Liverpool

Type and method of review

Narrative synthesis, Systematic review

Anticipated or actual start date

15 October 2021

Anticipated completion date

17 January 2022

Funding sources/sponsors

None

Conflicts of interest

Language

English

Country

England

Stage of review
Review Ongoing

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Child; Delivery of Health Care; Drug-Related Side Effects and Adverse Reactions; Humans; Iatrogenic Disease; Parents; Polypharmacy; Prospective Studies; Quality of Life; Surveys and Questionnaires; United Kingdom

Date of registration in PROSPERO
02 November 2021

Date of first submission
13 October 2021

Stage of review at time of this submission
The review has not started

Stage	Started	Completed
Preliminary searches	No	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Appendix 2: Systematic review data extraction form

Article title	Author(s)	Publication year	Citation	Type of publication	Country of origin	Study aims/objectives	Study design	Study setting
Elopement Patterns and Caregiver Strategies	Andersen, AM; Law, JK; Marvin, AR; Lipkin, PH	2020	Andersen AM, Law JK, Marvin AR, Lipkin PH. Elopement Patterns and Caregiver Strategies. J Autism Dev Disord. 2020 Jun;50(6):2053-2063. doi: 10.1007/s10803-019-03961-x. PMID: 30838492; PMCID: PMC6728233.	Journal article	USA	The purpose of this study was to leverage IAN's unique ability to administer large-scale surveys to members of the ASD community in order to address this gap in our knowledge of comparative effectiveness, burden of use, and cost of the wide variety of interventions for EB being employed in the real world by families and caregivers.	Cohort study	Community

Factors associated with caregiver burden among pharmacotherapy-treated children/adolescents with ADHD in the Caregiver Perspective on Pediatric ADHD survey in Europe	Fridman, M; Banaschewski, T; Sikirica, V; Quintero, J; Erder, MH; Chen, KS	2017	Fridman M, Banaschewski T, Sikirica V, Quintero J, Erder MH, Chen KS. Factors associated with caregiver burden among pharmacotherapy-treated children/adolescents with ADHD in the Caregiver Perspective on Pediatric ADHD survey in Europe. Neuropsychiatr Dis Treat. 2017 Feb 7;13:373-386. doi: 10.2147/NDT.S121391. PMID: 28223810; PMCID: PMC5308565.	Journal article	Denmark, Finland, France, Germany, Italy, the Netherlands, Norway, Spain, Sweden, and the UK	"The objective of this study was to analyze CAPPA survey data for caregiver burden relating to work, social and family life, and parental worry/stress, and to assess the effect of the severity of ADHD, comorbidities, and adherence to medication."	Cohort study	Community

Patient-Reported Complications, Symptoms, and Experiences of Living With X-Linked Hypophosphatemia Across the Life-Course	Cheung, M; Rylands, AJ; Williams, A; Bailey, K; Bubbear, J	2021	Moira Cheung, Angela J Rylands, Angela Williams, Karen Bailey, Judith Bubbear, Patient-Reported Complications, Symptoms, and Experiences of Living With X-Linked Hypophosphatemia Across the Life-Course, Journal of the Endocrine Society, Volume 5, Issue 8, August 2021, bvab070, https://doi.org/10.1210/jendso/bvab070	Journal article	USA	The objective of the present analysis was to qualitatively explore the symptoms, complications, and other experiences resulting from XLH reported within the survey and describe specifically how these change over the life-course.	Cohort study	Community

Quality of life of the family of children with asthma is not related to asthma severity.	Taminskiene, Vaida; Alasevicius, Tomas; Valiulis, Algirdas, Vaitkaitiene, Egle; Stukas, Rimantas; Hadjipanayis, Adamos; Turner, Steve; Valiulis, Arunas	2019	Taminskiene V, Alasevicius T, Valiulis A, Vaitkaitiene E, Stukas R, Hadjipanayis A, Turner S, Valiulis A. Quality of life of the family of children with asthma is not related to asthma severity. Eur J Pediatr. 2019 Mar;178(3):369-376. doi: 10.1007/s00431-018-3306-8. Epub 2019 Jan 4. PMID: 30607508.	Journal article	Lithuania	"The aim of our study was to assess in an Eastern European country the QoL in families where there is a child with asthma."	Cohort study	Outpatient visits

Support for children identified with acute flaccid paralysis under the global polio eradication programme in Uttar Pradesh, India: a qualitative study	Yotsu, RR; Abba, K; Smith, H; Das, A	2012	Yotsu RR, Abba K, Smith H, Das A. Support for children identified with acute flaccid paralysis under the global polio eradication programme in Uttar Pradesh, India: a qualitative study. BMC Public Health. 2012 Mar 22;12:229. doi: 10.1186/1471-2458-12-229. PMID: 22439606; PMCID: PMC3331818.	Journal article	India	"In this study, we aimed to explore what kind of support children with AFP were able to receive after their diagnosis under the global polio eradication programme through their experiences, their families' and healthcare providers' views on the given situation, and suggestions for change."	Cohort study	Community

Psychometric evaluation of the Cystic Fibrosis Questionnaire -Revised in a national sample	Alexandra L. Quittner; Gregory S. Sawicki; Ann McMullen; Lawrence Rasouliyan; David J. Pasta; Ashley Yegin; Michael W. Konstan	2011	Quittner AL, Sawicki GS, McMullen A, Rasouliyan L, Pasta DJ, Yegin A, Konstan MW. Psychometric evaluation of the Cystic Fibrosis Questionnaire-Revised in a national sample. Qual Life Res. 2012 Sep;21(7):1267-78. doi: 10.1007/s11136-011-0036-z. Epub 2011 Oct 14. Corrected and republished in: Qual Life Res. 2012 Sep;21(7):1279-90. PMID: 21993695.	Journal article	USA	"The overall objective of this study was to evaluate the psychometric properties of the CFQ-R in a national sample of children, teens, and adults with CF, as well as parent caregivers. Specific objectives included: 1. Evaluation of CFQ-R scores for children, teens, and adults with CF and parent caregivers to provide normative data, estimation of floor and ceiling effects, and internal consistency 2. Evaluation of discriminant validity comparing patients seen for ‘‘well’’ versus ‘‘sick’’ visits and among stages of lung disease based on pulmonary function 3. Evaluation of gender differences between males and females with CF on specific domains of functioning	Cohort study	Clinic/hospital

						4. Evaluation of agreement between parent–child dyads 5. Evaluation of convergence between CFQ-R scores and health outcomes, including pulmonary function, body mass index (BMI), and number of courses of intravenous (IV) antibiotics"		

Article title	Study inclusion and exclusion criteria	Recruitment procedures used	Number of participants	Age groups (paediatric patients)	Study population	Medical condition(s)	Method of assessing burden of care (interview/questionnaire/other)	Score(s) used to assess responses
Elopement Patterns and Caregiver Strategies	"All IAN participants were required to have an SCQ lifetime score of 12 to be eligible for participation in the current study." "Children/dependents under age 4 were excluded due the higher prevalence of EB among all children at younger ages"	"Participants in the Interactive Autism Network (IAN) research registry and database were invited to complete a questionnaire about their child/dependent's EB. IAN (https://iancommunity.org) is an internet-mediated research registry for individuals with ASD and members of their immediate family, including unaffected parents and siblings, with more than 55,000 individuals registered. Parents and children/dependents were consented into the IAN network registry and	515	4-17	Families of children/ dependents with ASD aged 4 and older	ASD	Questionnaire	Not applicable

		database on registration."						

Factors associated with caregiver burden among pharmacotherapy-treated children/adolescents with ADHD in the Caregiver Perspective on Pediatric ADHD survey in Europe	"Participants were eligible for inclusion if they were a parent or legal guardian of a child/adolescent aged 6–17 years diagnosed with ADHD at least 6 months before study enrollment and with no severe intellectual disability (cognitive impairment with an intelligence quotient ,70). Only one caregiver per child could participate and the child had to reside with the caregiver for at least 50% of the time during the 6 months immediately before the survey. This analysis includes children/adolescents who, at the time of the survey, were currently receiving, or had received in	"The online Caregiver Perspective on Pediatric ADHD survey was fielded in ten European countries." Potential participants were identified by two market research companies using patient panels comprising individuals who had agreed to be contacted to participate in research studies. These market research companies recruited patients from proprietary market research panels and those owned or maintained by various professional providers. Members were recruited to the market research panels using multiple approaches,	2,326	6-17	"Parent or legal guardian of a child/adolescent aged 6–17 years diagnosed with ADHD"	ADHD	Survey	Not applicable Responses were recorded as categorical variables unless stated otherwise.

	the previous 6 months, ADHD pharmacologic treatment, and had experienced periods where they were reported to be off medication."	including social media, online communities and website advertising. re https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5308565/						

Patient-Reported Complications, Symptoms, and Experiences of Living With X-Linked Hypophosphatemia Across the Life-Course	Inclusion: "parents/carers of children and adolescents (1-17 years) with XLH"	"Adults with XLH and caregivers of children with XLH were recruited through the sponsor, The XLH Network Inc., and clinicians. Respondents were asked to confirm diagnosis of XLH and whether a genetic confirmation of diagnosis (PHEX mutation) had been received; diagnosis was not verified with medical records."	86	1-17	"Parents/carers of children and adolescents (1-17 years) with XLH"	X-Linked Hypophosphatemia	Survey with 2 open-ended questions	Not applicable
Quality of life of the family of children with asthma is not related to asthma severity.	"Parents of children with asthma aged 2–17 years"	"Parents of children with asthma aged 2–17 years were asked to participate during the scheduled outpatient visit to pediatric pulmonologist. … Study data were collected in six policlinics in the two largest cities of Lithuania during the period between December 2014 and July 2016."	527	2-17	Parents of children with asthma	Asthma	Questionnaire	"Pediatric Quality of Life Inventory Family Impact Module (PedsQLFIM)"

Support for children identified with acute flaccid paralysis under the global polio eradication programme in Uttar Pradesh, India: a qualitative study	"In our study, we purposively selected the district of Muzaffarnagar as representative of the whole Uttar Pradesh, in terms of socio-economic development, geographic, and transportation condition."	"We obtained patient information for cases of AFP for the past three years (2005-2007) through primary health centres (PHCs) and local NGOs. We were able to identify 21 out of the 82 confirmed polio cases (25.6%) during this period."	26	8m-9y	"17 sets of parents" and "nine sets of parents of children with AFP, but whose stool exams were negative for wild poliovirus (non-polio AFP)."	Acute flaccid paralysis	Interview	Not applicable

Psychometric evaluation of the Cystic Fibrosis Questionnaire-Revised in a national sample	"A patient was considered ‘‘sick’’ when completing the CFQ-R if there was any indication of sickness (as noted by the clinician on the encounter form) within ±21 days of the CFQ-R date. A patient was classified as ‘‘well’’ when completing the CFQR if there was at least one well encounter within ±21 days of the CFQ-R date. If no encounters were observed within this window, the closest encounter within 90 days before administration of the CFQ-R was used; if this encounter was ‘‘well’’ and there were only well or missing pulmonary function tests since	"Data on patient demographics, spirometry, anthropometric characteristics, and therapies were collected at each clinic encounter. For children ages 6–11 years, the CFQ-R was administered by a trained nurse coordinator. Children were trained to use the rating scales on two practice items that corresponded to blue and orange rating cards, which were used during administration. Children and parents completed the CFQ-R in separate rooms. All sites entered the data using electronic data capture with edit checks." "all participants or their guardians provided written informed consent."	2068 school-age children and 2728 parents of school-age children	6-13	"School-age children (ages 6-13 years)" and "parents of school-age children"	Cystic fibrosis	Questionnaire	"CFQ-R Cystic Fibrosis Questionnaire-Revised"

	that date, then the patient was considered ‘‘well’’ at the point of CFQ-R administration. The remainder of CFQ-Rs (those not classified as sick or well) were considered ambiguous and excluded from analysis."							

Article title	Perceived effectiveness of medications	Ease of use/convenience	Medication side effects	Physical impact on everyday life	Psychosocial impact on everyday life	Time requirements	Caregiver responsibilities

Elopement Patterns and Caregiver Strategies	Yes - "For the following medication, please indicate how effective it has been in reducing elopement"	No	Yes - "For the following medication, please indicate how severe the side effects or adverse effects it caused have been"	No	No	No	No
Factors associated with caregiver burden among pharmacotherapy-treated children/adolescents with ADHD in the Caregiver Perspective on Pediatric ADHD survey in Europe	No	No	No	No	Yes - "Over the past 6 months, how much time did you spend worrying or stressing about your child?", How often did you plan your day around your child?", "How often did you avoid social activities when with your child?", "How often did you worry about other people's perceptions of	No	No

					you as a parent?" while on and off ADHD medication		
Patient-Reported Complications, Symptoms, and Experiences of Living With X-Linked Hypophosphatemia Across the Life-Course	Yes	Yes	Yes	No	No	Yes - timing/frequency of medication	No
Quality of life of the family of children with asthma is not related to asthma severity.	No	No	No	No	Yes - worry about child's treatment and side effects	No	No

Support for children identified with acute flaccid paralysis under the global polio eradication programme in Uttar Pradesh, India: a qualitative study	Yes - "How is your child now?"	No	No	No	No	No	No
Psychometric evaluation of the Cystic Fibrosis Questionnaire-Revised in a national sample	Yes - "How do you think your child's health is now?"	Yes - "How difficult is it for your child to do his/her treatments (including medications) each day?", "Doing your treatments bothered you"	No	No	Yes - "My child's treatments get in the way of his/her activities", "You had to stop fun activities to do your treatments"	Yes - "My child spends a lot of time on his/her treatments everyday"	No

Article title	Direct costs	Indirect costs	Use of healthcare resources	Work/school productivity/absenteeism?	support from/effect of medicines on family/friends	adherence to medicines	additional outcomes

Elopement Patterns and Caregiver Strategies	No	No	No	No	No	No	Overall burden of interventions.
Factors associated with caregiver burden among pharmacotherapy-treated children/adolescents with ADHD in the Caregiver Perspective on Pediatric ADHD survey in Europe	No	No	No	Yes - "Have you had to change your job, cut back your work hours, work schedule, or quit work altogether due to your child's ADHD?", "In the past 4 weeks, how many total hours of work did you miss due to your child's ADHD?" while on and off ADHD medication	Yes - "How much strain did your child's ADHD put on your relationship with your partner?", "How much strain did your child's ADHD put on your relationship with your other children?" while on and off ADHD medication	Yes	

Patient-Reported Complications, Symptoms, and Experiences of Living With X-Linked Hypophosphatemia Across the Life-Course	Yes - cost of treatment	Yes - costs due to illness, travel, insurance	Yes - "access to appropriate treatment"	Yes - impact on education and work	No	No	
Quality of life of the family of children with asthma is not related to asthma severity.	No	No	No	No	No	No	Frequency of rescue medication use
Support for children identified with acute flaccid paralysis under the global polio eradication programme in Uttar Pradesh, India: a qualitative study	Yes - "What did/do you feel about the cost of treatment?", "How is the treatment cost affecting your family?"	No	Yes - "Where are you getting treatment/support/care for your child? If Not getting any, then why?", "What kind of treatment/support/care?", "What were your difficulties getting treatment, support, and care at the time of onset of polio?", "What are your difficulties now getting treatment, support, and care for your child?"	No	No	No	Treatment provided by doctors/ANMs - "What kind of treatment, support, or care did you get after the stool test from the people visiting you at your house [ANMs, doctors]?". Information

							provided by doctors about treatment - "what information did they provide you regarding treatment, support, and care of the disease [polio]?".
Psychometric evaluation of the Cystic Fibrosis Questionnaire-Revised in a national sample	No	No	No	Yes - "How often your child was absent or late for school or other activities because of his/her illness or treatments"	No	Yes - "You were able to do all your treatments "	

Appendix 3: Newcastle-Ottawa Scale for cohort studies

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
a) truly representative of the average _____ (describe) in the community ❋
b) somewhat representative of the average _____ in the community ❋
c) selected group of users eg nurses, volunteers
d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
a) drawn from the same community as the exposed cohort ❋
b) drawn from a different source
c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure
a) secure record (eg surgical records) ❋
b) structured interview ❋
c) written self report
d) no description

4) Demonstration that outcome of interest was not present at start of study
a) yes ❋
b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
a) study controls for _____ (select the most important factor) ❋
b) study controls for any additional factor ❋ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
a) independent blind assessment ❋
b) record linkage ❋
c) self report
d) no description

2) Was follow-up long enough for outcomes to occur
a) yes (select an adequate follow up period for outcome of interest) ❋
b) no

3) Adequacy of follow up of cohorts
a) complete follow up - all subjects accounted for ❋
b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ❋
c) follow up rate < ____% (select an adequate %) and no description of those lost
d) no statement

Appendix 4: PANDA study protocol

PANDA Study

Polypharmacy ANd Drug optimisAtion (PANDA) study

Version 6.1
11.05.2022

MAIN SPONSOR: Alder Hey Children's Hospital

FUNDERS: No funding to be received.

IRAS reference: **304972**

Study Team

Chief Investigator:
Dr Daniel Hawcutt - Senior Lecturer in Paediatric Pharmacology (Women's and Children's Health)/ Consultant Paediatric Clinical Pharmacologist/ Theme Lead for Pharmacology (School of Medicine)

Co-investigators:
Louise Bracken - Senior Research Pharmacist
Matthew Ryan – Academic Foundation Year 1 Doctor
Tharshiya Thatparan – MPhil Student

Clinical Queries

Clinical queries should be directed to Dr Daniel Hawcutt who will direct the query to the appropriate person.

Sponsor

Alder Hey Children's Hospital is the main research Sponsor for this Study. For further information regarding the sponsorship conditions, please contact:

Mr Richard Kirk

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Clinical Research Division
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Funder

The project will be conducted by research professionals within Alder Hey, including Tharshiya Thatparan, MPhil student, University of Liverpool.

No consumables are required for the running of this study and therefore no additional funding will be required.

STUDY SUMMARY

This protocol describes the PANDA Study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the Study. Problems relating to this Study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

GLOSSARY OF ABBREVIATIONS

ADR(s)	Adverse Drug Reaction(s)
BD	Twice a day/Twice daily/2 times daily
CCC	Complex Chronic Conditions
CYP	Children and Young People
HCP	Healthcare Professionals
MRB	Medication Related Burden
OD	Once a day
PANDA	Polypharmacy and Drug optimisation (PANDA)
PLEM	Patients' Lived Experience with Medicines
PO	Orally/By mouth/Oral administration
PP	Problematic Polypharmacy
PRN	As needed
QDS	4 times a day
TDS	3 times a day
TPN	Total parenteral nutrition

TITLE

Polypharmacy ANd Drug optimisAtion (PANDA) study

DESIGN

A prospective qualitative cohort questionnaire study conducted in both inpatient and outpatient departments at a secondary/tertiary children's hospital. Children and their parents/primary carers will be asked to complete a questionnaire to assess the impact of medication burden and lived experience of medications.

AIMS

a) To explore the impact of polypharmacy on the lives of children and families.

OUTCOME MEASURES

- Patient and Family reported outcome measures (PROM)

POPULATION ELIGIBILITY

- Children and young people (<18yrs) who are receiving ≥5 regular medications and their respective families/primary carers.

DURATION

12 months

Table of Contents

1. INTRODUCTION

1.1 BACKGROUND

Polypharmacy is referred to as the concurrent use of multiple medications by an individual patient [1]. In adult patients the most common threshold for medication review used clinically when concerned about polypharmacy is five or more medications [2]. However, when children and young people (CYP) are concerned, a threshold for polypharmacy is not well-defined. A recent scoping review of the literature by Bakaki et al revealed that the most widely accepted definition of paediatric polypharmacy is 2 or more concurrent medications for ≥1 day [3]. Reasoning for the lower threshold is that children have less disease burden than adults [4]. Additionally, the majority of paediatric polypharmacy research has focused on harm caused by medication, not co-morbidities or medication related burden [3].

A recent study demonstrated the impact and scale of polypharmacy in CYP in Liverpool across primary, secondary and tertiary care centres. Of all the CYP registered in primary care in Liverpool 16% met the above threshold for polypharmacy of 2 or more medications. Extrapolating this data to a national scale would indicate that 1.8million CYP are currently deemed as polypharmacy patients. Understandably results from secondary and tertiary care centres displayed a larger percentage of CYP meeting the threshold for paediatric polypharmacy. 34% and 14% of CYP in secondary/tertiary care were prescribed ≥10 medications and ≥15 medications respectively. Literature has also displayed that the prevalence of paediatric polypharmacy is increasing [4,5]. Additionally, the number of CYP diagnosed with chronic conditions is increasing and as a consequence, the prevalence of paediatric polypharmacy is expected to continue to rise [6,7].

While polypharmacy is a widely recognised problem in geriatric medicine the growing prevalence and scale of polypharmacy in the paediatric population should be acknowledged [5,8]. Polypharmacy poses multiple risks and concerns to patients and clinicians, and financially to the health services [1]. Poor medication adherence, increased risk of hospital admissions, drug-drug interactions, medication related burden on day to day life and lower quality of life are all risks that a polypharmacy patient may face [9–13]. The number of adverse drug reactions (ADRs) also increases in both adults and paediatric polypharmacy patients [14–17]. Those ADRs themselves also increase hospital admissions, need for higher levels of care and permanent harm [15,17]. Additionally, with paediatric patients, the burden of medical care (e.g. appointments, organising prescriptions, ensuring dosing and regimes are met etc) will also affect the respective families and carers.

Solutions for the management of polypharmacy in adult patients are available in the form of deprescribing guidelines and medicines optimisation tools [18]. A recent systematic review of the literature by our department identified no published deprescribing tools for CYP [19]. This combined with the current prevalence of paediatric polypharmacy and the increasing number of CYP with chronic conditions poses a significant problem and challenge to paediatric polypharmacy patients and their clinicians [5].

1.2 RATIONALE FOR CURRENT STUDY

Like adult patients', children and young people (CYP) can experience polypharmacy. There is little evidence into the impact, scale and current management of paediatric polypharmacy in the United Kingdom (UK). Therefore, the department have recently completed the first comprehensive examination of paediatric polypharmacy in the UK, including primary and secondary/tertiary care prescribing data, the views of HCPs who look after children from across the UK, and systematic review of supporting evidence on available paediatric guidance for managing the issue.

Of the 110,097 CYP aged <18years registered in primary care (85 practices), in Liverpool, 17,271 (16%) were prescribed ≥2 medications, 3,507 (3·2%), 715 (0·7%) ≥10, and 202 (0·2%) ≥15. Extrapolating nationally, this equates to 1.8 million, 76,050 and 21,060 CYP, respectively. The median number of CYP prescribed ≥10 and ≥15 medications per primary care practice was 7 (range 0-34) and 2 (range 0-11), respectively.

Within secondary/tertiary care, 47/139 (34%) and 20/139 (14%) CYP were prescribed ≥10 or >15 medications, respectively.

Overall, 332 HCPs completed the survey. The most common thresholds for problematic polypharmacy were 3 (57/329, 17%), 5 (56/329, 17%) and 4 (52/329, 16%) medications. Most respondents (206/332, 62%) described concern about polypharmacy in CYP at least weekly. The most cited barrier to deprescribing was patient/family anxiety (198/323, 61%). Development of a deprescribing guideline for CYP was supported by 87% (287/330) supported development.

No paediatric-specific deprescribing tools or guidelines were identified through the systematic review.

This research has shown there are a considerable number of CYP nationally who meet the criteria for polypharmacy. Consequentially, the current definitions for paediatric polypharmacy need urgent review, with input from children, young people, and parents as well as HCPs. Furthermore, the study demonstrated that HCP in the UK have significant concerns about polypharmacy and support the development of evidence based paediatric deprescribing guidelines, however they do not currently exist. Additionally, we also know that patient and family anxiety regarding stopping medicines is a significant barrier to deprescribing. Therefore, the development of such evidence-based deprescribing guidance will require work with both children, young people, and families, to understand their views and experience about the concept.

Patient experience is a concept that is integral to quality of care [20]. Patient medication experience is described as 'the sum of all events involving drug therapy that a patient encounters in his/her life time' and thus includes both biomedical and psychosocial factors [12]. Therefore, clinicians must understand the impact of polypharmacy with regards to side effects, whilst also considering the need to explore the child and their family's reality of living with medicine, the burden they encounter in their day-to-day life and its impact on beliefs and behaviours, health and well-being [12]. Negative experiences can manifest as adverse events, poor disease control, inconvenience or inappropriate use of medicines. With regards to the paediatric population we must also consider other factors e.g. days of school (due to sides effects or drug monitoring appointments), receiving medications at school and formulation factors that children may struggle with. Therefore, children and their families may have to respond to the burden of polypharmacy in order to maintain therapy and 'normal life'. However, if the burden becomes too much for families, adherence to treatment may be disrupted and subsequently the patients' health may be affected negatively [21–23]. Therefore, when considering deprescribing guidelines, attention to patients' and their families lived experience is necessary in order to minimise medication related burden and optimise adherence. Hence there is a

need to explore the impact and burden of polypharmacy from the perspective of CYP and their families, assessing both biomedical and psychosocial experience.

This study aims to explore the experiences of polypharmacy in CYP and their families through a questionnaire study conducted in inpatient and outpatient departments at a secondary/tertiary children's hospital. A precursor systematic review is being conducted, which will inform the questions and any QoL (quality of life) forms that will be used in the questionnaire. Findings of this study and our previous investigations will help to define the impact of polypharmacy in children and guide the development of CYP and family guided paediatric deprescribing guidelines.

2. STUDY OBJECTIVES

Primary objective:

a) To understand children and their parents' lived experience of polypharmacy with regards to day-to-day life and its impact on beliefs and behaviours, health and well-being.

Secondary objective:

a) To explore how families using multiple medicines would define polypharmacy.
b) To understand families' perspectives on deprescribing medications.

3. STUDY DESIGN

Type of study:

A prospective qualitative cohort questionnaire study.

Duration:

Twelve months.

Study Setting:

Inpatients and Outpatients attending Alder Hey Children's Hospital.

3.1 STUDY OUTCOME MEASURES

- **PRIMARY OUTCOME MEASURE:**
  - Assessment of the burden of polypharmacy from the perspective of children and young people and their families/carers using a questionnaire.
- **SECONDARY OUTCOME MEASURES**
  - Children and Families definition of polypharmacy
  - Children and Families perspective on which medicines are most suitable for deprescribing, and how this could be achieved.

4. PARTICIPANT ENTRY

4.1 PRE-REGISTRATION EVALUATIONS

Attend Alder Hey Children's Hospital as either inpatient or outpatient.

4.2 INCLUSION CRITERIA

- All children attending Alder Hey children's hospital (inpatient or outpatient) aged from 0 days to 18 years on ≥5 regular medications.
    - Medications may be administered by any route including infusions
- Patients will be assessed for their ability to consent, and where possible will be encouraged to do so
    - IF age 16 or more, consent from patient is required, unless they do not have capacity in which case, we will consent the appropriate person. This would be the person responsible for providing consent for the patient's medical care and medical procedures, and this would be asked about in the relevant setting.
    - If age <16, ability to consent will be assessed on a case by case basis
    - Young people who are not capable of consent will be asked to assent. Refusal to assent in a young person who understands the study is an exclusion criteria
    - Parents of participants <16 who assent will be asked to consent on their behalf
- Parents will have to consent for their own participation.
- Good understanding of written and spoken English

4.3 EXCLUSION CRITERIA

Children on up to 4 regular medications.

Refusal to consent/assent in a participant who understands the study.

4.4 WITHDRAWAL CRITERIA

Patients may withdraw at any time, provided the results have not been published.

4.5 DRUG INCLUSION CRITERIA

Regular medications, as-required drugs, parenteral medications and infusions, enteral feeds.

4.6 DRUG EXCLUSION CRITERIA

Blood products

5. ASSESSMENT AND FOLLOW-UP

The study is single visit in design, targeting children in both the in-patient and out-patient setting. Children and their parents/primary carers will all be aware of the data collection. All staff in HDU (High Dependency Unit), ward 4B, ward 4C and ward 3C will be briefed about the study so that they can explain to children and parents/primary carers that the study is aiming to gain an insight into the impact that medication has on families.

The first approach made to the patient will be by a full-time research student, who will ask clinical or administrative members of the healthcare team if they have suitable participants for the study. Patients and family/carer will be presented with hard copies of information sheets and consent/assent forms. Typically, patients will be provided 24 hours to read over the information sheets, however through having a full-time research student who can answer any queries during the consent process, we hope to expedite this process, answering any real time queries. The usual path for consent will be that patients and family/carer will be asked for consent after this 24 hour period.

If patients and family/carers are not in the hospital after the first approach, we will obtain their contact details and send them an email after the 24 hour period to ask for consent. A QR code will also be provided to all participants so that they can access the study. However, if they can have their questions answered by the research student present, they will be allowed to consent earlier if they wish to. Questionnaires will take approximately 15 minutes to complete. Completed google docs form will be linked to an Alder Hey account to ensure confidentiality and encryption of data collected.

On completing the consent/assent form a study number will be assigned to the participant. To then access the google form the participant will have to input their assigned study number. This will ensure consent or assent has been undertaken.

Patients will not be followed up as part of the study. However, if participants have to leave midway through the questionnaire, we may request to contact patients by telephone to complete the questionnaire.

No children will receive any change to their treatment plan because of this study.

6. STATISTICS AND DATA ANALYSIS

Following completion of the questionnaires, statistical analysis will be conducted in order to determine significance of findings.

Appropriate statistical tests will be conducted using SPSS software and advice will be sought from a university statistician where required. 95% confidence intervals will be used where appropriate.

7. REGULATORY ISSUES

7.1 ETHICS APPROVAL

The Chief Investigator has obtained approval from the Wales Research Ethics Committee 4. The study must be submitted for Site Specific Assessment (SSA) at each participating NHS Trust. The Chief Investigator will require a copy of the Trust R&D approval letter before accepting participants into the study. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

7.2 CONSENT

Consent to enter the study will be sought from each participant following a full explanation and patient information leaflet provision. Different patient information leaflets will be used for the different age ranges involved in the study:

- Younger child patient information leaflet (≤ 10 years)
- Older child patient information leaflet (≤ 15years)

- ≥ 16 years old patient information leaflet
- Parent and Primary carer information leaflet

All leaflets will provide the same basic information but will be tailored to each of the age ranges that will be encountered in the study.

Consent forms will then be provided to both the patient (if appropriate) and the parent or primary carer in attendance as a paper form. All researchers conducting the study will have consent training beforehand. Additionally, assent forms will be provided to patients if the researcher deems appropriate.

Consent forms must be signed and dated by participants and then countersigned by the researchers who provided the consent. The signed consent/assent form(s) will then be scanned and stored on a secure Alder Hey account. A copy of the consent form will also be emailed to the patient/family member. A study number will be put on the consent/assent forms and will be entered onto the questionnaire(s) to enable validation that all completed questions have appropriate consent/assent.

The right for a participant patient or parent to refuse to participate without giving a reason will be respected. All participants are free to withdraw at any time from the study without giving a reason or effecting their further treatment. Information on how to withdraw will be verbally given and will also be included in the information leaflets. If participants withdraw from the study, any information collected from them will be deleted. However, as this is a student study that forms part of an MPhil degree, this information cannot be deleted if manuscripts have been submitted for publication.

7.3
CONFIDENTIALIT
Y

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act. Data will be recorded on a paper data collection form initially and then entered into a password locked study spreadsheet created for this study. The study spreadsheet will be stored on a password locked Alder Hey computer based at Alder Hey Children's Hospital that is backed up regularly according to Trust Computer Services protocol. Additionally, the PANDA folder on the computer which will hold the spreadsheet will only be accessible to members of the study team and will be located in the Clinical Research Division folder in the K: Drive.

7.4
INDEMNIT
Y

NHS indemnity

7.5
SPONSO
R

Alder Hey Children's Hospital will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

7.6 FUNDING

The project will be conducted by Tharshiya Thatparan, MPhil student, University of Liverpool.

No consumables are required for the running of this study and therefore no additional funding will be required.

7.7 AUDITS

The study may be subject to inspection and audit by Alder Hey Children's Hospital under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

8. STUDY MANAGEMENT

The day-to-day management of the study will be coordinated through Tharshiya Thatparan.

Any concerning behaviour noted throughout the duration of this study will be reported to the Chief Investigator, Dr Dan Hawcutt for further investigation.

9. END OF STUDY

Latest date of participant recruitment to the study: 1st July 2022

The spreadsheet used for the storage and analysis of data recorded in this study will be closed one month after the recruitment of the last participant.

Submission date: August 2022

10. ARCHIVING

Data will be retained for 10 years after the completion of this study

Work completed on this study will be stored on K drive at Alder Hey Children's Hospital

All data will be archived as per the guidance of the research and development department at Alder Hey and further advice sought if required.

11. PUBLICATION POLICY

Results of this study will be:

- Reported to Alder Hey R&D department
- Presented at European Society of Developmental, Perinatal and Paediatric Pharmacology Conference 2022
- Submitted for publication in a peer-reviewed journal

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13. APPENDICES

Schedule of events

Date	Event

Appendix 5: PANDA study parent questionnaire v1.0

PANDA Study

Study Questionnaire – Parent/Guardian

➢ General information about your child

Age: _____ years and _____ months

Gender:

- Male
- Female

What are your child's underlying medical conditions (or, if complex, is the person completing the questionnaire happy if we review clinic letters to collate these data Y / N)?

_____

_____

Was your child born prematurely?

- Yes
- No

How many weeks was your child born at? _____ weeks

Were there any complications during the pregnancy/childbirth? _____

Did the child's mother have a singleton/twin pregnancy?

- Singleton
- Twin
- Other multiple pregnancy: _____

➢ Quantity and type of medicines

How many different medicines is your child taking altogether? _____

For each medicine, please state the following (or, if unsure or complex, is the person completing the questionnaire happy if we review the current inpatient prescriptions and/or clinic letters to collate these data?) **Y / N**

- Drug: _____

- Dose: _____
- Frequency: _____

Is it a regular medicine or a medicine taken when needed (PRN)? _____

Formulation:

- Tablet
- Capsule
- Liquid
- Powder
- Inhaler
- Patch
- Other: _____

➢ How effective are your child's medicines?

Overall, please indicate how effective your child's medicines are in managing their condition(s):

- Very good
- Good
- Just adequate
- Poor
- Useless
- Don't know/can't tell

It is possible to manage my child's condition(s) so they are free of symptoms:

- Strongly agree
- Agree
- Disagree
- Strongly disagree
- Don't know/can't tell

It is possible to control my child's condition(s) so that they can play like other children:

- Strongly agree
- Agree
- Disagree
- Strongly disagree
- Don't know/can't tell

I worry about the effectiveness of my child's medicines:

- Strongly agree
- Agree
- Disagree
- Strongly disagree
- Don't know/can't tell

How do you think your child's health is now?

- Excellent
- Good

- Fair
- Poor
- Don't know/can't tell

Which medicine(s) do you think work well for your child?

_____

Which medicine(s) do you think do not work well for your child (if any)?

_____

- How easy is it to administer your child's medicines?

Has a doctor or health care provider ever given you written instructions for what to do about administering any of your child's medicines?

- Yes
- No

How difficult is it to administer your child's medicines each day (please tick the appropriate score)?

- 0 – not at all
- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9
- 10 – very difficult

Who is involved in administering your child's medicines? Tick all that apply:

- Mother
- Father
- Grandparent
- Child
- Carer
- Other: _____

Does your child take his/her medicines on his/her own?

- Not at all
- Once in a while
- Quite a bit
- Don't know/can't tell

Administering your child's medicines upsets you:

- Very true

- Mostly true
- Somewhat true
- Not at all true

Administering your child's medicines upsets your child:

- Very true
- Mostly true
- Somewhat true
- Not at all true

How many times a day does your child require administration of their regular medicines?

_____

How many times on average does your child require administration of their PRN (as required) medicines? _____

How many times does your child require regular medicines to be administered overnight (10pm – 6am)? _____

➢ Factors affecting adherence to medicines

Have you ever run out of medicines for your child's condition(s)?

- Yes
- No

Has your child ever missed a dose of their medications?

- Yes
- No

How often does your child miss doses of their medications (please tick the appropriate score)?

- 0 – not at all
- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9
- 10 – very often

Who issues the prescriptions for your child medicines? Tick all that apply:

- GP
- General paediatrician
- Specialist paediatrician
- Other: _____

Are all of your child's medicines on a single repeat prescription?

- Yes
- No

Do you receive any medicines through a "Homecare" delivery?

- Yes
- No

How many repeat prescription medicines does your child require per month? _____

How often are there difficulties getting prescriptions dispensed at the pharmacy?

- Never
- Once a year
- Once a month
- Once a week
- Every time

➢ Medication side effects

Do you think your child has had any side effects from their medicines?

- Yes
- No

Which medicine(s) do you think is causing these side effects?

_____

What side effect(s) does your child's medicines cause?

_____

When do these side effects occur?

_____

Who did you inform about the side effects your child has?

_____

Please indicate overall, how severe the side effects or adverse effects your child's medicines has caused are:

- Very serious - bad enough to go to hospital
- Somewhat serious - to see a healthcare professional like a doctor or pharmacist
- Was bad enough to affect what you do everyday
- Mild or uncomfortable
- Very mild or slightly uncomfortable
- Not serious
- Don't know

I worry about the side effects of my child's medicines:

- Strongly agree
- Agree

- Disagree
- Strongly disagree
- Don't know/can't tell

➢ How do your child's medicines affect your child physically?

My child's medicines stop my child from doing certain activities:

- Strongly agree
- Agree
- Disagree
- Strongly disagree
- Don't know/can't tell

➢ How do your child's medicines affect you psychologically?

How much time do you spend worrying or stressing about your child while your child is on medication?

- A tremendous amount of time
- A lot of time
- A moderate amount of time
- A little time
- No time

I often feel helpless in dealing with my child's condition(s):

- Strongly agree
- Agree
- Disagree
- Strongly disagree
- Don't know/can't tell

➢ How do your child's medicines affect your and your child's social life?

How often do you plan your day around your child while your child is on medication?

- Almost all the time (90% or higher)
- Most of the time (75%)
- Some of the time (50%)
- A little of the time (25%)
- Never (0%)

How often do you avoid social activities with your child while your child is on medication?

- Almost all the time (90% or higher)
- Most of the time (75%)
- Some of the time (50%)
- A little of the time (25%)
- Never (0%)

How often do you worry about other people's perceptions of you as a parent while your child is on medication?

- Almost all the time (90% or higher)
- Most of the time (75%)
- Some of the time (50%)
- A little of the time (25%)
- Never (0%)

➢ How much time is needed to administer your child's medicines?

My child spends a lot of time taking their medicines everyday:

- Strongly agree
- Agree
- Disagree
- Strongly disagree
- Don't know/can't tell

How long do you spend each day for your child's medicines? _____

➢ How much do your child's medicines cost?

Do you have to pay for any of your child's prescriptions?

- Yes
- No

How much do your prescriptions cost? £_____

What do you feel about the cost of treatment? _____

How is the treatment cost affecting your family? _____

➢ How much does it cost to access your child's medicines?

How much do you spend per month on fuel, parking charges, transport, etc. purely for accessing medicines for your child? £_____

➢ Other difficulties accessing and administering your child's medicines

Do you have any difficulties you haven't mentioned above?

- Yes
- No

If yes, please state: _____

For many reasons, children do not always get their medicines exactly when they are supposed to. On a scale of 1 to 10, how many problems do you usually face when trying to be sure your child gets their medicines?

- 1 - No problems
- 2
- 3
- 4
- 5

- 6
- 7
- 8
- 9
- 10 - A lot of problems

➢ How does administering your child's medicines affect work and school?

Does your child have any problems taking medicines at school?

- Yes
- No
- Not applicable

How often is your child absent or late for school or other activities because of their medicines?

- Always
- Often
- Sometimes
- Never
- Not applicable

Do you have to change your job, cut back your work hours, work schedule, or quit work altogether due to issues related to your child's medicines?

- Yes, have to change job
- Yes, have to change work shift
- Yes, have to cut back hours
- Yes, have to quit working
- No
- Not applicable

In the last 4 weeks, how many total hours of work did you miss due to issues related to your child's medicines? _____

➢ How does managing your child's medicines affect your relationships?

Does managing your child's medicines put strain on your relationships?

- A tremendous amount of strain
- A lot of strain
- A moderate amount of strain
- A little strain
- No strain

Thank you for taking the time to complete our questionnaire

Appendix 6: Content Evaluation Questionnaire

Why have I been asked to take part in this survey?

Why have I been asked to validate this questionnaire?

The PANDA (Polypharmacy ANd Drug optimisAtion) study is a questionnaire study that aims to determine the impact of polypharmacy on paediatric patients and their parents. This questionnaire was designed for parents who look after patients who are taking 5 or more medicines. It contains questions that aim to assess the impact of medicines on various aspects of their lives. We would like your opinion on the questions in this questionnaire.

What is your role in looking after children and young people?

How many years have you been in this role?

Evaluation of the PANDA study questionnaire

In this section, please answer the following questions to determine the relevance (how relevant the question is for this study), essentialness (how important the question is) and clarity (how clearly the questions are written) of each question. These questions have Likert scale options to rate these aspects and are mandatory.

There are also free text boxes for each question to suggest any changes for to improve the questions. These free text questions are optional unless a low score has been given for the question. If you rate a Likert score a Not... or Somewhat... for any of the categories please explain why and provide recommendations to improve the question as this forms part of the validation process.

The options for participants for each question are in the PDF copy of the original questionnaire. Please use this PDF version to supplement the content evaluation. Please note that some questions are branching questions that will only appear for participants if they select a certain answer.

There are 62 questions to assess. Thank you for taking part in this validation process.

General information about your child

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q1. What is your child's age in years and months?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 1 here - please leave this blank if no changes are required

General information about your child

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q2. What is your child's gender?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 2 here - please leave this blank if no changes are required

General information about your child

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q3. What are your child's underlying medical conditions?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 3 here - please leave this blank if no changes are required

General information about your child

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q4. If complex, is the person completing the questionnaire happy if we review clinic letters to collate these data?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 4 here - please leave this blank if no changes are required

General information about your child

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q5. Was your child born prematurely?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 5 here - please leave this blank if no changes are required

General information about your child

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q6. How many weeks was your child born at?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 6 here - please leave this blank if no changes are required

General information about your child

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q7. Were there any complications during the pregnancy/childbirth?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 7 here - please leave this blank if no changes are required

General information about your child

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q8. Did the child's mother have a singleton/twin pregnancy?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 8 here - please leave this blank if no changes are required

Quantity and type of medicines

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q9. How many different medicines is your child taking altogether?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 9 here - please leave this blank if no changes are required

Quantity and type of medicines

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q10. If the medicines your child is taking are complex or you are unsure about it, are you happy if we review the current inpatient prescriptions and/or clinic letters to collate these data?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 10 here - please leave this blank if no changes are required

Quantity and type of medicines

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q11. For each medicine, please state the following: drug, dose, frequency, "Is it a regular medicine or a medicine taken when needed (PRN)?" and formulation (e.g. salbutamol 100mcg, PRN/taken when needed, inhaler; omeprazole 40mg once daily, regular medicine, tablet)	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 11 here - please leave this blank if no changes are required

How effective are your child's medicines?

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q12. Overall, please indicate how effective your child's medicines are in managing their condition(s):	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 12 here - please leave this blank if no changes are required

How effective are your child's medicines?

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q13. It is possible to manage my child's condition(s) so they are free of symptoms:	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 13 here - please leave this blank if no changes are required

How effective are your child's medicines?

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q14. It is possible to control my child's condition(s) so that they can play like other children:	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 14 here - please leave this blank if no changes are required

How effective are your child's medicines?

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q15. I worry about the effectiveness of my child's medicines:	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 15 here - please leave this blank if no changes are required

How effective are your child's medicines?

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q16. How do you think your child's health is now?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 16 here - please leave this blank if no changes are required

How effective are your child's medicines?

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q17. Which medicine(s) do you think work well for your child?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 17 here - please leave this blank if no changes are required

How effective are your child's medicines?

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q18. Which medicine(s) do you think do not work well for your child (if any)?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 18 here - please leave this blank if no changes are required

How easy is it to administer your child's medicines?

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q19. Has a doctor or health care provider ever given you written instructions for what to do about administering any of your child's medicines?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 19 here - please leave this blank if no changes are required

How easy is it to administer your child's medicines?

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q20. How difficult is it to administer your child's medicines each day (please tick the appropriate score)?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 20 here - please leave this blank if no changes are required

How easy is it to administer your child's medicines?

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q21. Who is involved in administering your child's medicines? Tick all that apply	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 21 here - please leave this blank if no changes are required

How easy is it to administer your child's medicines?

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q22. Does your child take his/her medicines on his/her own?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 22 here - please leave this blank if no changes are required

How easy is it to administer your child's medicines?

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q23. Administering your child's medicines upsets you:	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 23 here - please leave this blank if no changes are required

How easy is it to administer your child's medicines?

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q24. Administering your child's medicines upsets your child:	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 24 here - please leave this blank if no changes are required

How easy is it to administer your child's medicines?

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q25. How many times a day does your child require administration of their regular medicines?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 25 here - please leave this blank if no changes are required

How easy is it to administer your child's medicines?

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q26. How many times on average does your child require administration of their PRN (as required) medicines?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 26 here - please leave this blank if no changes are required

How easy is it to administer your child's medicines?

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q27. How many times does your child require regular medicines to be administered overnight (10pm – 6am)?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 27 here - please leave this blank if no changes are required

Factors affecting adherence to medicines

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q28. Have you ever run out of medicines for your child's condition(s)?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 28 here - please leave this blank if no changes are required

Factors affecting adherence to medicines

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q29. Has your child ever missed a dose of their medications?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 29 here - please leave this blank if no changes are required

Factors affecting adherence to medicines

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q30. How often does your child miss doses of their medications (please tick the appropriate score)?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 30 here - please leave this blank if no changes are required

Factors affecting adherence to medicines

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q31. Who issues the prescriptions for your child medicines? Tick all that apply	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 31 here - please leave this blank if no changes are required

Factors affecting adherence to medicines

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q32. Are all of your child's medicines on a single repeat prescription?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 32 here - please leave this blank if no changes are required

Factors affecting adherence to medicines

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q33. Do you receive any medicines through a "Homecare" delivery?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 33 here - please leave this blank if no changes are required

Factors affecting adherence to medicines

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q34. How many repeat prescription medicines does your child require per month?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 34 here - please leave this blank if no changes are required

Factors affecting adherence to medicines

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q35. How often are there difficulties getting prescriptions dispensed at the pharmacy?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 35 here - please leave this blank if no changes are required

Medication side effects

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q36. Do you think your child has had any side effects from their medicines?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 36 here - please leave this blank if no changes are required

Medication side effects

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q37. Which medicine(s) do you think is causing these side effects?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 37 here - please leave this blank if no changes are required

Medication side effects

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q38. What side effect(s) does your child's medicines cause?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 38 here - please leave this blank if no changes are required

Medication side effects

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q39. When do these side effects occur?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 39 here - please leave this blank if no changes are required

Medication side effects

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q40. Who did you inform about the side effects your child has?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 40 here - please leave this blank if no changes are required

Medication side effects

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q41. Please indicate overall, how severe the side effects or adverse effects your child's medicines has caused are	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 41 here - please leave this blank if no changes are required

Medication side effects

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q42. I worry about the side effects of my child's medicines	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 42 here - please leave this blank if no changes are required

How do your child's medicines affect your child physically?

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q43. My child's medicines stop my child from doing certain activities	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 43 here - please leave this blank if no changes are required

How do your child's medicines affect you psychologically?

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q44. How much time do you spend worrying or stressing about your child because of your child's medicines?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 44 here - please leave this blank if no changes are required

How do your child's medicines affect you psychologically?

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q45. I often feel helpless in dealing with my child's condition(s)	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 45 here - please leave this blank if no changes are required

How do your child's medicines affect your and your child's social life?

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q46. How often do you plan your day around your child because of your child's medicines?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 46 here - please leave this blank if no changes are required

How do your child's medicines affect your and your child's social life?

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q47. How often do you avoid social activities with your child because of your child's medicines?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 47 here - please leave this blank if no changes are required

How do your child's medicines affect your and your child's social life?

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q48. How often do you worry about other people's perceptions of you as a parent because of your child's medicines?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 48 here - please leave this blank if no changes are required

How much time is needed to administer your child's medicines?

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q49. My child spends a lot of time taking their medicines everyday	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 49 here - please leave this blank if no changes are required

How much time is needed to administer your child's medicines?

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q50. How long do you spend each day for your child's medicines (in hours and minutes)?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 50 here - please leave this blank if no changes are required

How much do your child's medicines cost?

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q51. Do you have to pay for any of your child's prescriptions?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 51 here - please leave this blank if no changes are required

How much do your child's medicines cost?

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q52. How much do your prescriptions cost?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 52 here - please leave this blank if no changes are required

How much do your child's medicines cost?

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q53. What do you feel about the cost of treatment?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 53 here - please leave this blank if no changes are required

How much do your child's medicines cost?

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q54. How is the treatment cost affecting your family?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 54 here - please leave this blank if no changes are required

How much does it cost to access your child's medicines?

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q55. How much do you spend per month on fuel, parking charges, transport, etc. purely for accessing medicines for your child?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 55 here - please leave this blank if no changes are required

Other difficulties accessing and administering your child's medicines

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q56. Do you have any difficulties you haven't mentioned above?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 56 here - please leave this blank if no changes are required

Other difficulties accessing and administering your child's medicines

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q57. For many reasons, children do not always get their medicines exactly when they are supposed to. On a scale of 1 to 10, how many problems do you usually face when trying to be sure your child gets their medicines?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 57 here - please leave this blank if no changes are required

How does administering your child's medicines affect work and school?

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q58. Does your child have any problems taking medicines at school?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 58 here - please leave this blank if no changes are required

How does administering your child's medicines affect work and school?

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q59. How often is your child absent or late for school or other activities because of their medicines?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 59 here - please leave this blank if no changes are required

How does administering your child's medicines affect work and school?

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q60. Do you have to change your job, cut back your work hours, work schedule, or quit work altogether due to issues related to your child's medicines?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 60 here- please leave this blank if no changes are required

How does administering your child's medicines affect work and school?

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q61. In the last 4 weeks, how many total hours of work did you miss due to issues related to your child's medicines?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 61 here - please leave this blank if no changes are required

How does managing your child's medicines affect your relationships?

	Relevance				Essentialness				Clarity			
	Not relevant	Somewhat relevant	Quite relevant	Very relevant	Not essential	Somewhat essential	Quite essential	Very essential	Not clear	Somewhat clear	Quite clear	Very clear
Q62. Does managing your child's medicines put strain on your relationships?	○	○	○	○	○	○	○	○	○	○	○	○

Please state any suggested changes for Question 62 here - please leave this blank if no changes are required

Further comments

Thank you for taking part in evaluating this questionnaire. If you have any further comments, please state them below.

Appendix 7: PANDA study – Ethical approval

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Dr Daniel Hawcutt
University of Liverpool
Institute in the Park, Alder Hey Children's Hospital
Eaton Road, Liverpool
L12 2APN/A

Email: approvals@hra.nhs.uk
HCRW.approvals@wales.nhs.uk

14 February 2022

Dear Dr Hawcutt

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Polypharmacy ANd Drug optimisAtion (PANDA) study**
IRAS project ID:	**304972**
Protocol number:	**2.0**
REC reference:	**21/WA/0346**
Sponsor	**Alder Hey Children's NHS Foundation Trust**

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 standard conditions 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 **304972**. Please quote this on all correspondence.

Yours sincerely,
Tracy Biggs

Approvals Specialist

Email: HCRW.approvals@wales.nhs.uk

Copy to: *Ms Lucy Cooper*

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
IRAS Application Form [IRAS_Form_29092021]		29 September 2021
Non-validated questionnaire [Study questionnaire]	v1.0	26 January 2022
Other [16-18yrs information sheet]	v3.0	09 February 2022
Other [Parent information sheet]	v3.0	09 February 2022
Other [Assessment - Further Information]		09 February 2022
Other [GCP Certificate]		04 October 2021
Other [Response to REC opinion]		07 December 2021
Other [Study protocol - CLEAN]	v6.0	10 December 2021
Other [Study protocol - TRACKED]	v6.0	10 December 2021
Other [Under 6 information sheet]	v1.0	10 December 2021
Other [7-11yrs information sheet - CLEAN]	v2.0	10 December 2021
Other [7-11yrs information sheet - TRACKED]	v2.0	10 December 2021
Other [12-15yrs information sheet - CLEAN]	v2.0	10 December 2021
Other [12-15yrs information sheet - TRACKED]	v2.0	10 December 2021
Other [16-18yrs information sheet Tracked changes]	v3.0	09 February 2022
Other [Parent information sheet Tracked changes]	v3.0	09 February 2022
Participant consent form [Parental Consent Form]	v1.0	15 August 2021
Participant consent form [Over 16 participant consent form]	v1.0	15 August 2021
Participant consent form [Under 16 consent form]	v1.0	15 August 2021
Participant consent form [Assent form]	v1.0	15 August 2021
Summary CV for Chief Investigator (CI) [CV]		12 April 2021
Summary CV for student		04 October 2021
Summary CV for supervisor (student research) [CV]		12 April 2021

IRAS project ID	304972

Information to support study set up

The below provides all parties with information to support the arranging and confirming of capacity and capability with participating NHS organisations in England and Wales. This is intended to be an accurate reflection of the study at the time of issue of this letter.

Types of participating NHS organisation	Expectations related to confirmation of capacity and capability	Agreement to be used	Funding arrangements	Oversight expectations	HR Good Practice Resource Pack expectations
This is a single site study sponsored by the participating NHS organisation therefore there is only one site type.	This is a single site study sponsored by the participating NHS organisation. You should work with your sponsor R&D office to make arrangements to set up the study. The sponsor R&D office will confirm to you when the study can start following issue of HRA and HCRW Approval.	This is a single site study sponsored by the participating NHS organisation therefore no agreements are expected.	No external study funding has been sought	A Principal Investigator should be appointed at study sites	The sponsor has confirmed that local staff in participating organisations in England & Wales who have a contractual relationship with the organisation will undertake the expected activities. Therefore no honorary research contracts or letters of access are expected for this study.

Other information to aid study set-up and delivery

This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales in study set-up.
The applicant has indicated that they do not intend to apply for inclusion on the NIHR CRN Portfolio.

Appendix 8: PANDA Pilot Study – Table of all underlying medical conditions

Medical condition	Number of patients with the condition (n = 36)
Seizures/epilepsy	10
Global developmental delay	7
Gastroesophageal reflux	6
AKI	5
VSD	5
Constipation	4
Dystonia	4
Scoliosis	4
ASD	3
Cerebral palsy	3
Hydrocephalus	3
Blepharitis	2
CKD	2
Coarctation of aorta	2
Cystic fibrosis	2
Diabetes mellitus	2
Dry eye	2
Ketotic hypoglycaemia	2
Laryngomalacia	2
Learning difficulties	2
LRTI	2
Microcephaly	2
Migraine	2
Nephrocalcinosis	2
PDA	2
Pneumonia	2
Trisomy 21	2
Ventriculomegaly	2
Vocal cord palsy	2
Abnormal central respiratory drive	1
Acute renal failure	1
Adhesive intestinal volvulus (mid gut)	1
Adrenal insufficiency	1
Adrenocortical insufficiency	1
ALTE (apparent life threatening event) in newborn and infant	1
Anarthria	1
Anorexia nervosa	1
Antibody mediated rejection	1
Anxiety	1
Aortic valve regurgitation	1

Asthma	1
Atopic eczema	1
Autoimmune encephalitis	1
Autonomic dysreflexia	1
Bartter syndrome	1
Blind eyes	1
Breathing abnormalities	1
Bronchomalacia	1
Carrier of X linked dystrinopathy	1
Cataract	1
Central precocious puberty	1
Cerebral visual impairment	1
Childhood autism	1
Chronic lung disease	1
Complete AVSD	1
Complex neurodisability with motor issues, cognitive issues	1
Complex ventricular outflow tract obstruction	1
Congenital adrenal hyperplasia due to 3-beta hydroxysteroid dehydrogenase deficiency	1
Congenital heart defect	1
Congenital malformation of sternum	1
Congenital malformations of other endocrine glands	1
Congenital malformations of the ureter	1
Congenital obstructive defects of the renal pelvis	1
Congenital spleen malformations	1
Cranial nerve failure	1
Craniosynostosis	1
Dandy-Walker variant	1
Dental caries	1
Divergent convergent strabismus	1
Dravet syndrome	1
Dysarthria	1
Eating disorder	1
Esotropia	1
Excessive and frequent menstruation with regular cycle	1
Feeding difficulties	1
FRIES	1
General developmental delay	1
Hay fever	1
Hepatomegaly	1
HLA B51 positive	1
Hydronephrosis	1
Hyperglycaemia	1

Hypertelorism	1
Hypertension	1
Hypopituitarism	1
Hypoplastic aortic arch	1
Hypoplastic ventricle	1
Hypothyroidism	1
Hypotonia (severe)	1
Immunoglobulin deficiency	1
Inflammatory Bowel Diseases (IBD)	1
Intermittent transaminitis	1
Iron deficiency	1
Juvenile onset SLE with myositis overlap	1
Laryngeal webbing	1
Long segment Hirschsprung's disease	1
Low mood	1
MAPCAS (Major aortopulmonary collateral arteries)	1
Meibomian gland dysfunction	1
Metabolic bone disease	1
Methyl-CpG-binding protein 2 Xq28 duplication syndrome (MECP2 duplication syndrome)	1
Microphthalmia	1
Mowat-Wilson syndrome	1
Muscle tension dysphonia (inter-arytenoid muscle weakness)	1
Necrobiosis lipoidica diabeticorum (both legs)	1
Nephrotic syndrome	1
Non-cleft velopharyngeal insufficiency (NPI)	1
Osteopenia	1
Patent foramen ovale	1
Posterior urethral valves	1
Post-operative complete heart block	1
Precocious puberty	1
Pulmonary atresia	1
Pulmonary exacerbation	1
Recurrent respiratory infections	1
Reduced visual behaviour	1
Refractory error	1
Respiratory failure	1
Retinal detachment	1
Retinopathy of prematurity	1
Retrolental fibroplasia	1
Rett syndrome	1
Rubinstein-Taybi syndrome	1
Sandifer syndrome	1
Shone's syndrome/complex	1
Short bowel syndrome: acute ischaemic event	1

Significant Chiari malformation	1
Sleep apnoea	1
Small ventricle	1
Spina bifida with myelomeningocoele	1
Spinal muscular atrophy (SMARD type 1)	1
Stage 1 bleed on brain	1
Subaortic stenosis	1
Subglottic stenosis	1
Sulfite oxidase deficiency	1
SVT	1
Tracheomalacia	1
Transaminitis	1
Transposition of great arteries	1
Tricuspid atresia	1
Ulcerative colitis	1
Unexplained mild reduction of visual acuities	1
Uniparental disomy of chromosome 1	1
Urinary retention	1
Urosepsis	1
UTI	1
Ventricular hypertrophy	1
Vocal cord dysfunction	1