Paediatric Medicines Research Group

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Medicines adherence in children

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DEDICATION

I dedicate this work to my children, wife, parents and all of my family members who supported me during my academic studies.

ABSTRACT

Poor medicines adherence in children is one of the common problems in the health care system. Knowing the medicines adherence rate in individual children is important to understand the consequences of non-adherence. Different factors can contribute to poor adherence such as forgetting, lack of understanding about the treatment or disease, age of child, socioeconomic status, medicines schedule and taste. Strategies that target these factors may improve medicines adherence. This research explores methods of measuring medicines adherence and the barriers and facilitators to medicines adherence in children with diverse diseases.

A systematic review of measures of medicines adherence in children was conducted. Six databases were searched to identify studies published in the last ten years and therefore to focus on the methods recently used to assess medicines adherence in children. Inclusion criteria were original research studies measuring medicines adherence in children. Only 31 articles met the inclusion criteria and were included. The review identified seven methods which had been used to measure adherence; self-report, Electronic Monitoring Devices (EMD), dose count, canister weight, plasma level, checking medical records or pharmacy refill data, and contact by mobile phone. Currently, no gold standard method to measure adherence to medicines in children exists as each method has its own advantages and disadvantages.

A systematic review of the barriers and facilitators to medicines adherence in children was also conducted. Six databases were searched to identify the most common barriers and facilitators in the last ten years. Inclusion criteria were original research studies with stated objectives of identifying barriers and/or facilitators of medicines adherence in children. This review identified 177 articles that met the inclusion criteria. Reported barriers included forgetfulness, weak patient-provider relationships, stigma and discrimination, drug regimen complexity and lack of support from families. Factors reported to facilitate adherence include linking of medicine taking with daily life routines, using reminders to avoid forgetfulness, a higher level of caregivers and parental education and good communication between healthcare professionals, patients and parents.

Based on the findings from the two systematic reviews, two exploratory studies were conducted to measure medicines adherence in children in Saudi Arabia and the UK, and to explore the barriers to and facilitators of medicines adherence in these children. After confirming eligibility for inclusion in the two studies, the patients and their parents or guardians were asked to participate in the studies. The researcher provided them with written and verbal information about the study in age-appropriate language. In both studies, the patient or parent/guardian were asked to answer all questions in the Beliefs about Medicines Questionnaire (BMQ) and our own designed questionnaire, in order to measure medicines adherence and explore the barriers to and facilitators of

medicines adherence in children. One hundred children and their parents/guardians were recruited for each study. The study conducted in Saudi Arabia found substantial agreement between the study's two adherence measurement methods of self-report and Medication possession ratio (MPR) calculation. Additionally, this study identified that changes in daily routine, many doses each day, unpleasant medicine taste and fear of side effects were the most common barriers to medicines adherence. Using reminders, implementing a scheduled routine for taking medicines, measures to address poor taste, pain caused by administration or taking big tablets, and adequate family support were the most common facilitators for medicine adherence in children.

The study conducted in the UK found changes in daily routine, poor medicine taste, many doses each day, and being busy were the most common barriers to medicine adherence. This study similarly found that using reminders, measures to address poor taste, pain caused by administration or taking big tablets, following a scheduled routine for taking medicines, and family support were the most common facilitators in children's medicine adherence. Both studies found a statistically significant association between the participants' beliefs about medicines and adherence rates and between adherence rates and the education level of the patients' parents. However, there was no statistically significant association between adherence rates, age and gender in either study.

This project contributes to the field of medicines adherence in children by confirming that there is currently no gold standard method of measuring it, but that there is good agreement between the two adherence measurements of MPR and self-report. Additionally, parental education level and BMQ differential scores are factors significantly associated with medicines adherence. In addition, this project highlights the most common barriers to and facilitators of medicines adherence in children with diverse diseases in children's hospitals in Saudi Arabia and the UK.

Publications and presentations related to this thesis

Oral presentations:

- Medicines adherence in children, 18 months presentation event in Clinical Sciences building, City Hospital, 29th October 2019, Nottingham, UK.

Poster presentations:

- Systematic review of measuring medicines adherence in children. 24th Neonatal and Paediatric Pharmacists Group (NPPG) Annual Professional Conference & Exhibition (9 – 11 November 2018), Mercure Grand Hotel, Bristol.
    - Aldosari M, Oliveira A, Conroy S. Measuring Medicines Adherence in Children: A Systematic Review. *Arch Dis Child.* 2019;104: e2. Available from: https://adc.bmj.com/content/104/7/e2.10. (Published abstract)
- Systematic review of barriers and facilitators to medicines adherence in children. 25th NPPG Annual Professional Conference & Exhibition (8 – 10 November 2019) Ramada Plaza Sutton Coldfield, Birmingham.

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Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
BMQ	Beliefs About Medicines Questionnaire
CINAHL	Cumulative Index to Nursing and Allied Literature
EMD	Electronic Monitoring Device
GH	Growth Hormone
GORD	Gastro-Oesophageal Reflux Disease
HEDCs	High Economic Developed Countries
HDAS	Healthcare Databases Advanced Search
IBD	Inflammatory bowel disease
IPA	International Pharmaceutical Abstracts
IRB	Institutional Review Board
KFMC	King Fahad Medical City
LEDCs	Low Economic Developed Countries
MAM	Medical Adherence Measure
MARS	Medication Adherence Rate Scale
MEMS	Medication Event Monitoring System
MPR	Medication Possession Ratio
PIS	Participant Information Sheet
RCT	Randomised Controlled Study
STROBE	Strengthening the Reporting of observational studies in Epidemiology
TABS	Talking About Medicines Study
TB	Tuberculosis
VAS	Visual Analogue Scale
WHO	World Health Organisation

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Chapter 1: Introduction

1.1 Background

Around 400 BCE, Hippocrates was the first to note that some patients do not take their medicines as prescribed, and then complain that they do not work (1). In 1882, Robert Koch described noncompliant patients with tuberculosis (TB) as irresponsible and/or careless (1). McMaster University Medical Centre initiated the groundwork on patient compliance at the beginning of the 1970s, resulting in a book entitled Compliance with Therapeutic Regimens by Sackett and Haynes (2). According to Sackett and Haynes (1976), compliance is defined as **"**the extent to which the patient's behaviour coincides with the clinical prescription, regardless of how the latter was generated**"** (2).

Thus, the groundwork for the present adherence research was laid at the end of the 1970s. At that time, only the term compliance was used, and research studies concentrated on the influence of noncompliance on therapeutic results in clinical studies. Patients' perspectives had not yet been considered (3).

Later studies addressed how patients were affected, and how medicines were integrated into patients' daily routines (3). Parallel to this evolution, the term adherence was increasingly used instead of compliance (4). Medicines adherence and patient compliance have often been used synonymously. However, compliance has recently been associated with the negative connotation that patients are

subservient to healthcare professionals and now, the preferred terminology is 'adherence with medication' (3).

These changes led a joint working group convened by the Royal Pharmaceutical Society of Great Britain to suggest using the new term concordance in 1995 (5). In 1997, adherence was defined by the American Heart Association as: "a behavioural process, strongly affected by the environment in which the patient lives, including health care practices and systems" (6). This definition assumed that optimal adherence depends on patients having the motivation, skills, resources and knowledge required to follow healthcare professionals' instructions (6).

In 2003, adherence was defined by the World Health Organisation (WHO) as "the extent to which a person's behaviour—taking medication, following a diet and/or executing lifestyle changes corresponds with agreed recommendations from a healthcare provider" (7). Progressively, the idea of agreement and cooperation between patient and healthcare provider became associated with the idea of adherence, while 'compliance' referred only to following a healthcare provider's recommendations (7).

Concordance refers to involving patients in the treatment process to improve adherence. It is not synonymous with either adherence or compliance. It refers to the interaction between patients and healthcare providers, but it does not relate directly to a patients' medication-taking behaviour (8).

To achieve high levels of concordance patients should be involved in the decision of prescribing medicines. If a therapeutic partnership is not established non-concordance may occur and therefore may lead to failure of the interaction (9). Concordance is based on the assumption that discussion between patients and healthcare providers is a negotiation between equals. As such, how patients value the benefits and risks of a particular medicine may differ from the values determined by their healthcare providers (10). One of the differences between concordance and adherence or compliance is that adherence and compliance can be measured by pharmacy dispensing data, electric pill counters, prescription claim records or other validated survey instruments; however, concordance cannot be measured in these ways (9).

Persistence is another term associated with the optimal use of medicines by patients, however it is purely related to long-term therapy. The definition of persistence is **"**the length of time between the first and last dose, being applicable in the event that a patient discontinues treatment**"** (11). Whereas persistence refers to how long patients remain on therapy, adherence and compliance refer to how well patients follow the treatment (11).

Treatment outcomes are affected not only by how well patients follow the treatment but also by how long they remain on the treatment. Thus adherence and persistence should be measured and defined separately to achieve good outcomes of treatment (11). Patients' desire to take a

medicine plays an important role in adherence. Thus, compliance, persistence and adherence, but not concordance, are terminologies that may detect the level of inadequate medicine use (12). In 2009, medicine adherence was added as a MeSH term (13).

Medicines non-adherence is a multidimensional health care issue. Patients may be non-adherent during different stages of therapy; they may decide not to have their medicines dispensed and even not to start taking them at all. Furthermore, patients may take their medicines at the wrong times, or use less or more than the prescribed amounts. Patients may also discontinue treatment prematurely (12) .

1.2 Consequences and costs of medicines non-adherence

According to Chappell et al., 30 to 70% of children prescribed long-term medicines exhibit poor adherence (14). The consequences of medicines non-adherence may be disease progression, lower quality of life, wasted medicines, and increased use of medical resources, e.g., hospital visits, and increased admissions to nursing homes (15). Figure 1-1 shows the relationship between medicines non-adherence and associated health care costs. The risk of hospitalisation for non-adherent patients with congestive heart failure, hypercholesterolemia, diabetes mellitus, or hypertension is more than double that of the adherent patients (16). Non-adherence to medicines may also have negative consequences for healthcare providers, and medical researchers, as well as patients (17).

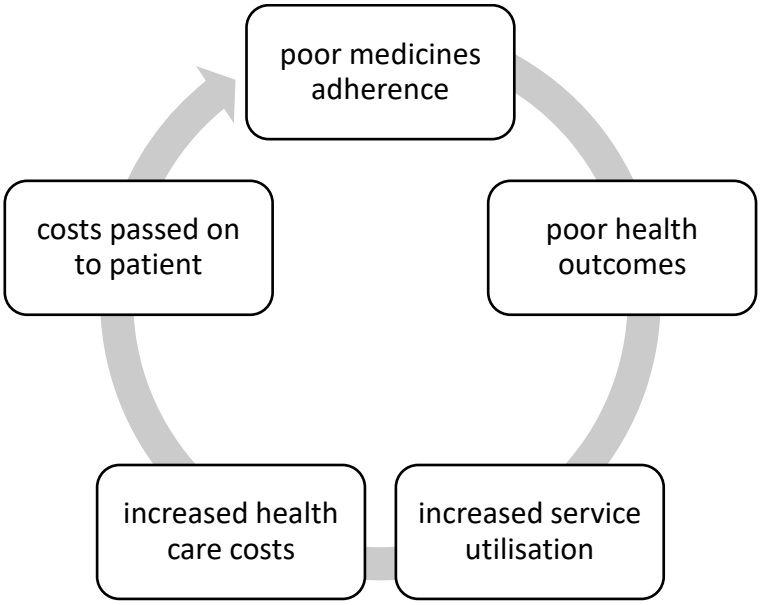


Figure 1-1 Relationship between medicine non-adherence and associated health care costs. Adapted from Aurel O Luga (17).

The health concern is that poor adherence can result in unsuccessful or inadequate therapies and unnecessarily prolonged therapies. It can also lead to additional visits to doctors or changed prescriptions (18). Premature discontinuation of treatment may lead to delayed recovery, and this may result in patients contracting additional diseases and more hospitalisation and costs. Additionally lack of adherence places patients at risk of complicating the doctor-patient relationship as well as extending periods of treatment (19). Non-adherence to antibiotic courses may lead to bacterial resistance and the increased probability of recurrent infections (18). When patients take extra doses of medicines without medical supervision, the possibility of toxicity increases, and this may lead to increased rates of mortality and morbidity among patients (16).

1.3 Medicines adherence measures

Knowing the degree to which patients adhere to medicines is important both in clinical practice and in medical research. Assessing medicine adherence in pharmaceutical trials is necessary to examine the dose–response relationship and enable an accurate analysis of treatment efficacy and toxicity (20). Inaccurate assessment may cause problems that are dangerous and costly, e.g. if an adolescent patient's adherence to antidiabetic medicines is estimated incorrectly to be high but their blood glucose is still high, the doctor may increase the dose of the prescribed medicines or add other antidiabetic medicines in addition (21). Many different methods are used to measure adherence to medicines (20). These methods may be categorised as either direct or indirect (22). Currently, no gold standard method exists, as each method has its own advantages and disadvantages (22).

1.3.1 Direct methods

Direct methods include:

- Measurement of the concentration of the medicine or a metabolite in a body fluid, usually urine or blood.
- Direct observation of the patient taking the medicine.

These methods can be used at specific intervals or randomly (20). The measurement of the drug plasma level is a good technique to assess adherence (22). For example, with some anti-epileptic drugs, such as valproic acid or phenytoin, the drug plasma level should reflect regimen

adherence with these medicines. Although these direct methods are considered more accurate than indirect methods, direct methods also have some disadvantages (22). Direct methods are difficult to perform, invasive, expensive, and may be susceptible to distortion by the patients, e.g., a patient may take a double dose of the medicine before the blood test and, thus, can give a false impression of adherence (23).

1.3.2 Indirect methods

Indirect methods are more commonly used to assess medicine adherence than direct methods. The most commonly used indirect methods are highlighted below:

A. Patient self-reports

To assess adherence to medicines clinicians traditionally rely on self-reports. Direct questions for patients regarding medicine use may be asked during consultations (24). Clinicians may ask judgmental, single closed-ended questions, such as, 'Do you take your medications as prescribed?' and because of worries in sharing difficulties associated with drug use, patients may answer 'yes'. This type of direct questioning has been suggested to be unreliable (25). More reliable and complete information may be obtained through alternative questioning (26). By posing non-judgmental, open-ended questions, such as 'Will you tell me how you take your medications?', patients may actually be encouraged by interviewers to share their difficulties with medicine use (26). Also, questions could be focused on how many

times a patient forgot to take their medicines and the reasons why a patient might not take his or her medicine (27). Medicines adherence in children can be assessed by asking the opinion of a caregiver (parents, school nurse or teacher) (16). Although self-report is easy to use and inexpensive, it is thought to be the least accurate method (28,29).

B. Dose counting

This method involves counting the number of doses that have been taken between two clinic visits or scheduled appointments, and comparing this number with the total number of doses dispensed for the patient in order to assess medicine adherence in research settings (30). For inhaler devices doses may be counted by weighing inhaler devices at the beginning of treatment and at each subsequent clinical visit until the devices are empty (24,31). This method is easy to use and inexpensive compared with other methods. The main disadvantages of this method are overestimates of the adherence rate, families may forget to bring their medicine containers to each visit, it counts the number of doses gone but this does not guarantee medicine ingestion, and it fails to provide information on the times that doses are taken which may be important in determining clinical outcomes (23). In addition, patients can manipulate the data, e.g., a patient may throw away some of their tablets (32).

C. Electronic monitoring devices (EMDs)

The EMD is a device that fits on a medicine bottle and contains microelectronics that record the time and date the bottle is opened. It can also record how many hours since it was last opened and how many times the bottle has been opened (24). Use of EMDs in practice and research is increasing because of their ability to provide adherence data to clinicians (28,33). Although EMDs may be considered to be the best method to assess adherence of medicines, EMDs are expensive, patients need to understand how to use the device, the opening of the medicine bottle does not necessarily mean that the dose was taken, and the presence of an electronic monitoring device may remind patients that they are under surveillance, which may affect their medicine-taking behaviour, thereby inflating their adherence rates (33,34).

D. Pharmacy refill data

Prescription data and data on pharmacy refills may be used to assess patient adherence. These data can show the frequency of refills and whether or not patients' prescriptions have been filled (35). Pharmacy refill data can measure adherence by calculating the medication possession ratio (MPR), which is defined as "the number of doses dispensed in relation to a dispensing period". (36,37).

The MPR is calculated by this equation:

$$\text{MPR} = \frac{\text{total days' supply for medicine dispensed}}{\text{the number of days that the patient should have been taking the medicine}}$$

The MPR will equal 1, representing the highest adherence, when the total days' supply is equal to the number of days between two prescription refill times. Assuming that the number of days of the supply is constant, the longer the duration between two prescription refills, the lower the MPR value, reflecting lower adherence (36). The disadvantages of this method are that patients may order refills but possess a large amount of unopened medicine, the method is useful to assess adherence for chronic diseases but not for acute diseases, and this method does not account for the timing of the doses (38).

1.4 Types of nonadherence

Nonadherence to medicines may be intentional or unintentional.

1.4.1 Intentional nonadherence

Intention is characterised as the determination to act in a certain way and is an element of human behaviour, including health behaviour (39). Intentional nonadherence can be described as **"**a process in which the patient decides not to follow therapy instructions or not to use medication**"** (40)**.** This generally reflects a decision-making process in which patients weigh the advantages and disadvantages of therapy (40). It is important to understand the cognitive factors (e.g., preferences and beliefs) that may affect medicines adherence (41).

The beliefs affecting patients' adherence to medicines can be divided into two groups: concerns about possible adverse effects (Concern beliefs) and perceptions about the need for medicines (Necessity beliefs) (42). This 'Necessity-Concerns Framework' may help healthcare providers elicit and address key beliefs that support patients' attitudes and decisions about medicines (41). Horne et al. developed a validated questionnaire (Beliefs about Medicines Questionnaire (BMQ)) to quantify patients' Concerns and Necessity beliefs and to assess their relationship with medicines adherence (42). A meta-analysis of 94 studies of patients with chronic diseases was then performed by Horne et al. to examine the value of the BMQ in predicting medicines adherence. It was concluded that the BMQ is useful for understanding patients' perspectives on their medicines and medicines adherence can be improved by addressing patients' concerns and explaining to them the importance of their medicines (41).

Beliefs about the necessity of medicines is assumed to be determined by quality of life, the severity of disease and patients' behaviours (43). There are many behavioural theories that are believed to have an impact on patients' beliefs about their medicines. For example, if the patients think that their disease can be controlled by the medicines, they are more likely to be adherent. This is guided by Weiner's attribution theory that is concerned how individuals' behaviour and thinking are related to how their interpret events

(44). Patients' beliefs about their medicines may have a greater impact on their adherence if they have a psychological need for autonomy (45). Self-determination theory (which refers to each patient's ability to make choices for their treatment) is another behavioural theory that argues that treatment environments that support confidence and affords autonomy for patients are likely to improve medicines adherence (45).

The health locus of control is another psychological construct that has been studied in relationship to adherence (46). Locus of control contributes to understanding health behaviours in chronic diseases (46). Locus of control is divided into two categories: internal (a belief that a person can have control over their health and refers to traits and behaviours) and external (a belief that results from outside factors which are independent of their own action) (47). It has been found that medicines adherence may be influenced by patients' health locus of control (47). For example, adherence rates may be improved by interventions that target patients' internal locus of control such as providing a positive feedback to the patient for their small success (48).

1.4.2 Unintentional nonadherence

Unintentional nonadherence refers to passive or unplanned behaviour and is less strongly related to individual cognition and beliefs than intentional nonadherence. It may be the consequence of not knowing precisely how to take medicine or of forgetfulness (49).

Patients may either not remember the instructions for medicine use or forget to take the medicines at the recommended times (39).

The use of multiple medicines is related to an increased chance of complex dosing schemes. The necessity to manage potential drug–drug interactions may also increase the risk of complex dosing schemes, such as the need to take bisphosphonates or tetracycline separately from iron salts, aluminium, magnesium or calcium. Other examples include the need to take thyroid hormones and bisphosphonates at least 30 minutes before breakfast. In contrast, some medicines should be taken with a meal, not on an empty stomach, leading to a complex dosing scheme that patients then have to follow (3).

1.5 Barriers to medicines adherence

Poor adherence may cause suboptimal results of treatment and increased morbidity and mortality (50). Enhancing medicine adherence for chronic conditions such as diabetes, hyperlipidaemia and hypertension creates significant economic and health benefits (7,50). To enhance adherence, the multifactorial causes of poor adherence should be understood. As shown in Figure 1-2, the World Health Organisation (WHO) classifies these factors into five categories: condition-related, social and economic, healthcare team and system-related, medicine-related, and patient-related factors (7).

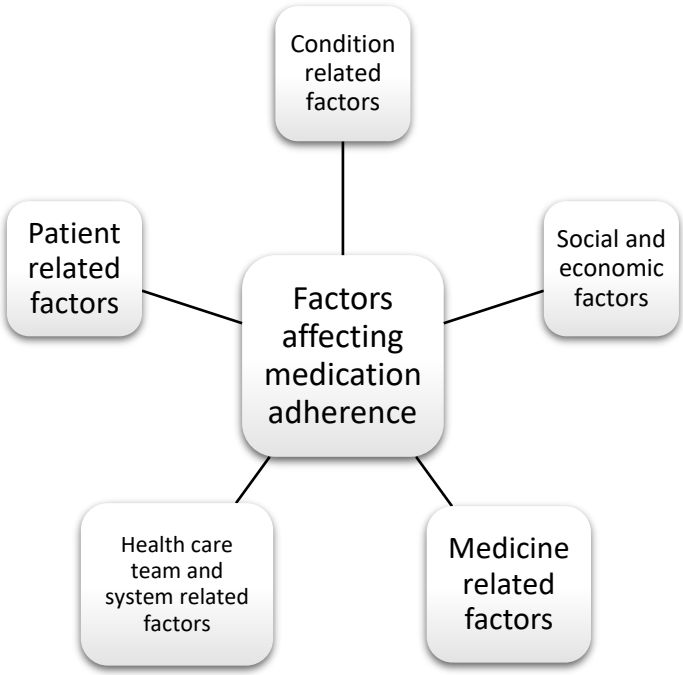


Figure 1-2 The five factors affecting medicine adherence. Adapted from WHO 2003 (7).

1.5.1 Patient-related factors

A. Patient-related factors: adults

Many patient-related factors, including suboptimal health literacy, lack of involvement in the therapy decision-making process, and lack of understanding of the disease, contribute to non-adherence to medicine (50–52). Health literacy is defined as "the degree to which patients have the ability to understand basic health information and services needed to make appropriate health decisions" (50,53). In 2000 in the United States alone, an estimated 90 million adults had low health literacy, placing them at risk of poor clinical outcomes and increased

rates of hospitalisation (54). In 2015 in England 42 % of adults were unable to make use of and understand everyday health information (55).

Medicines adherence in adults may be affected by patients' experiences with pharmacological treatment, their attitudes and beliefs about the effectiveness of the therapy, low self-efficacy, lack of knowledge about the disease, and lack of motivation (56). In older adults, cognitive limitations and physical impairments, e.g., the patient may be unable to open the medicine bottle, may further increase the risk of medicine non-adherence (56).

B. Patient-related factors: children

Medicines adherence in children is also an important topic for health care professionals. Lack of adherence may cause complications in children with chronic or acute diseases (19). For many children, the administration of medicine is a parent's responsibility, and parents' knowledge, beliefs and attitudes may also affect the timing and dosing of medicines (57). Clinical experience indicates that for children with chronic diseases, e.g. diabetes, asthma, epilepsy and cystic fibrosis, poor adherence is common (14,57).

One factor that affects adherence is age. Younger children appear to have higher rates of medicines adherence than adolescents (7,58). When children enter school, they spend less time with their family at home and they may be more influenced by the social environment and

their peers (7,58). Poor adherence is common in school-aged or adolescent patients who are taking multiple doses of medicine per day because of difficulty of using medicines at school (58,59). Children who are usually reminded by their parents to take their medicines may forget the doses during school time (49,58). Family conflict and stress for children and parents have been suggested to be some of the most significant reasons for medicine non-adherence (60). Other barriers reported by parents include not understanding the instructions of the treatment, changes in usual routine, being busy and forgetting (59,61,62).

1.5.2 Healthcare team and system-related factors

Healthcare providers may not only fail to recognise non-adherence to medicines in their patients, but they may also contribute to increasing the risk of non-adherence by inadequately considering the financial cost of medicines to the patient (in some countries some patients do not have health insurance and may have to buy their medicines) (63). In addition failing to explain the medicine's side effects and benefits, or prescribing complex medicine regimens may contribute to non-adherence (22,64). Communication between healthcare providers and patients may be inadequate and may also contribute to poor adherence (64).

Healthcare system-related factors that have a negative effect on medicines adherence include (37,38):

- Provider-patient relationships, as weak relationships between care providers and patients may lead to decreased medicine adherence.
- Lack of training and knowledge for healthcare providers.
- Overworked healthcare providers.
- Lack of provider knowledge about medicine adherence and how to improve adherence.

1.5.3 Condition-related factors

In some patients with chronic diseases requiring long-term administration of medicines, adherence may decline significantly over time (67). This poor adherence may happen when symptoms of the disease are few or disappear; the absence of symptoms may be a barrier for patients to follow their treatment. Some patients with few disease symptoms may believe they are healing, discontinue their treatments and thus have poor medicine adherence, e.g., if an asthmatic child begins to feel better and their symptoms have improved, the parent may stop administering daily inhaled steroids, believing this will prevent the medicine's side effects (68). It is imperative that patients understand the disease and the risks if they do not follow the treatment (56).

Severity of the disease and rate of progression may affect adherence to medicines; when the severity of a disease is high, the medicine adherence of the patient with the disease may reduce because the patients may lose trust in their treatment (69,70).

1.5.4 Socioeconomic-related factors

Family support is important for patients, especially children, who cannot be relied up on to take their medicines properly and may not realise the importance of the medicine or the seriousness of their disease. Patients who have less social support from caregivers, friends or family to assist with medicine regimens tend to have less medicines adherence (50,56).

In some countries, limited access to healthcare facilities or greater distance from medical centres has been reported as a barrier to adherence especially for patients who do not have enough money for transportation (71,72). Patient adherence to medicines can also be affected by the fear of stigma or discrimination, especially among adolescent patients (73,74). Adolescents with diseases such as HIV may be afraid to take their medicines in front of others because of fear of disclosure of their disease status and subsequent discrimination, stigma, rejection and isolation (49,58,72). This could cause adolescents to hide their medicines from others or not take them at all when out with friends, which may result in not taking medicines at the right time or missing doses (73).

High cost of medicine is another socioeconomic barrier to adherence in some countries, especially if patients do not have health insurance and have to pay for their medicine. In some cases, patients try to reduce the cost of medicine by decreasing the dosage and/or the frequency of a recommended treatment (56).

1.5.5 Medicine-related factors

Some medicines have different routes of administration. The oral route is the preferred and most frequently used route of administration for children (75). The most commonly acceptable dosage form for children's oral formulations is liquid, which also has the advantage of dosage flexibility. However, when the volumes to be administered are small, accuracy of measurement may become difficult and can confuse caregivers and parents (76). Furthermore, when the medicine is prescribed in a liquid formulation, parents may remember the volume of the dose but not necessarily the dosage in units. If a bottle is empty or broken, a different strength of medicine may be provided as a replacement e.g. many unlicensed products such as phenobarbital liquid are available on the market from different companies and in different strengths. Parents may continue to administer the original volume, resulting in the dose administered being up to tenfold lower or higher than prescribed (14). For example, in Sheffield, a four-month-old baby died after a GP prescribed furosemide liquid which was ten times stronger than the formulation previously prescribed by the hospital (77). The GP correctly prescribed a reduced volume (decreased from 5 ml to 0.5 ml), but the mother gave the baby 5 ml by mistake in accordance with the first volume prescribed (77).

Solid oral formulations have limited dose flexibility. In cases where no liquid formulation is available, carers and parents may be asked to

modify formulations, which can be difficult. For example, they may be asked to dissolve a capsule's content in a certain volume of water or to crush and disperse a tablet in water. Such drug manipulations may lead to inaccurate dosing and reduce desired drug effectiveness or cause toxicity (78). The need for complex manipulations, poor drug efficacy or side effects may negatively affect patient adherence (61,69).

Complexity of the medicine regimen is another medicine related barrier to adherence. When the number of medicines prescribed or the number of daily doses is increased, the possibilty of missing a doses increases (70,79). In addition, the longer the duration of treatment the less likely proper medicines adherence is maintained (80,81). Acute conditions are associated with greater adherence to medicine than chronic conditions (80).

In asthmatic patients, especially children, ensuring continued use of inhaled medicines can be difficult (82). A number of factors may influence adherence to inhaled medicines, such as difficulties with inhaler devices (e.g., inhalers can be difficult to use and mistakes in the technique can mean that little or no dose is inhaled by the patient) and regimen complexity (83,84).

Adverse effects of medicine have also been reported as a reason for discontinuing daily medicines (51,83). Adverse side effects can cause physical discomfort and decrease trust in doctors, causing scepticism

about the efficacy of the treatment (e.g. side effects have been reported as one of the most common reasons for non-adherence in children with chronic disease) (85).

1.6 Facilitators of medicines adherence

Understanding reasons for poor adherence and addressing them is important for improving medicines adherence (7). There are also factors that may help to improve medicines adherence, especially in children, such as family support, using reminders, establishing a routine, good knowledge about disease and treatment and masking poor taste/big tablet of medicine (50,75,86,87).

Knowledge of the possible outcomes of non-adherence to the medicine and a comprehensive understanding of the importance of the medicine have been reported among children with HIV, asthma, ADHD and their parents who were adherent (86,88–90). This knowledge and understanding of the disease and importance of treatment, combined with patients' desire to be healthy, motivated them to take their medicines as prescribed (86,88–90).

Some patients establish a routine and use reminder tools so they do not forget to take their medicine (87). Linking the medicines regimen with daily life routines and taking the drugs at the same time every day (e.g., before a meal or after brushing teeth) may reduce the probability of missed doses (87,88). Patients use different reminder tools to remember their medicines, such as marking a calendar,

keeping a tally sheet of doses, setting an alarm (phone, tablet device or clock) or using note reminders (e.g., notes on the refrigerator) (70,87,91).

The bad taste of some medicines is one of the reasons for poor adherence in children (92). Sweet tasting medicines can minimise resistance and enhance adherence for children as many have a low tolerance for disagreeable tasting medicines (75). However, these sweet medicines can cause problems with dental caries, especially if they are required on a long-term basis.

Family support is one of the most important factors that can help patients, especially children, adhere to medicine (50,56). Family members can help the child by reminding them it is time to take their medicine, helping them take their medicine and encouraging them to continue with adherence to the medicine (93–95). In addition, reinforcing medicine taking with rewards can motivate children to adhere to their medicine (59).

Healthcare providers can help improve adherence in children by clearly instructing the children and their parents on how to take their medicine, explaining any possible undesired aspects of taking their medicine and discussing options with them (e.g. some patients may prefer syrup formulations more than tablets) (59,96,97). In addition, discussing the rationale for the treatment and the benefits of adherence and offering written or verbal

information (e.g., telephone calls or home visits by nurses or educational books) about the nature of the medicines and the disease may also help improve adherence (59,96,97).

1.7 Research question, aims and objectives of this research

Most studies concerning medicines adherence have focused on adult patients rather than on children because of the practical difficulties and ethical issues in children's studies (98). Most previous paediatric studies have focused on children with a particular disease, for example HIV, asthma, epilepsy or diabetes. Only a few studies included children with any and therefore diverse diseases. Most of these did not explore both barriers to and facilitators of medicines adherence.

1.7.1 Research question

What are the most common barriers to and facilitators of medicines adherence in children with diverse diseases?

1.7.2 Aims of this research

We aimed to fill gaps in knowledge of the barriers to and facilitators of medicines adherence in children with diverse diseases in the UK and Saudi Arabia.

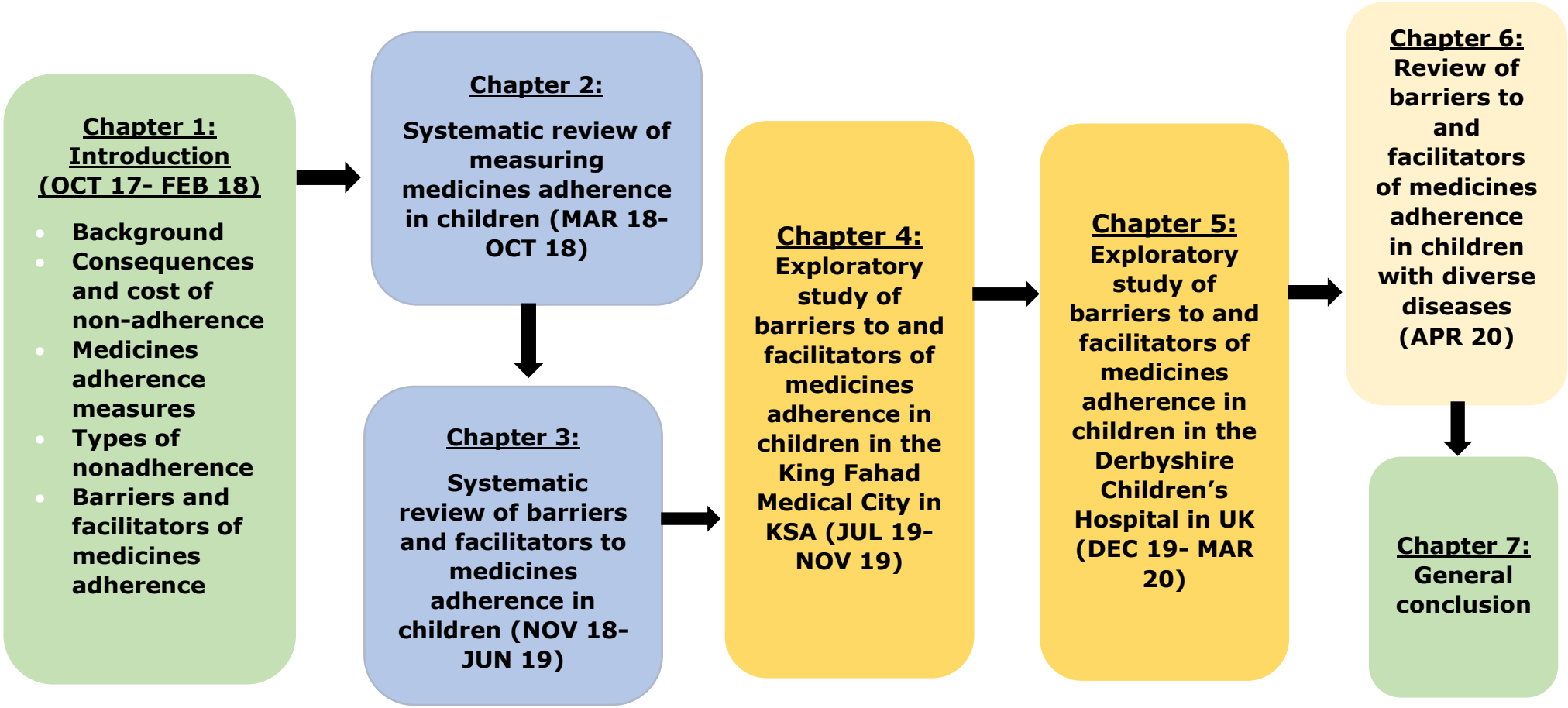
1.7.3 Objectives of this research

1. To identify and explore the strengths and weaknesses of methods of measuring medicines adherence in children **(Chapter 2)**.
2. To identify barriers to and facilitators of medicines adherence in children that have been reported in the last ten years **(Chapter 3)**.

3. To measure medicines adherence in children in Saudi Arabia and to explore all barriers to and facilitators of their adherence **(Chapter 4)**.
4. To measure medicines adherence in children in the UK and to explore all barriers to and facilitators of their adherence **(Chapter 5)**.
5. To summarise current knowledge on barriers to and facilitators of medicines adherence in children with diverse diseases **(Chapter 6)**, including the knowledge gained from our own work.
6. To describe implications for practice and recommendations for future research **(Chapter 7)**.

Figure 1-3 shows the relationship between the works involved in this thesis.

Figure 1-3 Flow chart showing the relationship between the works involved in this thesis



Chapter 2: Measuring medicines adherence in children: A systematic review

2.1 Introduction

As previously mentioned, for many children, the administration of medicine is a parent's responsibility, and parents' knowledge, beliefs and attitudes may affect the timing and dosing of medicines (57). Reasons for poor medicines adherence in children include concerns about treatment effectiveness, forgetfulness, parents' lack of understanding of the diagnosis, and fear of medicine side effects. Knowing the degree of medicines adherence in children is important to provide information on the consequences of non-adherence and to develop strategies to improve adherence (50). We wanted to find out the best method to measure adherence in children to inform the subsequent studies in this PhD project.

An ideal measure of medicines adherence should be easy to carry out and inexpensive, user friendly, highly reliable, flexible, and practical. It has been suggested however, that no single standard measure meeting all these criteria has been identified (99). We looked for a systematic review exploring measures of medicines adherence in children and could not find one. We therefore performed a systematic review to identify the measures of medicines adherence which have been used with children and to explore the strengths and weaknesses of those measures.

2.2 Methods

2.2.1 Search strategy

A systematic literature search was performed to identify all papers describing methods used to measure medicines adherence in children. Six databases were searched from March 2008 to July 2020 to focus on the methods recently used to assess medicines adherence in children. The initial search was performed using the Healthcare Databases Advanced Search (HDAS) platform, which allows the combination of several databases.

Four databases were searched through this platform:

- Medline
- Pubmed
- Embase
- Cumulative Index to Nursing and Allied Health Literature (CINAHL)

The search was also conducted separately using the Cochrane library and International Pharmaceutical Abstracts (IPA).

A hand search of the bibliographies of relevant papers was also performed in order to identify all studies related to our inclusion criteria.

The resulting studies were exported to Endnote and combined together to remove duplications.

The databases were searched for all studies which used a measure of medicines adherence and included paediatric patients aged ≤18 years of age. The following keywords were used: **measure* or scale* or**

assess* or screen* AND adhere* or complian* or nonadhere* or noncomplian* or patient compliance* or medication adherence* AND children* or child* or pediatrics* or paediatric* or adolescent* or infant* or newborn*or neonate*.

2.2.2 Justification of search strategy

In this systematic review, the specific keywords above were selected to integrate a wide variety of terms that met our aims and purposes. The first part of the search strategy covered the methods used to measure medicines adherence that we wanted to explore. Terms were selected to cover different permutations of plural, noun, singular and adjectives using asterisks (*). The keywords for the first part we selected were 'measure* or scale* or assess* or screen*'. Measure* and scale* were used as recommended by the BioMed Central Medical Research Methodology for systematic reviews which contained searches about measuring medicine adherence (100). In addition we added assess* and screen* from previous systematic reviews (101–103).

In the second part of the keywords, we covered terms for medicines adherence. The keywords that we used were 'adhere* or complian* or nonadhere* or noncomplian* or patient compliance* or medication adherence*'. These terms were taken from systematic reviews related to the subject of medicines adherence which were published in reputable journals (97,104–106).

The third part covered the paediatric age group. The keywords that we used were 'children* or child* or pediatrics* or infant* or neonate* or newborn* or adolescent*' to cover all paediatric patients aged ≤18 years. These terms were used as recommended by search strategies for MEDLINE (107). The English spelling 'paediatric' was not included as we were of the understanding that the term 'pediatrics*' covered this variation in spelling. We recognise now however that this is not the case and is therefore an omission in our search strategy.

2.2.3 Inclusion criteria

Inclusion criteria were original research studies measuring medicines adherence in children (age from birth to 18 years) and included all countries and all languages. To be included, the assessment tool used to measure adherence in each study needed to be clearly identified or discussed in some detail.

2.2.4 Exclusion criteria

Exclusion criteria included:

- Review articles, editorials, conference papers, reports.
- Studies reporting only adherence outcomes/rates without reporting methods of how these were measured.
- Studies that did not separately identify the methods which were used to measure medicines adherence in children.

2.2.5 Data collection and analysis

One reviewer (Aldosari M) examined all titles and abstracts identified by the search according to the inclusion and exclusion criteria. Where relevance was not clear from the title or abstract, full papers were obtained and reviewed. As a reliability measure, 5% of titles and abstracts were assessed independently by another researcher from our group (Smith C) and after discussion, Aldosari M and Smith C reached full consensus on which studies were relevant. All studies using methods to measure medicines adherence in children were analysed. The following data were extracted into a table:

- Name of authors.
- Publication year.
- Country where study was completed.
- Type of study.
- Number and age of participants.
- Type of measurement tool used to assess adherence.
- Type of disease.
- Reported outcome.

2.2.6 Quality assessment

Quality assessment is done in order to identify studies with a high risk of bias. The quality of the included observational cohort studies and observational cross-sectional studies was rated independently by two researchers (Aldosari M and Smith C) using the Strengthening the

Reporting of Observational studies in Epidemiology (STROBE) checklist (108). STROBE is a comprehensive quality tool which is designed to assess the quality of cohort and cross-sectional studies (108). The maximum STROBE score is 100% and the score required for inclusion was 70% as used in a previous systematic review by our research group published in a peer reviewed reputable journal (109). The STROBE checklist was appropriate because 25 of the included studies were observational cohort studies, six observational cross-sectional studies, and one was a randomised controlled trial (RCT).

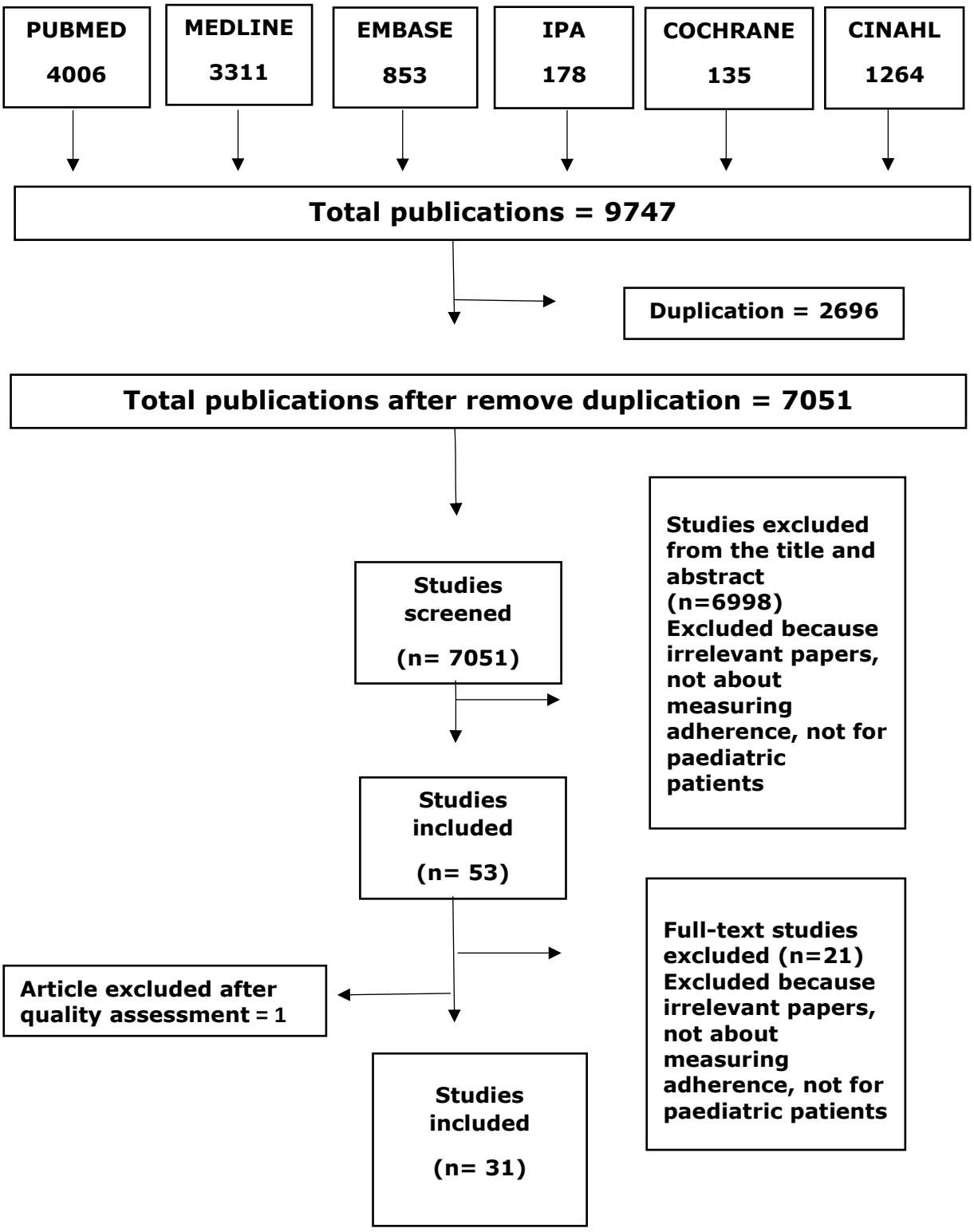
The quality of the included RCT was assessed using the Cochrane collaborations tool for assessing risk of bias in randomised controlled trials (110). The Cochrane process involves assessing the article against seven criteria and if the study shows a high risk of bias on two or more criteria then it should be excluded.

2.3 Results

2.3.1 Number of studies

9,747 studies were identified after searching the six databases. After removing duplication, 7051 papers were identified. Aldosari M screened these studies and in total 7,020 of them were excluded. Only 31 articles met the inclusion criteria and were included (Figure 2-1). All of the included studies were in English.

Figure 2-1 Flow chart of the literature search performed (PRISMA flow diagram) (111).



2.3.2 Quality of studies

Quality assessment of all studies was performed independently by the two researchers (Aldosari M and Smith C) and any discrepancies were resolved by discussion.

A. *Observational studies*

   Quality assessment of the 25 cohort and the six cross-sectional studies was done using the STROBE checklist. All studies met the standard for inclusion and scored ≥ 70%.

B. *RCT*

   Quality assessment for the one RCT study was done using the Cochrane collaboration tool. This study had three criteria with a high risk of bias, and was therefore excluded from the results (112).

2.3.3 Countries

Thirteen studies were conducted in the United States, four in South Africa and three in Kenya. Two studies were conducted in two countries Jordan and Northern Ireland and the remaining nine studies in the United Kingdom, Jordan, Australia, Ethiopia, Senegal, Uganda, France, Brazil and Netherlands.

2.3.4 Study design

All 31 studies were observational studies (25 cohort and six cross-sectional).

2.3.5 Type of assessment tools used to measure adherence

Various assessment tools were used in the studies. These are described below:

A. Self-report

Twenty-five studies used self-report tools to measure adherence (28,29,120–129,31,130–134,113–119).

These self-report tools consisted of multi-item questionnaires to identify the children's adherence with medicine regimens during a stated previous period of time. The self-report tools differed in their formats and questions, depending on which diseases and populations were being targeted. They were used to assess medicines adherence in HIV, asthma, inflammatory bowel disease (IBD), epilepsy, diabetes, migraine, thalassemia, malaria, and major depressive disorder patients. The validity of self-report was assessed in some studies by comparing results with those of other adherence-measurement tools, including pill counting, Medication Event Monitoring System (MEMS), pharmacy-refill data and plasma medicine levels (28,29,124–126,128,129,132,31,113,115–118,121,122). For children using liquid drug formulations, self-report was found to be an easier method of assessing adherence than pill counting due to difficulties in measuring returned liquid medicines (117).

Many studies found that self-report appears to overestimate the rate of adherence (29,31,117,118,122–124,126,129,132). Only two

studies suggested that self-reported adherence rates were lower than those measured by EMD and drug plasma level (128,134).

One study conducted anonymous self-report by which caregivers completed self-report without writing the patients' name (122).

Table 2.1 shows a summary of the self-report tools used to measure adherence.

Table 2-1 Summary of self-report tools used.

Study (Condition, year, country)	Details of self-reports used
HIV 2008 **United States** (114)	➢ Questionnaire began with identification of medicine. Asked about missed doses during past 3 days. ➢ Patients classified as adherent if no doses missed during past 3 days.
HIV. 2008 **South Africa** (117)	➢ Caregivers asked to rate medicine giving adherence on VAS. ➢ VAS covered range from 0% to 100% in steps of 10%. ➢ Higher scores indicated greater adherence.
HIV 2009 **United States** (119) **HIV 2009** **United States** (28)	➢ 3 days recall questionnaire-based interview by clinic staff with older children and caregivers at routine clinic visit. ➢ Questions included dosing schedule, time of last dose and number of missed doses in last 3 days. ➢ Adherence calculated as percentage of doses taken over previous 3 days.
HIV 2010 **South Africa** (120)	➢ 3 days recall questionnaire-based interview by clinic staff with caregivers at routine clinic visit. ➢ VAS used to rate adherence for the last 30 days, ranging from 0 to 100% in steps of 10%. ➢ Higher scores indicate greater adherence.
HIV 2010 **United States** (121)	➢ Caregivers asked single question to identify child's adherence to medicines as missed taking or never missed during last 6 months. ➢ Children classified as adherent when caregiver reported never missed taking or non-adherent when caregiver reported missed taking.
HIV 2012 **Uganda** (29)	➢ Adherence related questions requested information about patients' adherence. Completed by adolescents. ➢ No other details reported.
HIV 2013 **Ethiopia** (113)	➢ Nine questions used to assess adherence, completed by caregivers. Each question scored from 0 to 1. ➢ Median score taken as cut-off to classify adherence as good or poor. ➢ Adherence reported as good when median score >4. ➢ No other details reported.
HIV 2015 **Kenya** (116) **HIV 2014** **Kenya** (118)	➢ VAS used to assess number of doses taken in last month. Parents indicated doses taken on horizontal line; leftmost side indicated no doses taken, rightmost side indicated all doses taken.
HIV 2015 **South Africa** (115)	➢ Structured questionnaire to obtain information about infant adherence from mothers. ➢ Questions included whether infants missed doses since previous visit, reason for missed doses and number of days missed. ➢ Mothers reporting missing two or more doses classified as non-adherent.
Asthma 2008 **Australia** (122)	➢ At consultation visit caregivers asked about child's use of medicine: 'In the last month what percentage of the time would your child have taken their medication?' ➢ Physician wrote down estimate of medicine adherence based on caregiver answer.
Asthma 2008 **Brazil** (31)	➢ Self-report performed by filling out diary in which parents wrote time and date of medicine use. ➢ Completed every day by parents and collected every scheduled visit.

Study (Condition, year, country)	Details of self-reports used
Major Depressive Disorder 2010, United States (132)	➢ Adherence rate identified by calculating percentage of doses taken during period of treatment.
Asthma 2016 Netherlands (123) **Epilepsy 2013 United Kingdom** (126)	➢ Medication Adherence Report (or Rating) Scale (MARS) questionnaire used. Consisted of 10 questions to evaluate patient's behaviour towards medicines during past week. ➢ Each item scored from 1 to 5. ➢ Higher scores indicated higher adherence.
Inflammatory Bowel Disease 2009 United States (124)	➢ Medical Adherence Measure (MAM) questionnaire used. ➢ Measured adherence across 4 domains: adherence behaviour, knowledge, barriers to medicine adherence, and organisational system.
Epilepsy 2010 United States (125)	➢ Caregivers asked how many doses their child missed in past week. ➢ Adherence rate calculated by: [(number of doses prescribed per week - number of doses missed)/number of doses prescribed per week)]* 100. Range 0-100%.
Diabetes 2011 United States (127)	➢ Diabetes Self-Management Questionnaire (DSMQ) used. 25-item, validated, semi-structured interview assessing adherence to diabetes medicines. ➢ Higher scores indicate greater adherence.
Migraine 2016 United States (128)	➢ Self-report performed using diary in iMigraine Application via iPod touch where patients answered questions. ➢ Adherence rate determined by dividing number of times patients took medicines by 45 days study duration.
Thalassemia 2014 Jordan (129)	➢ Adolescents asked 'How do you rate your adherence to medicine in last four weeks from 0% to 100%?' ➢ Responses categorised: full adherence (>90%), partial adherence (61-90%), poor adherence (<60%).
Paediatric emergency department discharge medication 2009 France (130)	➢ Interview conducted with parents. ➢ Adherence scored on basis of 3 items: length of treatment, number of doses per day, and method of administration. ➢ Complete adherence defined as adherence to all 3 items; non-adherent as non-adherent to at least one item. ➢ No other details reported.
Malaria 2009 Senegal (131)**.**	➢ 3 days recall questionnaire-based interview by clinic staff with caregivers at routine clinic visit. ➢ Questions included dosing schedule, time of last dose, and number of missed doses in last 3 days. ➢ Adherence calculated as percentage of doses taken over previous 3 days.

B. Electronic monitoring devices (EMDs)

Fourteen studies used an EMD to measure adherence (28,29,125,128,132,135,31,34,116–118,120,122,123). The EMD is a device that fits on a medicine bottle and contains microelectronics that record the time and date the bottle or inhaler device is opened (24). Even though different models exist, the basic principle of this system is that whenever the medicine bottle is opened, a microprocessor embedded in the device records the exact dates and times (24).

Ten studies used an EMD called a Medication Event Monitoring System (MEMS) device, two studies used a Smartinhaler device, one study used a DOSER, and one study used an eCAPs device. When using these devices to measure adherence an assumption has to be made that the patient takes the medicine each time the bottle opened.

An EMD was used to assess medicines adherence in HIV, asthma, IBD, epilepsy, migraine, and major depressive disorder patients. At each visit, the data was downloaded from the EMD by the staff responsible for the study. Several studies found the EMD more accurate and reliable than other measures of adherence, including self-report, pill counting and pharmacy-refill records (28,29,31,116–118,120,122,132). In addition, several studies have considered the EMD to be highly accurate and used it as a reference standard by which to validate other adherence measurements (123,125,132).

C. Pill or dose count

Eight studies used pill or dose counting methods to measure adherence (28,29,113–115,124,132,136). With this method patients are required to bring their remaining medicine to each visit. The staff responsible for the study then count the number of doses (number of tablets for solid dose forms and volume of medicine for liquid dose forms) that have been taken between two clinic visits and compare this number with the total number of doses dispensed for the patient for that time interval. The percentage by volume of medicine consumed, or the percentage of pills taken, is calculated by dividing the actual volume or number of pills taken by the expected volume or number of pills, then multiplying by 100. This method has been used to assess medicines adherence in HIV, IBD and major depressive disorder. Several studies found the dose count less accurate than EMDs and medicine plasma level and more accurate than self-report (28,29,124).

D. Medical record or pharmacy refill data

Seven studies used medical record or pharmacy refill data to measure adherence (31,119–121,129,133,137). This method measures adherence by calculating the number of doses dispensed from pharmacy or the number of appointment visits in relation to the dispensing period or the appointment period (31,120,121,137). This method assumes that the medicine is taken exactly as prescribed. One study defined non-adherence as any missed refills or appointments, and adherence is defined as no missed refills or

appointments (121). This method has been used to assess medicines adherence in HIV, asthma, thalassemia, and sickle cell disease patients. Table 2.2 shows a summary of studies measuring adherence by medical or pharmacy refill data.

Table 2-2 Summary of measures of adherence by medical or pharmacy refill data.

Study (Condition, year, country)	Adherence calculated as:
HIV 2009 **United States** (119) **Asthma 2008 Brazil** (31)	Number of all doses taken/ Number of doses prescribed *100
HIV 2010 **South Africa** (120)	Occasions when medicine was dispensed/ occasions when medicine was supposed to be dispensed * 100
HIV 2010 **United States** (121)	No missing refill classified as adherent Any missed refill classified as non-adherent
Thalassemia 2014 **Jordan** (129)	Frequency of consistency of attendance to appointments rated 1-10. Higher frequency of consistency reported as higher level of adherence.
Sickle cell disease 2010 **United States** (137)	Ratio of number of expected days between refill periods (numerator) and observed days between refill periods for patient (denominator).

E. Medicine plasma level

Seven studies used medicine plasma level to measure adherence (115,124,126,129,134–136). In these studies, the concentration of medicine in plasma was measured and compared with the expected concentration. When the concentration of medicine in plasma was as expected, the patient was classified as adherent to medicine. This method was used to assess medicines adherence in HIV, IBD, epilepsy and

thalassemia patients. Several studies have suggested this method to be more accurate than other measures of adherence except EMD (124,126,135,136). Plasma drug concentrations have also been used as a reference standard by which to validate other adherence measurements (115,131)

F. Daily telephone calls

Two studies used daily telephone calls to measure adherence in asthma and diabetes patients (138,139). Patients were called daily to assess disease symptoms and rates of medicine adherence and it was found to be feasible for assessing both (138,139). The method was not compared with other methods to verify its efficacy. This method was more expensive than self-reporting and was difficult to perform (138). In addition, this method was susceptible to bias because a daily call may remind patients that they are under surveillance, which may affect their adherence rates (138).

G. Canister weight

One study used canister weight to measure adherence (31). This method is similar to dose count and involves weighing medicine devices such as inhalers, at the beginning of treatment and at each subsequent clinical visit until the devices are empty (31). This method was used to assess adherence only in asthma patients. The adherence rate was calculated by dividing the actual weight by the expected weight, then multiplying by 100. This method has been found to have the same efficacy as using an EMD and to be less

expensive, suggesting that the canister-weight method could be an alternative to expensive electronic devices for assessing medicine adherence in patients with asthma (31).

Each method had strengths and weaknesses. Table 2-3 Shows a summary of the strengths and weaknesses of the assessment tools.

Table 2-3 Summary of the strengths and weaknesses of the assessment tools

Assessment tools	Strengths	Weaknesses
Self-report	➢ Flexible. ➢ Most practical method. ➢ Less burdensome for staff. ➢ Inexpensive. ➢ Time saving.	➢ Least accurate. ➢ Overestimated adherence rates. ➢ Does not guarantee actual ingestion of medicines.
EMDs	➢ More accurate than self-report, pill count & pharmacy refill data.	➢ Expensive. ➢ Time consuming. ➢ Not easily available. ➢ Does not guarantee actual ingestion of medicines.
Pill count	➢ Easy to use. ➢ Inexpensive.	➢ Overestimated adherence rate. ➢ Less accurate than EMDs and medicine plasma level. ➢ Does not guarantee actual ingestion of medicines.
Pharmacy refill data	➢ Inexpensive. ➢ More accurate than self-report and pill count.	➢ Less accurate than MEMS and medicine plasma level. ➢ Does not guarantee actual ingestion of medicines.
Medicine plasma level	➢ More accurate than self-report, pill count and pharmacy refill data. ➢ Does guarantee actual ingestion of medicines.	➢ Costly. ➢ Time consuming. ➢ Difficult to perform. ➢ Invasive
Daily telephone calls	➢ Reported to be reliable method.	➢ Expensive. ➢ Difficult to perform. ➢ Does not guarantee actual ingestion of medicines.
Canister weight	➢ Same efficacy as using EMDs ➢ Less expensive than EMDs.	➢ Only applicable to inhalation devices. ➢ Does not guarantee actual ingestion of medicines.

2.3.6 Type of diseases

The studies measured medicine adherence for several diseases, which were, in order of frequency:

- HIV/AIDS (n=13)
- Asthma (n=4)
- Inflammatory bowel disease (IBD) (n=3)
- Epilepsy (n=2)
- Type 1 diabetes (n=2)
- Migraine (n=1)
- Thalassemia (n=1)
- Malaria (n=1)
- Major depressive disorder (n=1)
- Sickle cell disease (n=1).
- Kidney transplant (n=1).
- One study measured medicine adherence in all patients discharged from a French paediatric emergency department with at least one oral drug prescription, regardless of diagnosis.

The following sections summarise the included studies and are divided into the diseases covered.

A. HIV/AIDS

Thirteen studies measured medicines adherence in HIV/AIDS patients (28,29,121,135,136,113–120)(Table 2-4).

Self-report tools were used with both children and caregivers in three studies (28,114,119). In six studies, they were only administered to caregivers (113,115–118,120), and in one study were only given to adolescents (29). Good agreement was found between the reports from children and their caregivers (28,114,119).

Eight studies used viral load assessment as a confirmation of measures of adherence, and there was a significant association between viral response and full adherence measured by self-report, pill count, EMD and pharmacy refill data (28,114,116,117,119–121,136). Two studies used EMD, self-report, and plasma level without a validated measure (viral load) (118,135). They suggested that viral load assessment should be used in future studies for confirming adherence measures (118,135). One study used plasma nevirapine concentrations for confirming self-report and dose-count measures (115).

The EMD was directly compared with the self-report, pill counts, and pharmacy refill data in six studies (28,29,116–118,120), and in each study, the EMD was considered to be more reliable.

Five studies (28,113,116–118) found that self-reports were the least accurate method as they appeared to overestimate adherence rates when compared to other measures such as dose count and EMDs and it was

suggested that they should therefore not be used alone to assess adherence. Another study compared pill count, self-report measures and EMD and found that pill counts and self-reports both overestimated adherence rates (29).

Only one study reported that adherence rates measured by pill counts were very low; this study used unannounced home-based pill counts to avoid family forgetfulness and data manipulation by patients (113).

Table 2-4 Studies measuring medicines adherence in HIV/AIDS patients

Study	Brief study description	Adherence measurement tools	Reported outcome
Farley et al. 2008, United States (114)**.**	Multicentre cohort study. 151 participants. Ages 8-19 years.	1 - Self-report, completed by 146 parents and 132 children. 2 - Dose count; liquid formulation measured in millilitres and powder in scoops to count actual number of doses. 3 - Viral load assessment used as confirmation of measures of adherence.	Self-report useful for measuring adherence over longer period. Significant association between missed dose count and child questionnaire adherence rate (p=0.043).
Muller et al. 2008, South Africa (117)**.**	Prospective cohort study 73 participants Ages 51 ± 2.7 months	1 - Self-report, completed by 73 caregivers. 2 – EMD. 3 - Viral load assessment used as confirmation of measures of adherence.	Adherence rate measured by caregiver reports higher than that measured by EMD. Self-reporting classified 91% patients as >95% adherent; EMD classified 36% patients as >95% adherent. Comparing EMD and self-report adherence measures to viral load status, EMD was more accurate than caregiver reports.
Khan et al. 2009, United States (119)**.**	Retrospective cohort study 127 participants Ages 0-18 years	1 - Self-report, completed by 127 parents and 50 children over 13 years old. 2 - Pharmacy refill data; pharmacy records for previous 12 months obtained from clinical database. 3 - Viral load assessment used as confirmation of measures of adherence.	Despite potential for overestimating adherence, study supports use of self-report as efficient tool for measuring adherence. Good agreement between adult caregiver reports and child reports. Significant association between self-reported, pharmacy supply adherence, and virological outcome (p<0.001).
Martin et al. 2009, United States (28)**.**	Cohort study 24 participants Ages 8-18 years	1 - Self-report, completed by 24 parents and 24 children. 2 - EMD recorded dates and times when bottle was opened. 3 - Pill counts, clinician calculated percentage of pills taken over dispensing period. 4 - Viral load assessment used as confirmation of measures of adherence.	Pill counts inexpensive and relatively easy method of assessing adherence. EMD most effective method. Good agreement between adult caregiver reports and child reports. Adherence rates obtained: pill counts 86%, EMD 78%, caregiver reports 99%, and child reports 98%. Comparing both EMD and self-report adherence measures to viral load status, EMD more accurate than caregiver reports.

Study	Brief study description	Adherence measurement tools	Reported outcome
Burack et al. 2010, United States (121)**.**	Cross-sectional study 46 participants Ages 6-18 years	1 - Self-report, completed by caregivers. 2 - Pharmacy refill data; zero missing refills over previous 6 months classed as 'adherent'. 3 - Viral load assessment used as confirmation of measures of adherence.	No significant association between viral response and full adherence as defined by caregiver reports and pharmacy refill data. Use of multiple measures of adherence is important.
Muller et al. 2010, South Africa (120)**.**	Cohort study 53 participants Median age 3.7 years	1 - Self-report completed by caregivers. 2 - EMD which defined adherence by percentage of doses taken. 3 - Pharmacy refill data. 4 - Viral load assessment used as confirmation of measures of adherence.	No significant differences between adherence rates measured by self-reports 100%, EMD 92%, and pharmacy refill data 100% (p>0.1). Despite high cost of EMD, it was best method for measuring adherence. More effort should be directed towards development of cheaper EMD devices.
Wiens et al. 2012, Uganda (29)**.**	Cohort study 15 participants Ages 12-17 years	1 - Self-report completed by adolescents. 2 - EMD, missed doses identified by non-opening events. 3 - Pill counts.	Pill counts and self-reporting appeared to overestimate adherence rate. Adherence rates obtained: self-report 99%, pill count 97%, and EMD 88%. EMD more reliable measure of adherence in adolescents.
Biressaw et al. 2013, Ethiopia (113)**.**	Cross-sectional study 210 participants Ages 8-13 years	1 - Self-report, completed by caregivers. 2 - Pill count; home-based unannounced pill count conducted to avoid bias.	Unacceptably low adherence level estimated by pill counts. Using unannounced home-based pill count, only 34.8% of sample had adherence rate of at least 95%. Agreement between unannounced pill count and caregiver reports poor (kappa=0.032).
Vreeman et al. 2014, Kenya (118)**.**	Prospective cohort study 191 participants Mean age 8.2 years	1 - Self-report, completed by caregivers. 2 - EMD.	Adherence rates differed between measures. Caregiver reports estimated adherence higher than EMD.

Study	Brief study description	Adherence measurement tools	Reported outcome
Desmond et al. 2015, South Africa (115)**.**	Retrospective cohort study 225 participants Ages birth-6 weeks	1 - Self-report, completed by mothers. 2 - Dose count by assessment of unused returned medicine. 3 - Plasma level by measuring concentration in plasma and comparing with expected concentration used as confirmation of other measures.	Self-reporting could be useful in assessing adherence to antiretroviral treatment in infants < 6 weeks. Good agreement between self-report and dose count. Using multiple measures of adherence more useful than single measure. Plasma nevirapine concentrations used as objective measure to verify other measures: plasma level 85.6%, self-report 87.7%, and dose count 71.3%.
Vreeman et al. 2015, Kenya (116)**.**	Prospective cohort study 191 participants Ages 0-14 years	1 - Self-report, completed by caregivers. 2 - EMD. 3 - Viral load assessment used as confirmation of measures of adherence.	Self-reporting appeared to overestimate adherence rates. High correlation between viral load levels and adherence rate measured by EMD. EMD was more accurate adherence measure.
Smith et al. 2016 South Africa (136)**.**	Retrospective cohort study 78 participants Ages 6 months-13 years	1 - Pill count, calculating percentage of doses taken over dispensing period. 2 - Viral load assessment used as confirmation of measures of adherence.	Adherence of ≥95%, measured by pill count is not an ideal predictor of treatment outcomes. Low correlations between pill count and viral load measures were reported.
Tu et al. 2017, Kenya (135)**.**	Prospective cohort study 152 participants Mean age 7.7 years	1 - Plasma level measuring concentration in plasma and comparing with expected concentration. 2 - EMD.	No differences between adherence rates measured by plasma level and EMD. Study suggested that viral load should be used as objective measure to verify other measures of adherence.

B. Asthma

Four studies measured medicine adherence in patients with asthma (31,122,123,138) (Table 2-5).

Three studies (31,122,123) found that self-reports overestimated adherence rates and were the least accurate in assessing adherence.

Pharmacy refill data also overestimated adherence, but less so than self-reporting (31).

Daily calls to patients'/parents' mobile phones were reported to have an effectiveness close to that of self-reporting, but were more expensive and susceptible to bias because a daily call may remind patients that they are under surveillance, which may affect their medicine-taking behaviour, thereby inflating their adherence rates (138).

Two studies (31,122) reported that an EMD was the best method for assessing adherence rates for asthmatic patients, compared with self-report, pharmacy refill data, and daily telephone calls. One study (31) found that measuring canister weights had the same effectiveness as EMD and was less expensive.

Table 2-5 Studies measuring medicines adherence in patients with Asthma

Study	Brief study description	Adherence measurement tools	Reported outcome
Burgess et al. 2008, Australia (122)**.**	Prospective cohort study 51 participants Ages 18 months-7 years	1 - Self-report completed by 51 caregivers. 2 - EMD with an electronic monitoring device (Smartinhaler).	Poor correlation between adherence rates measured by self-report and EMD (r=0.31). EMD more accurate in assessing adherence than self-reporting.
Jentzsch et al. 2008, Brazil (31)**.**	Prospective cohort study 102 participants Ages 3-14 years	1 - Self-report, completed by 102 parents. 2 - Canister weight. 3 - Pharmacy refill data. 4 - EMD (DOSER).	High discrepancy between self-reporting and other methods. Adherence rates obtained: self-report 96.4%, pharmacy refill data 70%, canister weight 46.3%, and EMD 51.5%. Adherence rate by pharmacy refill data also overestimated, but to a lesser degree than self-reporting. EMD and canister weight were most reliable methods. Significant agreement (p<0.01) suggests that canister weight could be an alternative to expensive DOSER.
Mulvaney et al. 2013, United States (138)**.**	Cohort study 53 participants Ages 12-18 years	daily telephone call; participants called daily to report symptoms and missed doses.	daily telephone call is a feasible method of assessing asthma symptoms and adherence. More expensive than self-reporting while still susceptible to bias.
Garcia-Marcos et al. 2016, Netherlands (123)**.**	Prospective cohort study 133 participants Ages 2-13 years	1 - Self-report, completed by 133 parents. 2 - EMD used as reference standard (Smartinhaler).	Self-reporting overestimated adherence and was too inaccurate when validated using EMD.

C. Inflammatory Bowel Disease (IBD)

Three studies measured medicines adherence in patients with IBD (34,124,134) (Table 2-6).

Plasma level was reported to be the most reliable method of measuring adherence for patients with IBD, compared to self-report and pill count (124).

It was suggested that EMD may overestimate adherence as the devices document the time that a bottle was opened but cannot document actual ingestion of medicine or if the correct number of pills was taken (34). Additionally, participants enrolled in the study who are aware of being monitored may have had an increased adherence rate because of this awareness (34).

Alsous et al. found that adherence rates measured by self-report (39.4% classified as non-adherent) was lower than adherence rates measured by drug plasma levels (8.9% classified as non-adherent) (134).

Table 2-6 Studies measuring medicines adherence in patients with IBD

Study	Brief study description	Adherence measurement tools	Reported outcome
Hommel et al. 2009, United States (124)**.**	Observational cross- sectional study 42 participants Ages 13-17 years	1 - Self-report, completed by 42 parents and 42 children. 2 - Pill count; percentage of pills taken over dispensing period. 3 - Plasma level; medicine concentration in plasma compared with expected concentration.	No statistically significant correlation between measures of adherence (p>0.05). Measuring drug plasma levels most reliable method. Self-report and pill counts appeared to overestimate adherence rate.
LeLeiko et al. 2013, United States (34)**.**	Cohort study 79 participants Ages 8-17.5 years	1 - EMD. 2 - IBD symptoms used as confirmation of measure of adherence.	By comparing adherence rate reported by EMD and IBD symptoms, EMD monitoring appeared to overestimate medicine adherence rates.
Alsous et al. 2020, Norther Ireland and Jordan (134)**.**	Observational cross-sectional study 47 participants Ages 13-17 years	1 - Self-report completed by 33 children and 47 parents. 2 - Plasma level; medicine concentration in plasma compared with expected concentration.	Moderate agreement found between methods (Kappa = 0.463, p=0.013). Based on self-report 39.4% of children classified as non-adherent. Based on measuring drug plasma levels 8.9% of children classified as non-adherent.

D. Diabetes

Two studies measured medicine adherence in patients with diabetes (127,139) (Table 2-7).

Markowitz et al. (127) used finger-prick blood glucose tests taken at home every day by patients/parents as a confirmation of self-report to measure adherence rates and reported that self-report was a valid measure of adherence rate in research and clinical settings with no difference between children-report and parents-report.

Table 2-7 Studies measuring medicines adherence in patients with diabetes

Study	Brief study description	Adherence measurement tools	Reported outcome
Markowitz et al. 2011, United States (127)**.**	Retrospective cohort study 338 participants Ages 9-15 years	1 - Self-report, completed by 338 caregivers and 338 children. 2 - Blood glucose level used as objective measure to validate self-report.	Significant association between blood glucose level and adherence rate as measured by self-report (p<0.01). Self- report valid measure of medicine adherence. Good agreement between adult caregiver and child reports.
Mulvaney et al. 2012, United States (139)**.**	Cohort study 96 participants Mean age 14.96 years	daily telephone calls to participants twice daily for 10 days to report blood glucose readings and missed insulin doses.	Method provided good information about adherence and should be explored in clinical settings.

E. Epilepsy

As shown in Table 2-8, two studies measured medicines adherence in patients with epilepsy (125,126).

Plasma levels were more accurate and reliable than self-reports in assessing adherence rates of epileptic patients. Although plasma levels were said to be accurate in this study, the authors recommended the use of EMD to assess adherence as it can record multiple instances of taking medicines, rather than a single test at a later date (126).

Mohammed Shah et al. found that adherence rates measured by self-report were higher than adherence rates measured by drug plasma levels (126).

Table 2-8 Studies measuring medicines adherence in patients with epilepsy

Study	Brief study description	Adherence measurement tools	Reported outcome
Modi et al. 2010, United States (125)**.**	Prospective cohort study 119 participants Ages 2-14 years	1- Self-report completed by 119 caregivers. 2- EMD used as objective measure to validate self-report.	Significant associations found between EMD and self-report adherence rates (p<0.01). Self- report valid measure of medicine adherence.
Mohammed Shah et al. 2013, United Kingdom (126)**.**	Retrospective cohort study 173 participants Ages 0.9-16 years	1 - Self-report completed by 100 parents or children over 9 years of age. 2 - Plasma level by chromatographic analysis of dried blood spot.	Self-report appeared to overestimate adherence rates, with a reported 94% adherence. Dried blood spot analysis useful in estimating adherence, with reported 80.6% adherence.

F. Other diseases

As shown in Table 2-9, seven studies measured medicines adherence in patients with different diseases.

Although self-reporting appeared to overestimate adherence rates and had a potential recall bias, it was inexpensive and reliable (128–132). Chappuy et al. (130) reported that adherence rates measured by self-reporting were much lower than observed in previous studies because more data were taken into account, such as asking families about both the filling of prescriptions and their administration.

Only one study reported that adherence rates measured by self-reporting were lower than measured by EMD for patients taking once-daily medicines only (128). No explanation was provided for this finding.

Plasma levels were found to be more reliable and accurate than self-reports and pharmacy refill data because self-reports and pharmacy refill data did not guarantee that medicines were actually being taken (129).

Table 2-9 Studies measuring medicines adherence in patients with different diseases

Study	Brief study description	Adherence measurement tools	Reported outcome
Chappuy et al. 2009, France (130)**.**	Prospective cohort study 105 participants discharged with at least one oral drug prescription from a French paediatric emergency department Ages 0.2-12 years	Self-report, completed by 105 parents.	Adherence rate 36.2%. Adherence rate much lower than observed in previous studies on medicine adherence after discharge from emergency department.
Souares et al. 2009, Senegal (131)**.**	Retrospective cohort study 289 participants with malaria Ages 2 months-14 years	1 - Self-report, completed by 289 caregivers. 2 - Plasma drug level used as objective measure to validate self-report.	Self-reported data good tool in poor countries as less expensive than other methods such as EMD.
Nakonazny et al. 2010, United States (132)**.**	Cohort study 31 participants with major depressive disorder Ages 7-17 years	1 - Self-report, completed by parents or children. 2 - Pill count, calculating percentage of pills taken over dispensing period. 3 - EMD used as objective measure to validate others measures.	Self-reporting and pill counts overestimated adherence rates. Adherence rate differed significantly between methods (p=0.0002). Adherence rates: EMD 87.51%, pill count 90.55%, self-report 93.28%. Agreement between pill count and EMD reference standard stronger than agreement between EMD and self-report.
Patel et al. 2010, United States (137)**.**	Retrospective cohort study 93 participants with sickle cell disease Mean age 7 years	1 - Pharmacy refill data. 2 - Plasma level used as confirmation of measure of adherence.	Pharmacy refill data appeared to overestimate adherence rate. Adherence rate measured by pharmacy refill data correlated with plasma level. Pharmacy refill data reliable method to assess adherence.

Study	Brief study description	Adherence measurement tools	Reported outcome
Al-Kloub et al. 2014, Jordan (129)**.**	Cross-sectional study 164 participants with thalassemia Ages 12-19 years	1 - Self-report, completed by 164 adolescents. 2 - Plasma level compared with expected concentration. 3 - Medical records checking attendance at 10 follow-up appointments.	Adherence rates: plasma level 47%, medical records 57%, self-reporting 73%. Plasma level more accurate method to assess adherence. Self-reporting least accurate but less expensive and easier to obtain.
Van Diest et al. 2016, United States (128)**.**	Cohort study 56 participants with migraine Ages 11-17 years	1 - Self-report, completed by 56 adolescents. 2 - EMD.	Self-reported adherence rates lower than measured by EMD for patients taking once-daily medicine only. Self-reported adherence rates higher than measured by EMD for patients taking twice-daily medicines.
Almardini et al. 2019, Norther Ireland and Jordan (133)**.**	Observational cross-sectional study 33 participants with kidney transplant Ages ≤ 18 years	1 - Self-report, completed by 33 children. 2 - Pharmacy refill data.	14.8% of children non-adherent based on self-report. 24.2% of children non-adherent based on pharmacy refill data.

2.4 Discussion

Knowing the degree of medicines adherence in children is important in order to provide information on the consequences of non-adherence and to develop strategies to improve adherence (50). By appropriately assessing and understanding medicines adherence in children, we may be able to improve health outcomes and reduce healthcare costs (99). We performed a systematic review to identify the measures of medicines adherence that have been used in children and to explore the strengths and weaknesses of those measures. Seven methods to measure adherence were identified: self-report, EMD, dose count, canister weight, plasma level, medical record or pharmacy refill data and daily telephone calls.

Self-reports have been suggested to be the most practical measure of adherence in children and were the most commonly used (115,127). In addition, self-report is the only measure that asks patients directly about adherence (115). Some self-reporting questionnaires also collected information on the beliefs of children and caregivers that may affect adherence, such as medicine-taking behaviour and barriers to medicines adherence (116,120,131).

Most self-report tools contained three primary parts, including the question type, the recall period (x days, x weeks or x months), and the answer options (open-ended questions, closed questions or multiple choices questions). Each self-report tool used these parts differently. In the

included studies the recall period varied from 3 days to 6 months i.e. participants were asked to state their adherence over these time periods. Some tools used validated scales and others used different questions to assess this adherence (114,116,121,129). It has been suggested that self-report tools that require accurate recall data should focus on shorter periods (such as the last three days), whereas self-reports that only require estimated recall data can rely on longer time periods (114).

Each self-report had a different number of questions. In the included studies, the number of questions varied from a single question to multiple questions (118,129). Moreover, the self-report tools used in the included studies varied in their subjects (healthcare professionals, caregivers or patients) and their context (e.g., for a specific disease or for multiple diseases) (29,117,130).

Anonymous self-reporting (completed by caregivers) was found in one study to be a more accurate method of assessing adherence than regular self-reporting, possibly indicating that children/caregivers are more comfortable reporting poor adherence anonymously (122). However, this is not a useful method in the practical clinical setting (122).

We found three validated self-report tools which were used to assess adherence in children in the studies included in our search. The MARS questionnaire was used in one asthma study and one epilepsy study, the MAM questionnaire in one IBD study, and the DSMQ was used in one

diabetes study (123,124,126,127). The MARS questionnaire assesses both beliefs and barriers to medicines adherence. The results of this questionnaire were compared to plasma level measure and EMD to assess adherence and suggested that adherence was overestimated by the MARS (123,126). In one of the included studies the MAM questionnaire was compared with pill counts and plasma level to assess adherence in children with IBD and no significant correlation was found between the results ($p > 0.05$), suggesting that the MAM is not accurate to assess adherence (124). However, the adherence rate in children with diabetes, as measured by the DSMQ, appeared to be significantly associated with the adherence rate measured by EMD, pill count, plasma level, and pharmacy refill data ($p < 0.05$) (127).

Patients diaries were also used to measure adherence in two of the included studies (31,132), and these were the only self-report tools that daily reported how children used their medicine regimens (31,132). However, some factors may still have led to unreliable reporting. For example, patients may have reported incorrect adherence rates or forgot to return the diaries (132).

The accuracy of self-reporting differed in the included studies. Only one study with children with HIV found that there was no significant difference in the adherence rates as measured by self-report (single question), EMD, and pharmacy refill data ($p > 0.05$) (120). However, self-reporting was

suggested to overestimate adherence levels in ten studies when compared with other measures (29,31,117,118,122–124,126,129,132). In nine of these studies, the self-reports were completed by parents or caregivers (31,117,118,122–124,126,129,132). The suggested overestimated adherence rate measured by self-reporting could be caused by two major biases. The first is error in self-observation, or memory bias, which can result in both under- and over-reporting (31,118). The second is social desirability bias, which can occur when questions focus on an undesirable behaviour or on the most recent period (31,37,118). In contrast, two of the included studies found that adherence rates reported by participants were lower than those measured by EMD and drug plasma level (128,134). This unusual result may be explained by the self-reports in these studies being answered by children, who are perhaps more likely to answer the questions honestly because of their naive nature (128,134). Such findings suggest that the precision of self-report depends on the type of self-report used, the recall period and who is completing the self-report.

Our review indicates that the accuracy of self-reports may be strengthened by using a self-report scale validated for the same group of patients whenever possible; taking steps to reduce social desirability concerns (e.g. by writing questions carefully to assure the participant that their responses will not adversely affect their health care), and using clinical outcomes or other measurement methods to validate self-reports such as pill count, pharmacy refill data, or EMD (28,113,116–119).

One of the methods reported to be highly accurate in several studies is the use of EMDs (28,29,117,120,122,128). User-friendly EMDs that promote time efficiency and require minimal technical expertise are important facilitators in the clinical setting (117). They require a collaborative effort between healthcare professionals and patients to achieve accuracy (117). Feedback about medicines use provided by using EMDs may improve patients' medicines taking behaviour (128). EMDs help to identify if the non-adherence is consistent or sporadic (20,116,118). These features make EMDs more useful than self-report and plasma level measures (20,116,118). Additionally, when using EMDs, the tendency to deceive is lower than when using dose counts. In dose counts patients can manipulate the data by throwing pills away, but with EMDs if patients want to throw away the medicine they need to open the bottle at the same time every day to guarantee that the same adherence rate is reported (125,135,140).

Our review showed that several different types of EMDs have been used in children including MEMS, eCAP, DOSER, and Smartinhaler devices (28,116–118,120). From our review MEMS was the most commonly used and was most often used as a standard to validate other measures (123,125,132). MEMS is strongly associated with results from pharmacy refill data and plasma levels (120,135). MEMS also showed high correlation between lower viral loads in HIV patients and higher level of adherence rates (116,120,135,141). Data downloaded from MEMS can provide details related to medicines taking, such as delayed dosing, over dosing, under

dosing, and drug holidays (117). However, due to their expense, MEMS are only suitable in funded clinical research settings and may not be feasible for routine clinical use (117).

eCAP is very similar to MEMS, and is available for use in commercial packing and clinical trials (29). DOSER and Smartinhaler devices are used to measure inhaled medicines adherence and have similar weaknesses and strengths (31,122). It is difficult for young patients to press the DOSER device with enough force to register a puff, and the DOSER device cannot register double puffs because one second is required between puffs (31). Significant correlation ($p<0.05$) between adherence rates measured by canister weight and DOSER (DOSER showed 51% adherence while canister weight showed 46.3% adherence) has been seen suggesting that canister weight could be used as an alternative to DOSER (31).

The EMDs method have some limitations, including that they have not been used in large studies because of the amount of support required, mechanical malfunctions and their high equipment costs (120). In addition, patients may open the medicine bottle or puff a dose from an inhaler device without taking any medicine, which would result in overestimation of adherence rates (28,29,34,125,128,132,135). The EMD method is very time-consuming, particularly for staff, who must download data from a device for each patient (28). Finally, the presence of a EMD device may remind

patients that they are under surveillance, which may affect their medicine-taking behaviour, thereby inflating their adherence rates (34,116).

This review showed that dose counting was used to assess medicines adherence in HIV, IBD, and major depressive disorder patients (28,29,114,124,132,136). For medicines that are taken on as needed basis however, dose counts are not suitable (124). When patients are aware that the healthcare professional suspects non-adherence, they may be more likely to throw doses away resulting in overestimated adherence rates (132). In an adherence assessment study of 42 adolescents with IBD using oral medicines, both self-report and dose counts overestimated adherence as compared to assessments by plasma level (124). The reliability of dose counts could be improved by explaining to families the importance of bringing all medicine bottles to each visit and by calling them before each visit to remind them to do so (28).

The pharmacy refill data or medical record data have been used to measure adherence for chronic diseases, but they are not useful for medicines taken for a short period (31,119–121). Pharmacy refill data methods require computerised systems that can provide research scientists or clinicians with the information they need to measure adherence (101). Seven of the included studies used medical records or pharmacy refill data to measure adherence (31,119–121,129,133,137). This method is becoming more

widely used in research with children, especially in hospitals that can provide the information that is needed to measure adherence (120).

Pharmacy refill data has been reported to be a highly accurate method of measuring adherence in adults (142). However, two of the included studies have pointed out that pharmacy refill data may overestimate medicines adherence in children, possibly due to the different practise of dispensing for pills versus syrups (120,121). Dispensing and monitoring the use of exact amount of syrups is more complicated than pills because some of a liquid medicine may be lost during administration (121). Additionally this method has been found to overestimate adherence rates because it does not guarantee the actual ingestion of medicines (120,137). Furthermore, it does not account for the timing of the doses, which is important in assessing adherence (137). In addition, to use this method researchers should bear in mind that medicine cessation may have been verbally advised by healthcare professionals; otherwise, the patient may be incorrectly considered non adherent (143).

Measuring medicine concentration in plasma can provide a direct and accurate measurement of adherence and was most commonly used in several of the included studies to validate other measures of medicines adherence (22,115,124,126,129,135,136). Viral load assessments for HIV patients have also been used and recommended in several studies to validate other measures of medicines adherence (28,114,116,117,119–121,136). However, these methods can only detect whether the patient has

taken a medicine during a certain interval before the analysis. Bias can occur if a patient takes the medicine only during this time period (126,135). Other disadvantages of the plasma-level method are that it cannot provide data on dose timing, it is invasive, is expensive and is difficult to perform, requiring various professionals and technicians to conduct the tests and to interpret the results (126,135). Results may also be affected by food or drug interactions, half-life of the drugs and dosing schedule (126). The costs of tests to measure adherence to more than one medicine may be prohibitive, further limiting the feasibility of this method (126,135).

In measuring medicines adherence, a multimethod approach is often recommended (126,144). Since there is no ideal method to measure adherence, it would be appropriate to use two or more measures when researchers want to have more precise results (144). Using a single method to measure adherence in children with a low to moderate level of adherence may lead to an incorrect assessment (116,140). The use of another measure may help to strengthen the results.

2.5 Limitations

All titles and abstracts of the search results ideally should have been screened according to the inclusion criteria by two researchers. Due to the limited resources of our department, one researcher (Aldosari M) screened all titles and abstracts, but only 5% of titles and abstracts were assessed independently by another researcher from our group (Coral S). In addition, the term 'paediatric*' was omitted from the search and conference abstracts and the grey literature were not searched. It is therefore possible that studies have been missed.

2.6 Conclusion

This systematic review was performed to identify the measures of medicines adherence which have been used in children and to explore the strengths and weaknesses of those measures. An ideal measure of medicines adherence should be easy to carry out and practical, inexpensive, user friendly, flexible, and highly reliable. However, we found no single standard method that met all these criteria. This review should provide useful information for researchers and clinicians to choose the most useful methods for their objectives. The selection of suitable measures of adherence depends on the aims of each study, the resources available to the study and the properties of each measure. In a resource-limited clinical setting self-reports may be preferred. Balancing cost and accuracy, pharmacy refill data is more favourable for large studies than EMD. Measuring medicine plasma levels is a rarely used approach because it is

invasive, and the costs are often too high for both researchers and patients. Since there is no single ideal method to measure adherence, research groups need to recognise that multiple measures may minimise discrepancies and support their findings. Further research is required to discover a single method that can accurately measure medicines adherence in children and to evaluate interventions that can improve adherence.

Chapter 3: Barriers and facilitators to medicines adherence in children: A systematic review

3.1 Introduction

Medicines are an important aspect of treatment for many paediatric diseases (17). As mentioned previously, enhancing medicines adherence for chronic conditions may create significant health and economic benefits (7,50). To improve adherence, the multifactorial causes of poor adherence should be understood. As previously discussed, the World Health Organisation (WHO) classifies these factors into five categories: condition-related, social and economic related, healthcare team and system-related, therapy-related, and patient-related factors (7). Also, it is important to recognise that factors influencing a patient's adherence may change over time (14). In addition, because there is no single cause of non-adherence to medicines, it is unlikely that a single facilitator can improve adherence (14).

We searched for a systematic review in order to establish what is currently known about barriers and facilitators to medicines adherence in children and found a review from the Talking About Medicines study (TABS) published seven years ago (85). This review was a critical evidence synthesis of research to examine the factors influencing non-adherence to medicines in children with chronic diseases from 1970 to 2008 (85). We therefore performed a systematic review to update the TABS work and to identify barriers and facilitators to medicines adherence in children reported since this.

3.2 Methods

This systematic review was registered in PROSPERO, registration number: CRD42019116334.

3.2.1 Search strategy

A systematic literature search was performed to identify all papers describing barriers and facilitators of medicines adherence in children. Six databases were searched from November 2008 to July 2020 in order to update the TABS study work. The initial search was performed using the Healthcare Databases Advanced Search (HDAS) platform, which allows the combination of several databases.

Four databases were searched through this platform:

- Pubmed
- Medline
- Embase
- Cumulative Index to Nursing and Allied Health Literature (CINAHL)

The search was also conducted separately using the Cochrane library and International Pharmaceutical Abstracts (IPA).

A hand search of the bibliographies of relevant papers was also performed in order to identify all studies related to our inclusion criteria.

The resulting studies were exported to Endnote and combined together to remove duplications.

The databases were searched for all studies which identified barriers and facilitators of medicines adherence that included paediatric patients aged ≤18 years of age. The following keywords were used: **'barrier* or factor* or reason* or cause* or determinant* or predict* or challeng* or facilitator* or motivat* AND adhere* or complian* or nonadhere* or noncomplian* or patient compliance* or medication adherence* AND children* or child* or pediatrics* or paediatric* or adolescent* or infant* or newborn*or neonate*'.**

3.2.2 Justification of search strategy

In this systematic review, the specific keywords above were selected to integrate a wide variety of terms to meet our aims and purposes.

The first part of the search covered the barriers and facilitators of medicines adherence that we wanted to explore. Terms were selected to cover different permutations of plural, noun, singular and adjective using asterisks (*). The keywords selected were 'barrier* or factor* or reason* or cause* or determinant* or predict* or challeng* or facilitator* or motivat*'**.** These terms were a combination used in previously published peer-reviewed systematic reviews related to the subject of barriers and facilitators of medicines adherence including the TABs study (85,145–151).

The terms covering medicines adherence and children were the same as those used in the previous chapter.

3.2.3 Inclusion criteria

Inclusion criteria were original research studies with stated objectives of identifying barriers and/or facilitators of medicines adherence in children aged from birth to 18 years. The search was conducted to cover studies published since the TABs study in order to focus on more recently described barriers and facilitators to medicines adherence.

All countries and all languages were included. To be included, the barriers and facilitators of medicines adherence in each study needed to be described in some detail.

3.2.4 Exclusion criteria

Exclusion criteria included:

- Review articles, editorials, conference papers, reports.
- Studies that identified barriers and facilitators to medicines adherence in adults, or in both adults and children with no separate information about children being provided.

3.2.5 Data collection

One reviewer (Aldosari M) screened all titles and abstracts identified by the search according to the inclusion and exclusion criteria. Where it was not clear from the title or abstract, full papers were obtained and reviewed to find relevant papers. As a reliability measure, 5% of titles and abstracts were assessed independently by another researcher from our group

(Abramson J) and after discussion, Aldosari M and Abramson J reached full consensus on which studies were relevant.

3.2.6 Quality assessment

Quality assessment was done in order to identify studies with a high risk of bias. The quality of the included studies was assessed by one researcher (Aldosari M). As a reliability measure, 5% of the included studies were also quality assessed independently by another researcher from our group (Abramson J) and any discrepancies were resolved by discussion. The quality of observational studies was assessed using the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) checklist (108). STROBE is a comprehensive quality tool which is designed to assess the quality of cohort, case series, and cross-sectional studies (108). The maximum STROBE score is 100% and the score required for inclusion was 70% as used in a previous systematic review by our research group published in a peer reviewed reputable journal (109).

The quality of the included RCT studies was assessed using the Cochrane Collaborations tool for assessing risk of bias in randomised controlled trials (110). The Cochrane process involves assessing the article against seven criteria and if the study shows a high risk of bias on two or more criteria then it should be excluded.

3.2.7 Data analysis

All included studies were analysed and the following data were extracted into a table:

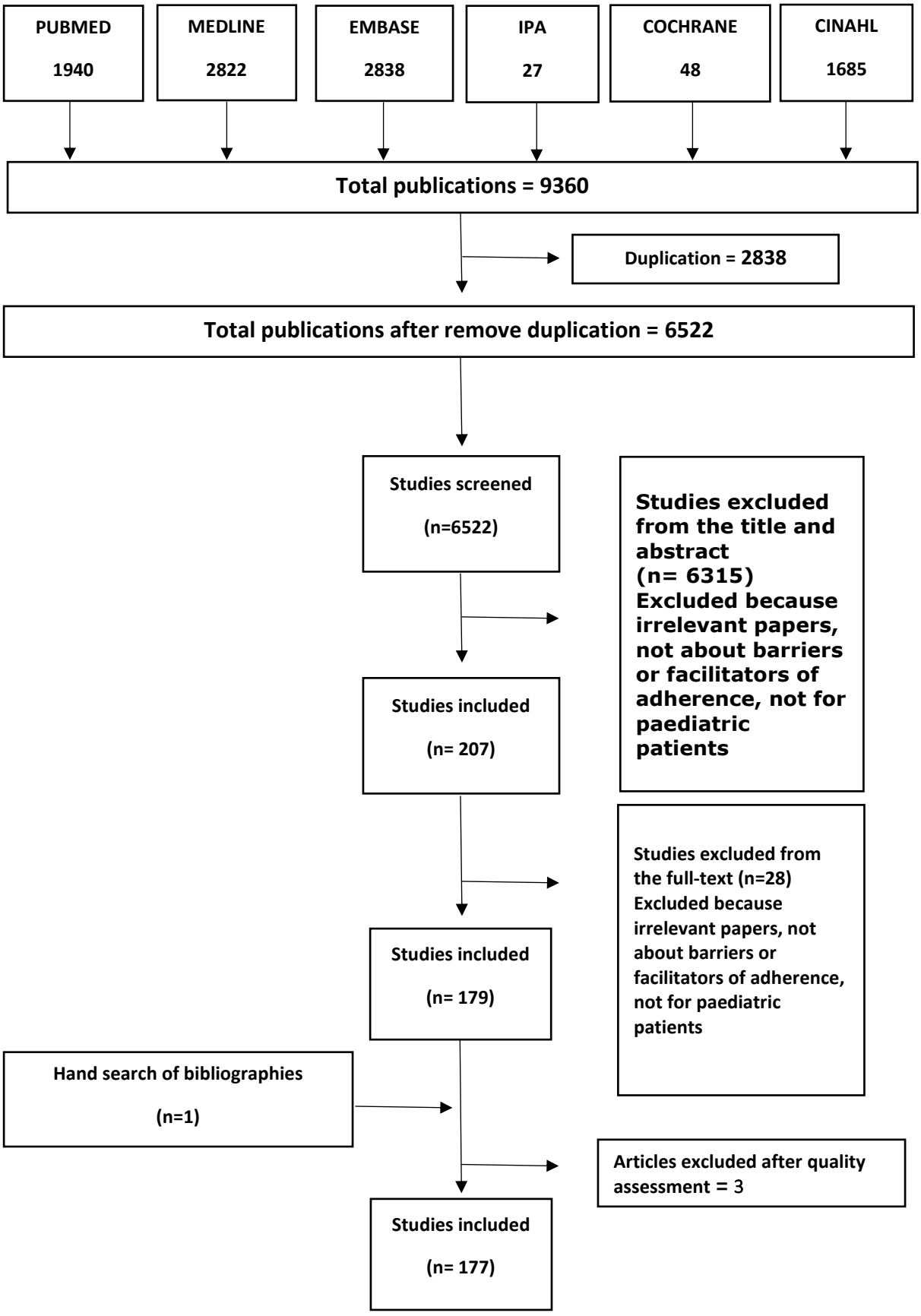
- Name of authors.
- Publication year.
- Country where study was completed.
- Type of study.
- Number and age of participants.
- Type of tools used to explore barriers and facilitators of medicines adherence.
- Type of disease.
- Reported barriers and facilitators.

3.3 Results

3.3.1 Number of studies

9360 studies were identified after searching the six databases. After removing duplication, 6522 papers remained. Aldosari M screened these studies and in total 6345 of them were excluded. One hundred and seventy-seven articles met the inclusion criteria and were included (Figure 3-1). All of the included studies were in English.

Figure 3-1 Flow chart of the literature search performed (PRISMA flow diagram) (111).



3.3.2 Quality of studies

A. Observational studies

Quality assessment of the one hundred and seventy-five observational studies identified was done using the STROBE checklist. One hundred and sixty-eight studies scored ≥ 70% and therefore met the standard for inclusion. Three studies scored <70%, and were therefore excluded from the results (152–154).

B. RCT

Quality assessment for the five RCT studies were done using the Cochrane collaboration tool. All studies met the standard for inclusion.

3.3.3 Countries

The studies identified came from thirty nine different countries, including both high economically developed countries (HEDCs) and less economically developed countries (LEDCs) (155). This classification allows for comparison as to what factors are reported to be barriers or facilitators to medicines adherence in children in both HEDCs and LEDCs.

A. Studies from HEDCs (n=130)

- United States (n=76)
- United Kingdom (n=12)
- Canada (n=6)
- Australia (n=5)
- Brazil (n=5)
- Netherlands (n=5)
- South Africa (n=4)
- Jordan (n=3)
- Spain (n=2)
- Two studies conducted in Jordan and Northern Ireland.
- One study conducted in the United Kingdom, Canada, Germany and France.
- Nine studies conducted in each of Belgium, Denmark, France, Germany, Japan, New Zealand, Lebanon, Saudi Arabia and Sweden.

B. Studies from LEDCs (n=47)

- Uganda (n=9)
- Ethiopia (n=7)
- Kenya (n=3)
- India (n=3)
- Iran (n=3)
- Cambodia (n=2)
- Nigeria (n=2)

- Peru (n=2)
- Tanzania (n=2)
- Zimbabwe (n=2)
- One study conducted in Kenya, Uganda and Tanzania.
- Eleven studies conducted in each of Congo, Cuba, Ghana, Guatemala, Jamaica, Mozambique, Pakistan, Thailand, Vietnam, Zambia and Togo.

3.3.4 Study design

One hundred and seventy-two studies were observational studies (95 cohort, 74 cross-sectional and three case series), and five were randomised controlled trial studies.

3.3.5 Tools used to identify barriers and facilitators

Various tools were used in the included articles, which are described in the following sections.

A. Patients' medical data

Nine studies with patients with HIV, kidney diseases, psychotropic disease, IBD, different chronic diseases and patients with high cholesterol level were based on patients' medical records or pharmacy refill data to assess factors associated with medicines adherence, such as age, gender, education level, complexity of regimen, dosage forms and duration of treatment (34,156–163).

B. Self-report

One hundred and sixty-three studies used self-report tools to identify barriers and facilitators. These self-reports were divided into validated questionnaires and individually designed questionnaires. The validated questionnaires were used for thirty-two studies. Table 3-1 provides a summary of validated questionnaires used to identify barriers and facilitators to medicines adherence.

Table 3-1 Summary of validated questionnaires used to identify barriers and facilitators.

Study (Condition, references)	Name of validate questionnaire	Details of validated questionnaires used
Inflammatory Bowel Disease (IBD) (164–168), **kidney or liver diseases** (169–172).	**Medical Adherence Measure** (MAM) questionnaire scale.	Adherence across 4 domains assessed: adherence behaviour, knowledge, barriers to medicine adherence and organisational system.
Asthma (68,173–175), **attention deficit hyperactivity disorder** (81), **IBD** (176), **epilepsy** (126,177), **cystic fibrosis** (178)	**Beliefs about Medicines Questionnaire-Specific** (BMQ) scale.	Ten questions, five on necessity and five on concerns about taking medicines. Questions involving concerns assess patients' concerns about taking the medicines prescribed; questions about necessity assess patients' beliefs in the need to take the medicines prescribed.
Solid organ transplantation (79), **psychotropic diseases** (179), **sickle cell disease** (180)	**Brief Medication Questionnaire** scale.	Three domains: belief screen (to assess patients' beliefs in the need to take medicines), regimen screen (number of missed doses within the previous week) and recall screen (rates difficulty remembering).
HIV (181), **diabetes** (182)	**Diabetes Family Responsibility Questionnaire**.	Assesses child and parent perceptions about responsibility for treatment adherence. Higher scores indicate lower level of parental involvement in treatment.
HIV (183)	**Beck Depression Inventory** to assess depression.	21 items, participant picks item describing how they have been feeling in last 14 days. Results categorised to: severe depression; moderate depression; mild depression; minimal depression.

Study (Condition, references)	Name of validate questionnaire	Details of validated questionnaires used
HIV (184)	**Conners' Parent Rating Scale** to evaluate children's behavioural functioning.	Questionnaire consists of 48 descriptors of behaviour including learning problems, conduct problems, general hyperactivity, anxiety, psychosomatic problems, and impulsivity-hyperactivity. Parent picks the one that they observed in the last month.
HIV (185)	**Beliefs about Medication Scale**.	Questionnaire consists of 59 items to assess positive and negative outcome expectancy, perceived threat of illness, and intent to adherence.
Asthma (186)	**Asthma Knowledge Questionnaire.**	25 items about childhood asthma. Any score ≤ 11 rated as poor knowledge about asthma.
Asthma (187)	**Asthma Expectation Questionnaire Scale**.	15 items covering outcome expectation, self-efficacy and barrier perceptions.
Renal failure (188)	**Adolescent Medication Barriers Scales**.	Designed to assess barriers to adherence in adolescent transplant recipients. Questionnaire consists of 16 questions about barriers and patients pick most frequent barrier to their medicines adherence.
Chronic kidney diseases (189)	**Child & Adolescent Adherence to Medication Questionnaire**.	To identify emotionality and variables that affect adherence. Two questions about demographic information, one about diagnosis, seven open ended questions on participants opinions about treatment and adherence, and nine closed questions.
Epilepsy (177)	**Morisky Medication Adherence Scale**.	Questionnaire with four items about forgetting, severity of disease, feeling better, and absence of symptoms with answer of yes=0 and No=1. Patients considered non-adherent with score of 1 or more.

Study (Condition, references)	Name of validate questionnaire	Details of validated questionnaires used
Epilepsy (190)	**Paediatric Epilepsy Medication Self-Management Questionnaire** scale (PEMSQ).	27 items to evaluate medicine self-management in children with epilepsy. Four scales (adherence to medicines, barriers to adherence, epilepsy and treatment knowledge and beliefs about medicines efficacy).
Epilepsy (190)	**Paediatric Epilepsy Side Effects Questionnaire** scale.	19 items to assess side effects of antiepileptic medicines for epilepsy.
Epilepsy (190)	**Parental Environment Questionnaire** scale.	42 items to assess parent-child relationship. Answers ranging from "definitely true" to "definitely false". Higher scores reflect higher parent involvement and higher conflict.
Sickle cell disease (SCD) (191)	**Disease Management and Barriers Interview-Sickle Cell Disease** scale.	60 items explore adherence barriers, behaviours, and facilitators.

The remaining 131 studies used individually designed questionnaires. The questionnaires consisted of multi-item questions to explore the barriers and facilitators to medicines adherence in children during a previous period of time. The questionnaire items differed in their formats and questions, depending on which diseases and populations were being targeted.

3.3.6 Types of diseases

The studies identified barriers and facilitators to medicines adherence for several diseases, which in order of frequency were:

- HIV/AIDS (n=60)
- Asthma (n=25)
- Kidney or liver diseases and solid organ transplant (n=19)
- Psychiatric disorders (n=13)
- Inflammatory bowel disease (IBD) (n=11)
- Epilepsy (n=10)
- Multiple chronic diseases (n=6)
- Sickle cell disease (n=5)
- Cystic fibrosis (n=4)
- Diabetes (n=4)
- Tuberculosis (n=4)
- Chronic rheumatic disease (n=3)
- Multiple sclerosis (n=3)
- Cancer (n=2)
- Growth hormone deficiency (n=2)

- Thalassemia (n=2)
- Patients taking antibiotics (n=1)
- Adolescent smoking cessation (n=1)
- Cystinosis (n=1)
- Patients with high cholesterol level (n=1)

Information on barriers and facilitators to medicines adherence were extracted from the studies for each disease based on the World Health Organisation (WHO) classification of patient-related factors, healthcare professional-and system-related factors, condition-related factors, medicine-related factors, and socioeconomic-related factors.

A. HIV/AIDS

As shown in Table 3-2, sixty studies identified barriers and facilitators to medicines adherence in HIV/AIDS patients (61,62,156,157,181,183–185,192–195,69,196–205,70,206–215,71,216–225,73,226–235,74,86,93,116).

- Patient-related factors

The most common barriers to medicines adherence in HIV patients were patient-related factors reported in thirty three studies (61,62,193–197,199–203,69,205,210,213,214,218,219,221,228,230,233,70,73,86,93,116,184,192). Twenty six studies reported that forgetting to take the medicine was

the most common barrier to medicines adherence in children (61,62,193–197,199–
201,205,213,69,214,218,219,221,228,230,70,73,86,93,116,184,192). Forgetfulness appeared more common among adolescents, who receive less parental supervision (61,62,228,70,93,184,192,194,200,201,218). Efforts to avoid forgetfulness to take medicines, such as using reminder tools, integrating medicine into daily routines and taking medicines at a specific time each day, were associated with medicines adherence (62,69,228,73,93,184,193,194,199,205,214).

Patient age was related to adherence in five studies (202,203,210,214,233). Three of these studies found that patients aged > 12 years are more likely to have poor adherence to treatment than younger patients (203,210,233). Factors linked to decreased adherence with increasing age included close relationship with peers, less parental involvement and breakdown of family routines (203,210,233). By contrast, two studies reported that children aged < 5 years are less likely to be adherent than those aged > 5 years (202,214). Wadunde et al. also found that patients aged < 10 years are more likely to have poor adherence than older children ($p = 0.002$) (199).

Suboptimal relationships between children and their parents and families are reported as barriers to medicines adherence (62,73,93,196,205,210). Factors such as a ‘bad home life’ and ‘family stress’ were associated with

medicine non-adherence (62,73,205,210). Children with alcoholic parents appeared less likely to adhere to treatments (196,205).

Knowledge of a disease and its treatment varied among patients and their families. Good knowledge of the disease and its treatment was associated with good adherence to medicines (70,86,192,196,199,221). Parents and children with good knowledge of the disease and its treatment recognised the severity of the disease and the necessity for medicine (70).

- Socioeconomic-related factors

The second most common barrier to medicines adherence among HIV patients were socioeconomic-related factors reported in twenty six studies (61,62,196–199,201,203,204,206,214,215,71,217–221,223,224,231,232,235,73,74,86,93,156,193,194). Among these factors, fear of stigma and discrimination was reported in sixteen studies (62,71,218,219,221,224,231,232,73,86,93,193,194,201,206,217). Galea et al. found that children hid their antiretroviral therapy medicines when going out with friends (73). Fetzer et al. reported that children were frustrated with their HIV medicine regimens because they compared themselves to their peers and found that other children were not administered such medicine regimens (93).

Failure of parents to tell their children about their condition lead to poor adherence as reported by twelve studies (61,93,231,235,196,198,203,204,217,218,221,224). Reasons for non-

disclosure included: the child being too young, the child would tell others or the child would suffer negative consequences (204,217). Nine of these studies showed that patients who knew about their HIV condition were more likely to adhere to medicines compared with individuals not aware (93,194,196–198,214,218,223,235). Bulali et al. found that good adherence is significantly associated with HIV disclosure ($p<0.05$) (235).

Economic problems may also influence medicines adherence, such as when medicines are not free or when patients live far from healthcare facilities and may need to pay for travel expenses. Twelve studies conducted in LEDCs reported that financial problems, limited access to healthcare facilities, long distance from medical centres and lack of transportation result in poor adherence to medicines (71,73,220,232,74,86,156,193,196,199,203,215).

- Medicine-related factors

The third most common barrier to medicines adherence for patients with HIV were medicine-related factors reported in 22 studies (62,70,200,201,203,208,210,213–216,218,71,226,227,74,86,192,193,196–198). Experiencing side effects of medicines was one of the most common barriers reported in ten studies (70,86,198,200,201,214,216,218,226,227). In addition, five studies have showed an association between the fear of the side effects of medicines and poor adherence (71,192,196,197,203).

Medicines characteristics, such as bad taste or large pill size, were associated with non adherence. Six studies showed that children could not swallow bad-tasting medicines (193,197,198,208,213,215). Pills that were too large and could become stuck in a child's throat or cause vomiting resulted in poor adherence (61,193,195,215,216). Five studies showed that the administration of multidrug regimens was associated with poor adherence (62,70,74,210,216).

- Condition-related factors

The fourth most common barriers in HIV patients were condition-related factors reported in nine studies (61,70,71,192,196,216,221,229,232). Decreased HIV severity was reported to be associated with poor adherence. When patients began to feel better and their symptoms decreased, they stopped taking daily medicines (61,71,221). By contrast, greater disease severity increased patient adherence (70,196). However, depression or anxiety symptoms in patients with HIV lead to poor adherence (61,192,216,229,232).

Table 3-2 Studies reporting barriers and facilitators to medicines adherence in HIV/AIDS patients. For barriers and facilitators numbers are reported as % or significant association (if no numbers given numbers not reported in study).

Study	Design	Tools used	Barriers identified	Facilitators identified
White et al. 2008, Jamaica (192).	Cross-sectional study, 63 participants, aged 18 months to 18 years.	Completed by children and caregivers 54-item questionnaire: caregiver/child health status, sociodemographic characteristics, knowledge of disease and therapy, and concerns about side effects. Adherence rate assessed by self-report.	· Forgetting (35.1%) · Change in caregiver (35.1%) · Parents busy (27%) · Child outside home 27%. · Medicines unavailable at pharmacy 18.9%. · Child depressed 16.2%. · Fear of side effects 16.2%. · Can't swallow pills 16.2%. · Sleeping 13.5%. · Feel too ill 13.5%. · Medicines taste bad 13.5%.	· Caregivers having good knowledge of adherence and therapy.
Polisset et al. 2009, Togo (200)	Cross-sectional study, 63 participants, aged 8 to 18 years.	Questionnaire completed by caregivers to evaluate adherence to treatment. Participants given list of barriers to adherence and asked to tick factors they have faced. Adherence rate assessed by self-report.	· Out of stock medicines 43%. · Forgetting 22%. · Vomiting 14%. · Child's refusal 11%.	Did not report facilitators.
Naar-King et al. 2009, United States (181)	Cross-sectional study, 123 participants, aged ≥ 15 years.	Diabetes Family Responsibility Questionnaire (DFRQ) completed by children and parents (see table 3.1.). Adherence rate assessed by self-report.	Did not report barriers.	· Caregivers reported youth with greater responsibility for treatment have better adherence (p=0.004). · Adolescents reported degree of responsibility for treatment was not correlated with adherence.
Kourrouski et al. 2009, Brazil (201)	Cohort study, 9 children aged 12 to 18 years.	Questionnaire completed by children and caregivers about treatment aspects, disease experience, family support, and daily routine. Adherence rate assessed by self-report.	· Forgetting. · Non-acceptance of disease. · Experience of side effects. · Fear of stigma and discrimination.	Did not report facilitators.

Study	Design	Tools used	Barriers identified	Facilitators identified
le Roux et al. 2009, United States (202)	Randomised controlled trial, 339 participants, aged ≥ 8 weeks.	Questionnaire completed by caregivers. At each visit, caregivers asked questions about medicines administration difficulties. Adherence rate assessed by self-report.	· Children aged < 4 years old. · Children in house with large number of people. · Long duration of treatment.	· Children aged > 4 years old. · Children in small household. · Children with less duration of treatment.
Vreeman et al. 2009, Kenya (203)	Cohort study, 120 parents and caregivers of children aged up to 14 years.	Questionnaire completed by caregivers and parents open-ended questions related to knowledge of disease and therapy, factors associated with adherence, barriers and facilitators of adherence. Adherence rate assessed by self-report.	· Children aged > 10 years. · Child's refusal. · Greater child responsibility for medicines-taking. · Difficult relations between child and caregiver. · Lack of transportation. · Fear of side effects. · Lack of financial resources. · Non-disclosure HIV status to household members.	· Children aged < 10 years. · Caregiver solely responsible for medicine. · Disclosure HIV status to house hold members.
Biadgilign et al. 2009, Ethiopia (193)**.**	Cohort study, 12 participants. Age not reported but study mentioned that it targeted children population.	Questionnaire completed by caregivers open-ended questions related to knowledge of disease and therapy, factors associated with adherence. Adherence rate assessed by self-report.	· Leaving home to visit relatives. · Nondisclosure of patient HIV status. · Lack of transportation and economic problems. · Lack of food (fear of taking medicines on empty stomach). · Fear of stigma and discrimination. · Patient dislike of taking the medicine. · Patient spitting out the medicine. · Time of administration.	· Presence of medicines reminders. · Good relationship between health workers and caregivers. · Good taste medicine.
Park et al. 2009, United States (183)	Cross-sectional study, 18 participants, aged 14 to 22 years.	Questionnaire completed by adolescents about religious beliefs and practises.	· Lower religious belief (p<0.05). · Lower religious practise (not significant due to small sample size).	Did not report facilitators.

Study	Design	Tools used	Barriers identified	Facilitators identified
		Standardised depression questionnaire (BDI-II) completed by adolescents (table 3.1). Adherence rate assessed by self-report.	· Higher depression score (not significant due to small sample size).	
Rudy et al. 2010, United States (207)	Cross-sectional study, 368 participants, aged 12 to 24 years.	Questions completed by patients to investigate environment factors that may influence adherence. Adherence rate assessed by self-report.	· Problems with medical insurance (p<0.04). · Problems dealing with family or taking care of children (p<0.04). · Low self-efficacy (p<0001).	· High self-efficacy associated with good adherence (p<0.001).
Castro et al. 2010, Cuba (194)**.**	Cohort study, 21 participants, aged 3 to 16 years.	Questionnaire completed by caregivers to explore factors associated with adherence to medicines: psychosocial (factors external to family, family environment, characteristics of caregiver), and factors related to therapy. Adherence rate assessed by self-report.	· Fear of stigma or discrimination. · Children aged > 11 years. · Absence of both parents associated with poor adherence. · Psychosocial factors, such as parents suffering with his or her own HIV diagnosis.	· Psychological adaptation by families. · Reducing dose frequencies and using medicines reminders.
Lin et al. 2011, Canada (208)	Cross-sectional study, 119 participants, aged 0 to 18 years.	Questionnaire completed by physicians to explore physicians' perception about factors that caused medicines discontinuation. Medicine discontinuation assessed by medical record.	· Ritonavir was the least palatable medicine associated with medicine discontinuation (p=0.01). · Male gender associated with medicine discontinuation (p=0.001).	Did not report facilitators.
Skovdal et al. 2011, Zimbabwe (209)	Cross-sectional study, 25 nurses and 8 grandparents of children with HIV.	Questionnaire completed by nurses and elderly caregivers (grandparents) covered experiences of AIDS, personal background, stigma and challenges faced with adherence to treatment. Adherence rate assessed by self-report.	· Poverty. · Immobility of caregivers. · Deteriorating memory of caregivers. · Poor comprehension of complex treatment.	Did not report facilitators.

Study	Design	Tools used	Barriers identified	Facilitators identified
Malee et al. 2011, United States (184)	Cross-sectional study, 1134 participants, aged 3 to 17 years.	Conners' Parent Rating Scale (CPRS) completed by parents or caregivers (table 3.1). Adherence rate assessed by self-report.	· Learning problems 22%. · Somatic complaints 22%. · Impulsivity-hyperactivity 20%.	· Use of daily activities as an adherence support. · Adult responsible for medicine administration
Fetzer et al. 2011, Congo (93)**.**	Cohort study, 20 participants, aged 8 to 17 years.	Questionnaire completed by children and caregivers - questions about children/caregiver relationships, then open-ended questions to explore beliefs on ART and HIV and factors related to adherence. Adherence rate assessed by self-report.	· Forgetting. · Frustrated with medicine regimen. · Lack of food (fear of taking medicines on empty stomach). · Lack of assistance from family. · Medicine characteristics (high dose frequencies, large quantity, and bad taste). · Fear of stigma and discrimination.	· Presence of medicines reminder such as, Electronic Monitoring Devices (EMDs). · Living with two parents. · Belief itself that medicine was helping. · Having strategy or routine related to medicine administration. · Patient disclosed HIV status. · Convince or motivate children to be committed to taking their medicines.
Mahloko et al. 2012, South Africa (204)	Cross-sectional study, 149 participants, aged 4 to 17 years.	Questionnaire completed by caregivers covering socio-demographic, marital status, level of education, and reasons for non-disclosing HIV status. Adherence rate assessed by self-report.	· Non-disclosure was reason for not adhering to medicine 39%. · Reasons for non-disclosure include child too young (72%), child would tell others about disease (21.1%), child would be socially rejected (18.6), fear of negative consequences for child (13.3%).	Did not report facilitators.

Study	Design	Tools used	Barriers identified	Facilitators identified
Haberer et al. 2012, Ugand (205)	Cohort study, 121 participants, aged 2 to 10 years.	Questionnaire completed by caregivers. Open-ended questions covered socio-demographic, behavioural, and factors with potential to affect adherence. Adherence rate assessed by pill count and EMDs.	· Hospitalisation of children in last three months. · Use liquid formulations. · Caregiver's use of alcohol. · Caregivers had depression. · Caregivers ashamed of child's diagnosis.	· Well-established medicine taking routine (e.g. take medicine before school). · Use drug combinations.
Martinez et al. 2012, United States (206)	Cohort study, 178 female participants, aged 15 to 24 years.	Questionnaire completed by adolescents. Open-ended questions to explore HIV related stigma, depression, social support, and health care satisfaction. Adherence rate assessed by self-report.	· Fear of stigma and discrimination caused poor adherence but was not significantly associated with poor adherence.	Did not report facilitators.
Chandwani et al. 2012, United States (62)	Cohort study, 104 participants, aged 13 to 17 years.	Questionnaire completed by children. Open-ended questions identified predictors of medicines adherence. Adherence rate assessed by self-report.	· Forgetting. · Complexity of medicine regimen. · Busy and varying schedules. · Feeling better. · Fear of stigma and discrimination. · Nondisclosure. · Unstable housing.	· Have someone to remind. · Educating children about importance of adherence.
Nichols et al. 2012, United States (210)	Cross-sectional study, 151 participants, aged 8 to 18 years.	Questionnaire completed by children and parents. Open-ended questions identified medicine use, quality of life, demographic information, stressful life events, and children-parents relationship. Adherence rate assessed by self-report and pill count.	· Child aged > 12 years ($p<0.05$). · Greater child responsibility for medicines-taking ($p<0.05$). · Poor relationships with parents ($p<0.05$). · Complexity of medicine regimen ($p<0.05$).	Did not report facilitators.

Study	Design	Tools used	Barriers identified	Facilitators identified
Buchanan et al. 2012, United States (61)**.**	Cohort study, 120 participants, aged 8 to 18 years.	Children and parents asked: "People may miss their medications for various reasons. In the past month, how often have you/your child missed taking medication because of the following reasons?" Adherence rate assessed by self-report.	· Forgetting. · Delaying taking medicine in front of others. · Feeling well. · Sleeping. · Pill burden. · Depressed. · Did not refill. · Change daily routine.	Did not report facilitators.
Bn et al. 2013, Uganda (211)	Case series study, applied on 4 adults and one adolescent aged 14 years.	Questionnaire completed by participants to collect medical history, patient information, and personal barriers to medicines adherence. Adherence rate assessed by self-report.	· Lack of family support. · Orphan. · Feel sick and weak.	Did not report facilitators.
Chimhuya et al. 2013, Zimbabwe (212)	Cross-sectional study, 216 caregivers and children, aged ≤ 10 years.	Questionnaire completed by caregivers to obtain demographic information, treatment information, and family status. Adherence rate assessed by self-report and pill count.	· Two or less children in household (OR 6.26). · Two or less adults in the household (OR 3.73).	Did not report facilitators.
MacDonell et al. 2013, United States (213)	Cross-sectional study, 993 adolescent, aged 12 to 24 years.	Questionnaire completed by participants. Participants given list of barriers to adherence and asked to tick factors they have faced. Adherence rate assessed by self-report.	· Forgetting 73.6%. · Did not feel like taking medicines 30%. · Taking medicines reminds of disease 28.9%. · Bad taste 20.5%. · Ran out of prescription 20.5 %. · Fear of stigma and discrimination 16.3%.	Did not report facilitators.

Study	Design	Tools used	Barriers identified	Facilitators identified
Ugwu et al. 2013, Niegeria (214)	Cross-sectional study, 213 caregivers and their children, aged 3 months to 18 years.	Questionnaire completed by caregivers and children. Open-ended questions covered socio-demographic, level of education, age, sex, and duration of treatment. Participants given list of barriers to adherence and asked to tick factors they have faced. Adherence rate assessed by self-report.	· Forgetting 55.2% of caregivers. · Travelling 25.3% of caregivers. · Medicines finished 18.4% of caregivers. · Child reused to take medicines 11.5% of children. · Sleeping 9.2% of children. · Vomiting 9.2% of children. · Younger than 5 years (OR 2.62).	· Having medicine strategy or reminder (OR 6.34). · Regular clinic visits (OR 8.55). · Status disclosure (P=0.008).
Barrenes et al. 2014, Cambodia (215)	Cross-sectional study, 183 participants, aged 7 to 15 years.	Questionnaire completed by children and parents. Participants given list of barriers to adherence and asked to tick factors they have faced. Adherence rate assessed by self-report.	· Difficulty in going to hospital 61.7%. · Difficulty in swallowing drugs 12.6%. · Bad taste 7.6%. · Lack of money 7.1%.	Did not report facilitators.
Navarra et al. 2014, United States (185)	Cross-sectional study, 50 participants, aged 13 to 24 years.	Beliefs about Medication Scale (BAMS) completed by adolescents (table 3.1). Adherence rate assessed by self-report.	· Adolescents with low level of literacy · (p<0.05). · Adolescents with higher negative expectancy.	· Adolescents with higher positive expectancy (OR 1.07).
Eticha et al. 2014, Ethiopia (216)	Cross-sectional study, 193 participants, mean age 7.8 years.	Questionnaire completed by caregivers covered socio-demographic, factors related to adherence, and reasons for missing doses. Participants given list of barriers to adherence and asked to tick factors they have faced. Adherence rate assessed by self-report.	· Child feels depressed 24.4%. · Experienced side effects 16.3%. · Multi-drugs 15.5%. · Difficulty in swallowing medicines 13.3%. · Child too ill 8.9%.	· Orthodox religion caregivers (OR 4.15). · Married caregivers (OR 3.75). · Caregivers aged 25-34 (OR 2.58).

Study	Design	Tools used	Barriers identified	Facilitators identified
Mburu et al. 2014, Zambia (217)	Cross-sectional study, 53 participants, aged 10 to 19 years.	Questionnaire completed by adolescents focused on sexual needs and experiences of disclosure. Questionnaire completed by health care providers to explore barriers to disclosure HIV status. Adherence rate assessed by self-report.	· Non-disclosure was reason for non-adherence to medicine. · Reasons for non-disclosure included: presumption that children would not understand consequences of HIV disclosure on their lives, fear of stigma and discrimination, child would be socially rejected.	Did not report facilitators.
Dachew et L. 2014, Ethiopia (218)	Cross-sectional study, 342 participants, aged 2 months to 15 years.	Questionnaire completed by caregivers. Participants given list of barriers to adherence and asked to tick factors they have faced. Disease disclosure and knowledge also assessed. Adherence rate assessed by self-report.	· Forgetting 52.3%. · Medicine fatigue 26.2%. · Fear of stigma and discrimination 14.3% · Caregivers' illness 11.9%.	· Disclosure of the child's HIV status to the child. · Good caregiver knowledge of treatment.
Kunapareddy et al. 2014, Kenya (195)**.**	Cohort study, 78 participants, aged 10 to 16 years.	Questionnaire completed by children including questions about medicine handling, interactions around medicines, cultural context of HIV treatment, and barriers to adherence. Adherence rate assessed by self-report.	· Forgetting. · Delaying taking medicine in front of others. · Feeling well. · Sleeping. · Pill burden.	Did not report facilitators.
Arage et al. 2014, Ethiopia (196)**.**	Cross-sectional study, 464 participants, aged 2 months to 14 years.	Questionnaire completed by caregivers, questions about most common barriers including medicines factors, socioeconomic factors, and patient factors. Participants given list of barriers to adherence and asked to tick factors they have faced. Adherence rate assessed by self-report.	· Forgetting 28.5%. · Refused to take medicines 19.3%. · Lack of transportation 19.1%. · Run out of pills 13.2%. · Illness of the caregivers 5.5%. · Pill burden 4.3%. · Fear of side effects of medicines 4.3%. · Illness of child 3.2%. · Taste of medicines 1.8%.	· Caregivers have good knowledge of disease and therapy. · Disease severity motivated patient's adherence. · Higher education level. · Short distance between home and hospital. · Patient disclosed their HIV status.

Study	Design	Tools used	Barriers identified	Facilitators identified
Gultie et al. 2015, Ethiopia (197)**.**	Cross-sectional study, 226 participants, aged < 15 years.	Questionnaires were completed by caregivers to explore factors associated with ART therapy adherence. Participants given list of barriers to adherence and asked to tick factors they have faced. Adherence rate assessed by self-report.	· Illness of the child 23.8%. · Fear of side effects 23.8%. · Child refusal 14.3%. · Busy caregiver 14.3%. · Forgetting 9.5%. · Lack of trust in the treatment 9.5%. · Taste of the drug 4.8%.	· Patients disclosed their HIV status. · Male were more likely to adherent than female. · Patients who are on first line ART are more adherent than those on second line drug.
Coetzee et al. 2015, South Africa (198)**.**	Cohort study, 11 participants, aged ≤ 5 years old.	Questionnaires completed by caregivers including open-ended questions to explore parents' understanding of treatment and barriers to adherence. Adherence rate not assessed.	· Lack of food (fear of taking medicines on empty stomach). · Non-disclosure. · Lack of knowledge about treatment. · Lack of transportation and economic problems. · Experienced side effects (vomiting).	· Good relationship between child and caregivers. · Sweet tasting medicines. · Patients disclosed their HIV status
Kim et al. 2015, United Kingdom (219)	Cross-sectional study, 138 participants aged 12 to 24 years.	Questionnaire completed by adolescents to explore treatment adherence information. Participants given list of barriers to adherence and asked to tick factors they have faced. Adherence rate assessed by self-report.	· Forgetting 23.9%. · Fatigue 10.1%. · Stigma 9%. · Experienced side effects 7.5%.	· Self-motivation 33.4%. · Family and friends support 27.7%.
Nakigozi et al. 2015, Uganda (71)	Cross-sectional study, 18 participants aged 15 to 24 years.	Questionnaires completed by caregivers including open-ended questions to explore barriers of adherence including, socioeconomic factors and medicines factors. Adherence rate not assessed.	· Fear of stigma. · Non-disclosure. · High transportation costs. · Fear of side effects. · Lack of disease' symptoms. · Lack of money.	Did not report facilitators.

Study	Design	Tools used	Barriers identified	Facilitators identified
Olds et al. 2015, Uganda (220)	Cross-sectional study, 35 caregivers of children aged 2 to 10 years.	Questionnaires completed by caregivers including open-ended questions to explore barriers and facilitators of adherence including, patient factors, socioeconomic factors and medicines factors. Adherence rate assessed by self-report.	· Lack of money, food, and transportation. · Lack of social support. · Weak relationship between caregivers and their children.	· Good relationship between caregivers and their children. · Greater responsibility of children for their treatment (who were cognitively mature). · Good social support.
Nyogea et al. 2015, Tanzania (221)	Cross-sectional study, 116 participants, aged 2 to 19 years.	Questionnaires completed by children and caregivers to identify predictors of adherence such as, parental status, awareness of disease, duration of treatment, and knowledge about disease and treatment. Adherence rate assessed by pill count.	· Living with non-parental caretakers (p=0.042) · Fear of stigma and discrimination. · Forgetting. · Lack of knowledge about disease and treatment. · Feeling better. · Non-disclosure HIV status. · Treatment longevity.	· Good knowledge about disease and treatment. · Positive attitudes towards treatment.
Nabukeera-barungi et al. 2015, Uganda (156)	Cohort study, 1824 participants, aged 10 to 19 years old.	Factors associated with poor adherence like age, sex, medicine regimen, age at last visit, distance to hospital, date of medicine initiation were extracted from medical records. Adherence rate assessed by self-report.	· Male sex (OR 1.38) (p=0.048). · Rural location (OR 2.67) (p=0.000). · Less than one year on treatment (OR 1.45) (p=0.022).	Did not report facilitators.
Bermudez et al. 2016, Uganda (222)	Cross-sectional study, 702 participants, aged 10 to 16 years.	Questionnaire completed by children and caregivers. Different economic and social variables assessed such as, caregiver employment status, available cash, material housing value, food security, distance to health care services, and social support. Adherence rate assessed by self-report.	Did not report barriers.	· Adolescents with caregiver employment (OR 1.70). · Greater familial asset ownership (OR 1.69). · Short distance to a clinic (OR 1.49).

Study	Design	Tools used	Barriers identified	Facilitators identified
Madiba et al. 2016, South Africa (223)	Cross-sectional study, 37 participants, aged 12 to 18 years.	Questionnaires completed by adolescents to explore perceptions of disclosure, reaction to disclosure, and association between adherence and HIV disclosure. Adherence rate assessed by self-report.	Did not report barriers.	· Disclosure HIV status. · Positive attitudes towards treatment.
Ankrah et al. 2016, Ghana (86)	Cross-sectional study, 116 participants, aged 12 to 19 years.	Questionnaires completed by adolescents. Open-ended questions to identify barriers and facilitators of medicines adherence. Adherence rate assessed by self-report.	· Forgetting. · Fear of stigma and discrimination. · Financial barriers. · Experienced side effects.	· Family support. · Health care providers support. · Good knowledge about disease and treatment.
Inzaule et al. 2016, Uganda (224)	Cross-sectional study, 33 health care providers.	Questionnaire completed by health care providers. Open-ended questions to explore barriers to medicines adherence in adolescents and adults. Adherence rate assessed by self-report.	· Unstructured treatment holidays. · Fear of stigma. · Non-disclosure HIV status. · Lack of family support.	Did not report facilitators.
Ricci et al. 2016, Brazil (225)	Cross-sectional study, 77 participants, aged 2 to 12 years.	Questionnaires completed by caregivers to identify predictors of adherence such as, relationship with the child, functional status, medicines problems and family's income. Adherence rate assessed by self-report.	· High family income was associated with poor adherence ($p<0.05$). · Liquid formulation. · Mothers with HIV who did not adhere to their treatment.	Did not report facilitators.
Mehta et al. 2016, India (226)	Cross-sectional study, 164 participants, aged > 18 years.	Questionnaires completed by caregivers to explore barriers to adherence such as medicine related factors, patients or caregivers related factors, and health care related factors. Adherence rate assessed by self-report.	· Experienced side effects ($p=0.01$). · Child refused to take medicines ($p=0.01$). · Running out of medicines ($p=0.02$).	Did not report facilitators.

Study	Design	Tools used	Barriers identified	Facilitators identified
Vreeman et al. 2016, Kenya (116)	Cohort study, 191 participants, aged 0 to 14 years old.	Questionnaires completed by caregivers including open-ended questions to assess adherence and identified barriers to adherence. Adherence rate assessed by self-report and EMDs.	· Forgetting. · Child refusal to take medicine. · Caregivers not being around to give the medicines. · Fear of stigma.	Did not report facilitators.
Cote et al. 2016, Brazil (227)	Cohort study, 268 participants, aged 13 to 21 years old.	Questionnaires completed by adolescents. Open-ended questions to assess adherence, self-efficacy, and medicines symptoms. Adherence rate assessed by self-report.	· Lower self-efficacy. · Experienced high numbers of side effects.	· Higher self-efficacy. · Lower numbers of medicine side effects.
Hawkins et al. 2016, United Kingdom (228)	Cohort study, 17 female, aged 14 to 22 years old.	Questionnaires completed by adolescents. Open-ended questions to assess adherence, and behavioural and psychological factors that influenced adherence. Adherence rate assessed by self-report.	· Poor adherence was associated with weekend days. · Lack of routine. · Being out of the home.	· Higher self-efficacy. · Having a strategy or routine related to medicine administration.
Kolmodin Macdonell et al. 2016, United States (229)	Cohort study, 956 participants, aged 12 to 24 years old.	Questionnaires completed by adolescents. Open-ended questions to assess adherence, self-efficacy, motivation for adherence, depression and social support. Adherence rate assessed by self-report.	· Lower self-efficacy. · Lower level of social support. · Psychological symptoms and substance use.	· Higher self-efficacy. · Higher level of social support.

Study	Design	Tools used	Barriers identified	Facilitators identified
Feyissa. 2017, Ethiopia (69)**.**	Cohort study, 120 participants, aged ≤ 15 years.	Questionnaires completed by caregivers and included four main parts: clinical markers in children, sociodemographic characteristics, medicine taking behaviour, and access to care. Adherence rate assessed by self-report.	· Forgetting. · Younger children more likely to be non-adherent. · Child with a caregiver who works was more likely to be non-adherent. · Low educational level of caregivers.	· Using medicines reminder or diary reminder. · Children in early stage of HIV were more likely to adhere to medicine. · High educational level of caregivers.
Kendre et al. 2017, India (70)**.**	Cohort study, 78 participants < 15 years old.	Questionnaire completed by children, asked a single question about reasons for missing doses. Reasons options given to patients to choose which one caused missing dose. Also factors that may lead to good adherence were assessed. Adherence rate assessed by pill count.	· Forgetting 37.1%. · Travel 14%. · Missed appointment 13%. · Experienced side effects 12%. · Pill burden 10%. · Lack of knowledge and motivation 10%.	· Education of caregiver. · Disease severity. · Caregivers have good knowledge of disease and therapy.
Xu et al. 2017, Thiland (230)	Cross-sectional study, 275 participants, aged 12 to 19 years.	Questionnaire completed by adolescents. Open-ended questions to explore barriers of medicines adherence. Adherence rate assessed by self-report.	· Forgetting. · Weak relationships with caregivers. · Fear of disclosing disease status to others. · Large household.	Did not report facilitators.
Mafune et al. 2017, South Africa (231)	Cross-sectional study, 16 caregivers, caring for children aged 0 to 15 years.	Caregivers were asked "What are the challenges you experience when caring for a child on ARV treatment?" Adherence rate not assessed.	· Financial burden. · Fear of stigma. · Non-disclosure. · Lack of family support. · Lack of government support services.	Did not report facilitators.

Study	Design	Tools used	Barriers identified	Facilitators identified
Tran et al. 2017, Vietnam (232)	Cross-sectional study, 209 caretakers, caring for children.	Questionnaire completed by caregivers. Participants given list of barriers to adherence and asked to tick factors they have faced. Adherence rate not assessed.	· Financial burden 69%. · Lack knowledge of disease and treatment 68%. · Depression 41%. · Fear of stigma 14.8%.	Did not report facilitators.
Garvie et al. 2017, United States (233)	Cohort study, 256participants, aged 7 to 16 years.	Questionnaire completed by caregivers and professionals. Open-ended questions identified medicine adherence, responsibility, and executive function. Adherence rate assessed by self-report.	· Children aged >12 years. · Greater children responsibility for medicine. · Caregivers with low education level.	· Younger child age. · Caregiver solely responsible for medicine. · Caregivers with high school graduates.
Galea et al. 2018, Peru (73)**.**	Cohort study, 18 participants, aged 13 to 17 years.	Questionnaire completed by caregivers and professionals. Open-ended questions identified barriers and facilitators to medicines adherence. Adherence rate not assessed.	· Lack of knowledge about disease. · Fear of stigma and discrimination. · Family's economic problems. · Weak relationship with caregivers. · Health system delays.	· Personal strategies. · Peer support. · Living with two parents. · Caregivers support.
Wadunde et al. 2018, Uganda (199)**.**	Cross-sectional study, 153 participants, aged 0 to 14 years.	Questionnaire completed by caregivers assessing: child-related factors, caregiver-related factors, and drug regimen related factors that may affect adherence. Adherence rate assessed by self-report.	· Children aged < 10 years more likely to be non-adherent to medicine (p=0.002). · Lack of transportation and economic problems. · Forgetting. · Parents busy.	· Older children were more likely to adhere. · Using medicines reminder. · Caregivers have good knowledge of disease and therapy.

Study	Design	Tools used	Barriers identified	Facilitators identified
Vreeman et al. 2018, Kenya, Uganda, and Tanzania (157)	Cohort study, 3304 children, aged 0 to 13 years.	Demographic factors that may affect adherence such as, clinical factors, duration of treatment, family status, and medical regimen factors were identified from, medical records. Adherence rate assessed by self-report and pill count.	· Orphan children were more likely to have lower adherence rate (OR 0.78).	· Longer duration on medicines was associated with higher adherence rate (OR 1.10, p<0.001).
Chhim et al. 2018, Cambodia (234)	Cross-sectional study, 328 participants, aged 15 to 17 years.	Questionnaires completed by adolescents to identify predictors of adherence such as, parental and caregiver information, social support, duration of treatment, and knowledge about disease and treatment. Adherence rate assessed by self-report.	· Longer duration on medicines more than 9 years (AOR 0.35). · Main caregiver was a relative (OR 0.37). · Did not belief there is a cure for disease (OR 0.40)	Did not report facilitators.
MacCarthy et al. 2018, Uganda (74)	Cross-sectional study, 2 health care providers, 4 patients aged 14 to 24 years.	Questionnaire completed by health care providers and patients. Open-ended questions identified barriers to medicine adherence. Adherence rate assessed by self-report.	· Poverty. · School attendance limited patients' privacy. · Lack family support. · Multi-drugs regimen.	Did not report facilitators.
Bulali et al. 2018, Tanzania (235)	Case series study, 309 Participants, aged 6 to 17 years.	Parents asked:" Does the child know his/her HIV status?" Association between adherence rates and disclosure status was tested. Adherence rate assessed by medication possession ratio (MPR) calculation.	· HIV disclosure was less among male and children aged <10 years (p<0.05).	· HIV disclosure was associated with good adherence (p<0.05). · HIV disclosure was high among female, children aged >10 years, and those living with their biological parents.

B. Asthma

As shown in Table 3-3, twenty five studies identified barriers and facilitators to medicines adherence in patients with asthma (68,87,187,236–244,88,245–249,90,94,122,173–175,186).

- Patient-related factors

The most common barriers to medicines adherence in patients with asthma are patient-related factors reported in twelve studies (87,88,246,249,90,122,186,240–243,245). Eight of these studies reported that children and their parents who lack knowledge about asthma and its treatment are more likely to have poor adherence (87,88,90,186,240,242,246,249). Conversely, children and their parents who have good knowledge about asthma and its treatment are more likely to have good adherence (87,88,240). Another common barrier to adherence in this group is forgetting (87,88,122,241,243,245). Factors affecting forgetting include being away from home and changes in daily routines (243). Measures taken to avoid forgetting to take medicines include the use of reminders, such as notes on the refrigerator and the use of an alarm clock; these efforts were associated with good adherence (87,122,241,243).

- Medicine-related factors

The second most common barriers to medicines adherence in patients with asthma are medicine-related factors reported in nine studies (122,173,175,236,240,242,245,247,248). Some patients and their parents

are concerned about side effects, and they considered medicines as unnecessary in an attempt to avoid any side effects (173,175,242,245,247,248). Children and parents who have weak beliefs on the necessity of medicines use are more likely to have poor adherence (173,175,245,247). Fear of side effects is also associated with poor adherence (242,248). Moreover, complex medicine regimens, such as high dosing frequencies, multidrug administration and evening doses, are associated with poor adherence (122,236,240,245).

- Condition-related factors

Condition-related factors were reported in four studies (68,173,174,240). The severity of asthma is associated with adherence to medicines. For instance, patients with mild asthma are more likely to have poor adherence (68,173,174,240). Klok et al. reported that for patients with mild asthma and parents who believe that medicines may cause harm are less likely to adhere because they do not believe that their child needed treatment (173).

- Healthcare professional and system-related factors

Healthcare professional and system-related factors were reported in four studies (87,88,236,240). A weak relationship between healthcare providers and patients may lead to lack of confidence in healthcare providers and lack of patients' knowledge about their disease and its treatment. Poor communication between healthcare professionals and patients and their parents has been shown to result in non-adherence to medicines (87,88,236,240). According to Mirsadraee et al. if healthcare professionals

fail to provide sufficient information to patients and their parents about their disease and about the efficacy of the treatment, this can result in poor adherence (240). The same study also showed that being visited by several doctors due to an unavailability of doctors or a lack of confidence in doctors are associated with poor adherence (240).

Table 3-3 Studies reporting barriers and facilitators to medicines adherence in patients with asthma. For barriers and facilitators numbers are reported as % or significant association (if no numbers given, numbers not reported in study).

Study	Design	Tools used	Barriers identified	Facilitators identified
Lasmar et al. 2008, Brazil (236)	Cohort study 168 participants Aged 1 to 12 years	Last appointment clinical symptoms, adherence rate, morbidity features, factors that may influence adherence and knowledge about disease were recorded. Adherence rate assessed by MPR calculation.	· Mother's low education level · High frequency doses, (> two sprays/day) · Poor communication with healthcare providers · Absence of allergic rhinitis	Did not report facilitators.
Orrell-Valente et al. 2008, United States (237)**.**	Cross-sectional study, 351 parents of children, aged 4 to 19 years.	Questionnaires completed by parents about socio-demographic information, educational level, family status, symptom control and extent of child responsibility. Association of adherence rates with different factors assessed. Adherence rate assessed by MPR calculation.	· Males less likely to adhere to medicines than females. · Non-white parents reported to have significantly (p<0.05) lower adherence than white parents. · Adolescents had lower adherence rates than younger children.	· Parents solely responsible for medicines. · Females more likely to adhere to medicines.
Burgess et al. 2008, Australia (122)**.**	Cohort study, 51 participants, aged 18 months to 7 years.	Questionnaire completed by caregivers covered asthma symptoms, medicine usage, who was responsible for remembering to take medicine and barriers to adherence. Adherence rate assessed by EMDs.	· Forgetting. · Busy. · High frequency doses. · Taking more than one medicine.	· Using medicines reminder. · Using child-friendly spacer device. · Using less frequent doses.

Study	Design	Tools used	Barriers identified	Facilitators identified
Dellen et al. 2008, Netherlands (239)**.**	Cross-sectional study, 232 participants, aged 7 to 17 years.	Questionnaires completed by children and caregivers: asked about asthma knowledge, motivational factors, socioeconomic information and self-management. Association of adherence rates with different factors assessed. Adherence rate assessed by MPR calculation and self-report.	· Less parent motivation to use inhaled corticosteroids. · Children with less self-efficacy.	· Positive motivation. · Children with high-self-efficacy.
Bracken et al. 2009, United Kingdom (238)	Cohort study, 71 participants, aged 4 to 18 years.	Questionnaires completed by children and parents about: home life, asthma treatment, understanding of treatment and how these factors affect adherence. Adherence rate assessed by self-report.	· Child depression 28%. · Parental depression 28%. · Inappropriate inhaler devices 15%.	Did not report facilitators.
Bin Aref et al. 2011, Lebanon (242)	Cross-sectional study, 389 participants, aged 3 to 15 years.	Questionnaire completed by parents asked about concerns and worries about use of medicine and if they had been educated about asthma and its treatment. Adherence rate not assessed.	· Fear of side effects 56%. · Parents worried that inhaler may cause addiction 48%. · Low socioeconomic status. · Lack of knowledge about asthma and treatment. · Complex medicine regimen. · Weak communication between physician and patient. · Difficulty with inhaler devices.	Did not report facilitators.

Study	Design	Tools used	Barriers identified	Facilitators identified
Koster et al. 2011, Netherlands (175)	Cohort study, 527 participants, aged 4 to 12 years.	Beliefs about Medicines Questionnaire (BMQ) scale completed by parents (table 3.1). Adherence rate assessed by self-report.	· Low parental education level. · Weak parental necessity beliefs about medicine use.	· High parental education level. · Strong parental necessity beliefs about medicine use. · High severity of asthma.
Wamboldt et al. 2011, United States (90)	Cohort study, 26 participants, aged 12 to 20 years.	Questionnaires completed by children about treatment and disease knowledge and barriers to adherence. Adherence rate assessed by self-report.	· Lack of knowledge about asthma and treatment. · Incorrect assumptions about asthma. · More chaotic current life situation.	· Understood importance of daily medicine. · Family support. · Good long-term relationship with provider.
Riekert et al. 2011, United States (244)	Cohort study, 37 participants, aged 10 to 15 years.	Questionnaires completed by children and parents about adherence, motivation, self-efficacy, knowledge and responsibility for treatment. Study assessed adherence before and after motivational interviewing intervention. Adherence rate assessed by self-report.	Did not report barriers.	· Motivational interviewing promoted medicine adherence among adolescents.
Klok et al. 2012, Netherlands (173)	Cohort study, 103 participants, aged 2 to 6 years.	Beliefs about Medicines Questionnaire (BMQ) scale completed by parents (table 3.1). Adherence rate assessed by EMDs.	· Parents of children with mild asthma expected high harm of inhaled corticosteroids (ICS). · Parental perceived medicine necessity was low.	· Parental perceived medicine necessity was high. · Parental expected little harm of ICS.

Study	Design	Tools used	Barriers identified	Facilitators identified
Schultz et al. 2012, Australia (245)	Randomised controlled trial, 220 participants, aged 2 to 6 years.	Questionnaires completed by parents about family and personal history of asthma, asthma symptoms, and reasons for non-adherence. Adherence rate assessed by EMDs.	· Forgetting. · Child refusal. · Too busy. · Thought the child not need medicine. · Evening doses.	Did not report facilitators.
Mirsadraee et al. 2012, Iran (240)**.**	Case series study, 150 participants, aged ≤ 15 years.	Children asked single question about reasons for missing doses. Options given to patients to choose which caused missing dose. Caregivers' knowledge about asthma and treatment, asthma symptoms and education level assessed. Adherence rate assessed by self-report.	· Long term treatment 76.7%. · Patients visited several doctors because lack of confidence in doctor 75.3%. · Complex regimen 72%. · Delayed therapeutic response 43.3%. · Concern about medicine dependency 38.7%. · Costs of medicines 34.7%. · Caregivers' poor knowledge about disease and therapy. · Children with mild asthma symptoms.	· High educational level of caregivers. · Caregivers have good knowledge of disease and therapy. · Children aged >10 years.
Bruzzese et al. 2013, United States (94)	Cohort study, 168 participants, aged 12.01 to 17.25 years.	Adolescents asked to assess factors that associated with adherence and family support. Adherence rate assessed by self-report.	Did not report barriers.	· Family routines around asthma care. · More family sharing and support.
Chan et al. 2015, New Zealand (241)**.**	Randomised controlled trial, 220 participants, aged 6 to 15 years.	Questionnaires completed by caregivers about educational level of caregivers, family size, family status, and other factors that may affect adherence. Adherence rate assessed by EMDs.	· Forgetting. · Male sex. · Large household size.	· Medicines reminder · Female sex.

Study	Design	Tools used	Barriers identified	Facilitators identified
Koster et al. 2015, Netherlands (243)	Cohort study, 192 participants, aged 12 to 16 years.	Participants asked to describe thoughts about asthma, reasons for not using medicines, role of parents, and solutions to improve adherence. Adherence rate assessed by self-report.	· Feeling of being different from other children. · Interfere with daily activity. · Forgetting. · Busy.	· Parents support. · Use of medicine reminder. · Having strategy to remember medicine time such as, taking medicine before school.
Pelaez et al. 2015, Canada (88)	Cohort study, 8 participants, two adolescents ages 15 and 18 years and six parents of children aged 2 to 12 years.	Questionnaire completed by children and parents to explore use of asthma medicines, patients' perceptions of their asthma, self-management, and patient-doctor relationship. Adherence rate assessed by self-report.	· Lack of knowledge about asthma and treatment. · Forgetting. · Lack of motivation. · Poor communication with healthcare providers.	· Having established routines for taking medicine. · Perceiving the necessity of medicine. · Good knowledge about disease and treatment.
Klok et al. 2015, Netherlands (68)	Cohort study, 135 participants, aged 2 to 12 years.	Beliefs about Medicines Questionnaire (BMQ) scale completed by children and parents (table 3.1). Adherence rate assessed by EMDs.	· Patients with poor adherence had mild asthma symptoms. · Child's age not associated with adherence.	· Parent perceived medicine necessity was high. · Parents expected little harm of ICS.
Mosnaim et al. 2015, United States (246)	Randomised controlled trial, 107 participants, aged 11 to 16 years.	Questionnaires completed by children asked about treatment and disease knowledge and barriers to adherence. Adherence rate assessed by MPR calculation.	· Older age. · Male. · Lack of knowledge about asthma and treatment.	Did not report facilitators.

Study	Design	Tools used	Barriers identified	Facilitators identified
Pappalardo et al. 2017, United States (247)	Cross-sectional study, 175 participants, aged 5 to 18 years.	Questionnaires completed by caregivers about asthma medicines, asthma control, medicine technique and caregiver depressive symptoms. Adherence rate assessed by self-report.	· Weak parent-child relationships. · Patient perception of need. · Family beliefs. · Belief that medicine is not necessary. · Cost of medicine.	Did not report facilitators.
Sonney et al. 2017, United States (174)	Cross-sectional study, 34 participants, aged 6 to 11 years.	Beliefs about Medicines Questionnaire (BMQ) scale completed by children and parents (see table 3.1). Adherence rate assessed by self-report.	· Patients with poor adherence had mild asthma symptoms.	· Children beliefs about treatment efficacy. · Parents expected little harm of ICS.
Butz et al. 2017, United States (248)	Cross-sectional study, 222 participants, with mean age 0f 6.4 years.	Caregivers were asked: "How worried or concerned about your child's asthma medications and side effects?" Adherence rate not assessed.	· Fear of side effects.	Did not report facilitators.
RK et al. 2017, India (249)	Cohort study, 53 participants, aged > 5 years.	Questionnaire completed by children and parents. Gender of participants, age, distance from hospital, located in rural or urban area, knowledge about disease, concerns about side effects, treatment duration assessed. Adherence rate assessed by self-report.	· Younger age. · Lack of knowledge about asthma and treatment.	· Older age children had a better adherence · ($p<0.005$). · Good knowledge about asthma and treatment ($p<0.001$).

Study	Design	Tools used	Barriers identified	Facilitators identified
Kuti et al. 2017, Neigeria (186)	Cohort study, 106 participants, aged 2 to 14 years.	Asthma Knowledge Questionnaire scale completed by caregivers (table 3.1). Sociodemographic information obtained. Adherence rate assessed by self-report.	· Low socioeconomic status. · Poor caregivers' knowledge about disease and treatment.	Did not report facilitators.
Holley et al. 2018, United Kingdom (87)	Cohort study, 75 participants, aged 12 to 18 years.	Children and parents asked several questions to explore barriers and facilitators to adherence. Adherence rate not assessed.	· Forgetting. · Burden of treatment. · Lack of knowledge about asthma and treatment. · Feeling embarrassed. · Lack of motivation. · Difficult communication with healthcare professionals.	· Routines and medicines reminder. · Acceptance of asthma and medicine. · Good knowledge about asthma and treatment. · Support from friends. · Good communication with healthcare professionals.
Rhee et al. 2018, United States (187)	Cohort study, 373 participants, aged 12 to 20 years.	Asthma expectation questionnaire scale completed by adolescents (table 3.1). Adherence rate assessed by self-report.	· Younger adolescents. · Lower self-efficacy. · Higher barrier perceptions.	· Older adolescents. · Higher self-efficacy. · Lower barrier perceptions.

C. Kidney or liver diseases and solid organ transplant patients

Table 3-4 shows the nineteen studies which identified barriers and facilitators to medicines adherence in patients with kidney or liver diseases and solid organ transplants (79,91,189,250–257,133,158,159,169–172,188).

- Patient-related factors

The most common barriers to medicines adherence in patients with kidney or liver disease and solid organ transplant were patient-related factors reported in eight studies (91,169,170,172,189,252,254,256). Six of these studies reported that forgetting to take medicine was the most common barrier to medicines adherence (91,169,170,189,254,256). Two studies showed that to avoid forgetting to take medicines, patients used reminders (e.g. alarm watch and notes posted on their fridge door), integrated taking medicines into their daily routines and used a medicines checklist. These practices were associated with good adherence (91,189). Lack of knowledge about a disease and its treatment were associated with poor adherence (170,172,252).

- Medicine-related factors

The second most common barriers to medicines adherence in these patients were medicine-related factors, such as high dosing frequencies (159,169), multidrug regimen (79,188), bad taste (170,254) and difficulty of swallowing medicine (171). In addition, having had an experience of side effects of medicines resulted in non-adherence (171,250,254).

- Socioeconomic-related factors

Other barriers reported in patients with kidney or liver disease and solid organ transplant were socioeconomic-related factors. In the US, patients with public health insurance were less likely to adhere to treatment compared with those who had private health insurance (158,253,257).

Table 3-4 Studies reporting barriers and facilitators to medicines adherence in patients with kidney or liver diseases or solid organ transplant. For barriers and facilitators numbers are reported as % or significant association (if no numbers given numbers not reported in study).

Study	Design	Tools used	Barriers identified	Facilitators identified
Simons et al. 2008, United States (169)	Cohort study, 80 children with solid organ transplant, aged 11 to 21 years.	Medical Adherence Measure (MAM) questionnaire scale completed by adolescents and parents (table 3.1). Adherence rate assessed by self-report and EMDs.	· Forgetting. · Scheduling problems. · Poor planning. · Time and number of dose frequencies. · Attempts to be normal.	Did not report facilitators.
Zelikovsky et al. 2008, United States (170)**.**	Cohort study, 56 children with end-stage renal disease, aged 11 to 18 years.	Medical Adherence Measure (MAM) questionnaire scale completed by adolescents (table 3.1). Adherence rate assessed by self-report and EMDs.	· Poor knowledge of disease and treatment. · Forgetting. · Not at home. · Interferes with activity. · Bad taste.	Did not report facilitators.
Van Herzeele et al. 2009, UK, Canada, Germany, and France (250)	Cohort study, 744 children with nocturnal enuresis, aged 5 to 17 years.	Questionnaires completed by children and parents-open-ended questions to assess medicine efficacy and factors related to poor adherence to medicine. Adherence rate assessed by pill count.	· Long duration of treatment. · Experienced of side effects.	Did not report facilitators.
Simons et al. 2010, United States (171)	Cohort study, 82 children with solid organ transplant, aged 11 to 20 years.	Medical Adherence Measure (MAM) questionnaire scale completed by adolescents (table 3.1). Adherence rate assessed by self-report.	· Disease frustration. · Concerns regarding peers. · Tired of taking the medicine. · Difficulty of swallowing medicine. · Experienced of many side effects.	Did not report facilitators.

Study	Design	Tools used	Barriers identified	Facilitators identified
Wu et al. 2010, United States (251)	Cohort study, 55 children with liver or kidney transplant, aged ≤ 18 years.	Questionnaires completed by children and parents-open-ended questions to assess psychological function, anxiety, and depression symptoms and their influence on adherence. Adherence rate assessed by EMDs.	· Lower level of anxiety.	➢ Higher level of anxiety.
Fredericks et al. 2010, United States (252)	Cohort study, 71 children with liver transplant, aged 11 to 20 years.	Questionnaire completed by adolescents-open questions about self-management, regimen knowledge, demonstrated skills, and psychosocial adjustment. Adherence rate assessed by medicine plasma level and medical records.	· Patients being monitored less by parents. · Lack of knowledge of disease and medicine.	Did not report facilitators.
Vasylyeva et al. 2013, United States (189)	Cohort study, 34 children with chronic kidney diseases, aged 10 to 21 years.	Child & Adolescent Adherence to Medication Questionnaire (CAAMQ) completed by children (table 3.1). Adherence rate assessed by self-report.	· Forgetting. · Weekend. · Bad tasting medicine. · Interfere with daily routine.	· Using reminder. · Pill boxes. · Better tasting medicine.
Blydt-Hansen et al. 2014, Canada (159)	Cohort study, 558 children with chronic kidney diseases, aged 7 to 14 years.	Study based on medical history data, including, sex, age, drug, doses, age of disease, and annual household income. Effect of these on adherence assessed. Adherence rate assessed by self-report.	· Older age. · High doses frequency.	Did not report facilitators.

Study	Design	Tools used	Barriers identified	Facilitators identified
Javalkar et al. 2014, United States (253)	Cohort study, 52 children with chronic kidney diseases, aged 13 to 21 years.	Questionnaire completed by adolescents and parents-open questions about socioeconomics factors related to medicines adherence. Adherence rate assessed by self-report and MPR calculation.	· Younger adolescents. · Patients had public insurance. · Low education level.	· Older adolescents. · Patients had private insurance. · High education level.
Silverstein et al. 2014, United States (188)	Cohort study, 22 children receiving dialysis, aged 13 to 21 years.	Adolescent Medication Barriers Scales (AMBS) completed by adolescents (table 3.1). Adherence rate assessed by self-report.	· Male. · High number of pills prescribed.	· Did not report facilitators.
Claes et al. 2014, Belgium (254)**.**	Cross-sectional study, 18 children had received a liver or kidney transplant, aged ≤ 18 years.	Questionnaire completed by caregivers asked about medicine management in view of time of administration and preparation, regimen complexity and factors negatively or positively affecting medicine intake (barriers and facilitators). Adherence rate assessed by self-report.	· Forgetting 70%. · Vomiting 70%. · Bad taste 60%. · Interfering in routine 60%. · Refusing medicine 50%.	· Using alarms to avoid forgetfulness. · Using a medicine checklist. · Medicine box for medicine storage. · Having a reliable babysitter. · Guidance from health care workers. · Preparing medicine in advance. · Having spare medicine bottle.
Danziger-Isakov et al. 2015, United States (79)	Cross-sectional study, 368 children with solid organ transplant, aged 6 to 21 years.	Brief Medication Questionnaire (BMQ) scale completed by children and parents (table 3.1). Adherence rate assessed by self-report.	· Older age. · Multidrug. · Medicine/disease frustration. · Lack of supervision by family. · Poor family cohesion.	Did not report facilitators.

Study	Design	Tools used	Barriers identified	Facilitators identified
Ramay et al. 2017, Guatemala (255)**.**	Cross-sectional study, 103 children with chronic kidney diseases, mean age 13.5 years.	Questionnaire completed by children-open-ended questions to explore barriers and facilitators to medicines adherence. Adherence rate assessed by self-report.	· Lower socioeconomic status. · Difficulty with access to healthcare services. · Lower educational level of parents.	· Higher educational level of parents. · Higher reported income. · Living in metropolitan areas.
Mehta et al. 2017, United States (91)	Cohort study, 110 healthcare providers of paediatric solid-organ transplant patients. Did not report age.	Questionnaire completed by healthcare providers to evaluate clinical practice, transplant providers' attitudes, and beliefs regarding adherence among children. Adherence rate assessed by self-report.	· Forgetting 94%. · Desire to be normal 86%. · Lack of support 86%. · Poor parental monitoring 79%.	Did not report facilitators.
Varnell et al. 2017, United States (256)	Cohort study, 97 children with kidney transplant, aged 1 to 24 years.	Questionnaires completed by patients and caregivers-open questions about barriers to treatment adherence. Adherence rate assessed by self-report.	· Forgetting. · Bad taste. · Experienced side effects.	Did not report facilitators.
Lee et al. 2017, United States (172)	Cohort study, 78 children waiting solid organ transplant, aged 0 to 20 years	Medical Adherence Measure (MAM) questionnaire scale completed by caregivers (table 3.1). Adherence rate assessed by self-report.	· Greater time since patient's diagnosis. · Lower levels of medicine knowledge.	Did not report facilitators.

Study	Design	Tools used	Barriers identified	Facilitators identified
Killian et al. 2017, United States (257)	Cohort study, 105 children heart and lung transplant recipients. Aged 0 to 18 years.	Psychological and family demographic information collected through first year post-transplant treatment notes. Effect on adherence assessed. Adherence rate assessed by medicine plasma level.	· Older age. · Experience of childhood maltreatment. · Families with psychosocial problem. · Difficulties with familial communication.	· Parental education of a college degree or more. · Two parents in home. · Families had at least adequate financial resources. · Families had private insurance.
Shemesh et al. 2018, United States (158)	Cohort study, 400 children with liver transplant, aged 1 to 17 years.	Study based on patient medical chart to assess adherence, socioeconomic factors, and effect of age and length of treatment on adherence. Effect on adherence assessed. Adherence rate assessed by medicine plasma level.	· Older age. · One parent households. · Patient who had public health insurance. · Length of treatment did not affect adherence.	· Younger age. · Two parent households. · Patient who had private health insurance.
Almardini et al. 2019, Norther Ireland and Jordan (133)**.**	Cross- sectional study 33 participants with kidney transplant Ages ≤ 18 years	Beliefs about Medicines Questionnaire (BMQ) scale was completed by children and parents (table 3.1). Adherence rate assessed by self-report and pharmacy refill data.	· Presence of side effects. · Males were more likely to be non-adherent.	· Females were more likely to be adherent.

D. Psychiatric disorders

As shown in Table 3-5, thirteen studies identified barriers and facilitators to medicines adherence in patients with psychiatric disorders (81,89,263–265,160,161,179,258–262).

- Medicine-related factors

The most common reported barriers to adherence in patients with psychiatric disorders were medicine-related factors in nine studies (81,89,161,258,259,261–264). Low beliefs on the necessity of medicine were associated with poor adherence in three studies (81,259,264). Conversely, high beliefs on the necessity of medicine were associated with good adherence (89,258,259,261,264).

Poor adherence to treatment was associated with complex medicine regimens, such as multidrug administration and high dosing frequencies (81,89,161,262), and bad taste (259). Fear of side effects (89,263) or having had an experience of side effects (262) also resulted in non-adherence to medicine.

- Socioeconomic-related factors

The second most common barriers to medicines adherence in patients with psychiatric disorders were socioeconomic-related factors. Patients may be ashamed if other people know that they are taking psychiatric medicines (263). Three studies showed that fear of stigma and discrimination was associated with poor adherence (81,89,263).

- Patient-related factors

Medicines taking responsibilities are different among children, which affects adherence. Two studies showed that children were less likely to adhere to medicines when they are responsible for medicine taking without their parents' assistance (179,261).

Table 3-5 Studies reporting barriers and facilitators to medicines adherence in patients with psychiatric disorders. For barriers and facilitators numbers are reported as % or significant association (if no numbers given numbers not reported in study).

Study	Design	Tools used	Barriers identified	Facilitators identified
Munson et al. 2010, United States (258)	Cohort study, 70 adolescents receiving psychotropic medicines, aged 12 to 17 years.	Adolescents' demographic and clinical characteristics assessed. Questionnaire completed by adolescents to assess perceptions toward disease and treatment. Adherence assessed by self-report.	· Younger adolescents (p<0.05). · Low family income (p<0.01).	· High education level (p<0.01). · Positive attitudes towards treatment (p<0.05). · Perception that their disease may have serious consequences (p<0.05).
Dean et al. 2011, Australia (179)	Cohort study, 27 children receiving psychotropic medicines, aged 6.9 to 18.9 years.	Brief Medication Questionnaire (BMQ) scale completed by children and parents (table 3.1). Adherence assessed by self-report.	· Lack of parental involvement in medicine taking. · Forgetting.	· Involvement of a parent in medicine taking.
Fontanella et al. 2011, United States (160)	Cohort study, 27 children diagnosed with depression, aged 5 to 17 years.	Demographic factors, clinical factors, and medical regimen factors identified from medical records and effect on adherence assessed. Adherence assessed by MPR calculation.	· Older age. · Ethnic disparities in access to and quality of mental health care for minority population.	· Adequate dosing of antidepressants. · Children in foster care had higher adherence rates.
Coletti et al.2012, United States(89)	Cohort study, 27 parent of children diagnosed with ADHD, aged 5 to 12 years.	Questionnaire completed by parents. Open-ended questions identified barriers and facilitators. Adherence assessed by self-report.	· Fears of personality changes. · Fears of side effects. · Complex medicine regimen. · Fear of stigma and discrimination.	· High levels of self-efficacy. · Parent beliefs that treatment was imperative for children's safety.

Study	Design	Tools used	Barriers identified	Facilitators identified
Hebert et al. 2013, Canada (259)	Cohort study, 33 children with ADHD, mean age 8.7 years.	Questionnaire completed by children and parents to assess severity of disease symptoms, and attitudes towards medicine. Adherence assessed by self-report.	· Lower parental beliefs about necessity of medicine. · Lower child's beliefs about necessity of medicine. · Fear of stigma and discrimination. · Low medicine acceptability.	· Higher parental beliefs about necessity of medicine. · Higher child's beliefs about necessity of medicine.
Logan et al. 2014, United States (161)	Cohort study, 525 autism spectrum disorders diagnosed children. Age not reported.	Study based on medical records of patients to determine predictor of adherence to medicines. Adherence assessed by MPR calculation.	· Medicine regimen complexity most common barrier to medicine adherence.	· Male sex. · Non-Hispanic whites more adherent than minorities.
Nagae et al. 2015, Japan (260)	Cross-sectional study, 30 children with psychiatric disorders, aged 7 to 17 years.	Questionnaire completed by children and parents assessed children's trust in their parents and parents' trust in their children's medicine and effect on adherence. Adherence assessed by self-report.	Did not report barriers	· Parent felt that their child's condition improved with medicines. · Children trust their parent ($p<0.05$).
Ramdour et al. 2015, United Kingdom (261)	Cross-sectional study, 60 healthcare professionals of children diagnosed with first episode psychosis. Age not reported.	Questionnaire completed by healthcare professionals identified barriers and facilitators. Participants given a list of barriers and facilitators to	· Fear of side effects 87%. · Children were responsible for medicine taking 78%.	· Medicines will make them better 93%. · Good relation with staff 85%. · Medicine will prevent relapse 83%.

Study	Design	Tools used	Barriers identified	Facilitators identified
		adherence and asked to tick factors that may affect adherence. Adherence assessed by self-report.	· Not trusting treatment 71%. · Fear of stigma 59%. · Family do not think their child is ill 58%.	· Family support 67%.
Goldstein et al. 2016, United States (262)	Cohort study, 21 adolescents with bipolar disorder. Aged 12 to 22 years.	Questionnaire completed by adolescents to assess: illness specific factors, patient factors, treatment factors, provider factors and developmental factors that may cause poor adherence. Adherence assessed by self-report and EMDs.	· Greater disease severity. · Adolescents who weighed more. · Experienced side effect. · High daily dosing.	Did not report facilitators.
Emilsson et al. 2017, Sweden (81)	Cross-sectional study, 101 children with ADHD, mean age 15.6 years.	Beliefs about Medicines Questionnaire (BMQ) scale completed by children (table 3.1). Adherence assessed by self-report.	· Forgetting. · Longer duration on treatment. · Dosage alterations. · Experienced side effects. · Lower of belief in necessity of medicine.	Did not report facilitators.
Ahmed et al. 2017, Australia (263)	Cohort study, 16 parents of children with ADHD. Age of children not reported. Study mentioned that targeted children population.	Questionnaire completed by parents to assess adherence to medicine and explore impact of positive and negative experience on adherence. Adherence rate not assessed.	· Experienced side effects. · Concern about long-term consequences of medicine. · Fear of stigma.	Did not report facilitators.

Study	Design	Tools used	Barriers identified	Facilitators identified
Zehgeer et al. 2018, United States (264)	Cohort study, 349 children with anxiety disorder. Aged 7 to 17 years.	Questionnaire completed by children and parents to discuss anxiety symptoms, treatment response, functioning, side effects, and influences on adherence. Adherence assessed by self-report.	· Children living with single parent. · Lower parental beliefs about necessity of medicine. · Lower child's beliefs about necessity of medicine.	· Children living with two parents. · Higher parental beliefs about necessity of medicine. · Higher child's beliefs about necessity of medicine.
Safavi et al. 2019, Iran (265)	Cross-sectional study, 118 children with ADHD, aged 6 to 12 years.	Beliefs about Medicines Questionnaire (BMQ) scale completed by parents (table 3.1). Demographic information obtained. Adherence rate assessed by self-report.	· Low paternal education level. · Low socioeconomic status. · History of psychopharmacologic treatment in family.	Did not report facilitators.

E. Inflammatory bowel diseases (IBD)

As shown in Table 3-6, eleven studies identified barriers and facilitators to medicines adherence in patients with IBD (34,134,268,164–168,176,266,267).

- Medicine-related factors

The most common barriers to medicines adherence in patients with IBD were medicine-related factors reported in eight studies (164–168,266–268). Low beliefs on the necessity of medicine were associated with poor adherence (164–167,267). Two studies showed that poor adherence to treatment is associated with complex medicine regimens, bad taste and large pill size (266,268). Reed-Knight et al. reported that a long duration of treatment was significantly associated with poor adherence (p<0.05) (168).

- Patient-related factors

The second most common barriers to medicines adherence in patients with IBD were patient-related factors. Six studies reported that forgetting and being outside the home resulted in poor adherence to medicines (164–167,266,268).

- Condition-related factors

Condition-related factors such as the severity of IBD were reported as a common barrier to adherence. Five studies showed that patients who feel ill were less likely to adhere to medicines (164–167,267).

Table 3-6 Studies reporting barriers and facilitators to medicines adherence in patients with IBD. For barriers and facilitators numbers are reported as % or significant association (if no numbers given numbers not reported in study).

Study	Design	Tools used	Barriers identified	Facilitators identified
Kitney et al. 2009, Canada (266)	Cross-sectional study, 74 participants, mean age 13.2 years.	Questionnaire completed by children. Participants given list of barriers to adherence and asked to tick factors they have faced. Adherence rate assessed by self-report.	· Forgetting 56%. · Too busy 55.6%. · Uncomfortable with prescribed enemas 18.2%. · Difficult to swallow medicine 17.8%. · Too many medicines 13.4%.	Did not report facilitators.
Ingerski et al. 2009, United States (164)**.**	Cohort study, 74 participants, aged 13 to 17 years.	Medical Adherence Measure (MAM) questionnaire scale completed by caregivers (table 3.1). Adherence rate assessed by self-report and pill count.	· Forgetting 87.8%. · Outside home 47.3%. · Interference with activity 44.6%. · Refused to take medicine 17.6%. · Didn't fill/ran out 16.2%. · Feeling sick 16.2 %. · Belief that medicine is not necessary 14.9%.	Did not report facilitators.
Hommel et al. 2009, United States (165)**.**	Cohort study, 16 participants, aged 13 to 17 years.	Medical Adherence Measure (MAM) questionnaire scale completed by caregivers (table 3.1). Adherence rate assessed by self-report and pill count.	· Forgetting 87.5%. · Was not in home 75%. · Interference with activity 68.8%. · Refusal/defiance 25%. · Feeling sick 25%. · Didn't fill/ran out 18.8%. · Belief that medicine is not necessary 12.5%.	Did not report facilitators.
Greenley et al. 2010, United States (267)	Cross-sectional study, 64 participants, aged 11 to 18 years.	Questionnaire completed by adolescents and parents.	· Lack of time 33% of adolescents and 32% of parents. · Feeling sick 16% of adolescents and 7% of parents.	Did not report facilitators.

Study	Design	Tools used	Barriers identified	Facilitators identified
		Participants given list of barriers to adherence and asked to tick factors they have faced. Adherence rate assessed by self-report.	· Experienced side effects 14% of adolescents and 20% of parents. · Medicine was ineffective 14% of adolescents and 13% of parents.	
Reed-Knight et al. 2011, United States (168)	Cross-sectional study, 90 participants, aged 11 to 18 years.	Questionnaire completed by adolescents to explore factors affecting adherence and test association to adherence rates. Adherence rate assessed by self-report.	· Long duration of treatment (p<0.01). · Parent-adolescent conflict (p<0.001). · Lack of motivation (p=0.02).	· Higher perceived disease severity (p=0.01). · Maternal involvement in the treatment (p<0.01).
Hommel et al. 2011, United States (268)	Cross-sectional study, 16 participants, aged 13 to 17 years.	Questionnaire completed by children and parents to explore factors affecting medicines adherence. Adherence rate assessed by self-report.	· Forgetting. · Complex regimen. · Weak parent-child relationship. · Lack knowledge about disease and treatment.	· Family support. · Good parent-child relationship. · Using medicines reminder.
Hommel et al. 2011, United States (166)	Cohort study, 62 participants, aged 13 to 17 years.	Medical Adherence Measure (MAM) questionnaire scale completed by caregivers (table 3.1). Adherence rate assessed by self-report.	· Forgetting 85.5%. · Not at home 43.5%. · Interfere with activity 38.7%. · Feeling sick well 14.5%. · Ran out/didn't fill 14.5%. · Bad taste 12.9%. Don't think necessary 12.9%.	Did not report facilitators.
Gray et al. 2012, United States (167)**.**	Cohort study, 79 participants, aged 13 to 17 years.	Medical Adherence Measure (MAM) questionnaire scale completed by caregivers (table 3.1). Adherence rate assessed by self-report.	· Forgetting 84.8%. · Was not in home 43%. · Interference with activity 34.2%. · Didn't fill/ran out 15.3%. · Hate taste 12.7%. · Feeling sick well 12.7%. · Refusal/defiance 11.4%. Do not think necessary 10.1%.	Did not report facilitators.

Study	Design	Tools used	Barriers identified	Facilitators identified
LeLeiko et al. 2013, United States (34)	Cohort study, 62 participants, aged 8 to 17.5 years.	Demographic factors, clinical factors, and medical regimen factors were identified, based on medical records. Adherence rates are compared with different factors. Adherence rate assessed by EMDs.	· Only older age was significantly associated with poor adherence (p<0.05).	Did not report facilitators.
Jeganathan et al. 2017, Australia (176)	Cross-sectional study, 79 participants, aged 12 to 25 years.	Beliefs about Medicines Questionnaire (BMQ) scale completed by children (table 3.1). Adherence rate assessed by self-report.	· Young adults (12-18 years) had lower adherence than transitioned patients (18- 25 years). · More concerns about medicines in young adult patients.	Did not report facilitators.
Alsous et al. 2020, Norther Ireland and Jordan (134)**.**	Cross- sectional study 47 participants Ages 13-17 years	Beliefs about Medicines Questionnaire (BMQ) scale completed by children and parents (table 3.1). Adherence rate assessed by self-report and plasma level.	· Higher scores in the concern-necessity differential.	· Higher scores in the necessity-concern differential.

F. Epilepsy

Table 3-7 shows the ten studies which identified barriers and facilitators to medicines adherence in patients with epilepsy (126,177,190,269–275).

- Socioeconomic-related factors

The first most common barriers to medicines adherence in patients with epilepsy were socioeconomic-related factors as reported in nine studies (126,177,190,269–274). Economic status could affect therapy depending on the level and the type of therapy, especially when medicines were not free (271). Five studies conducted in the US, Uganda and Pakistan showed that lack of money was a common barrier to adherence (190,269–272). Several other social factors were reported to be associated with poor adherence including divorce of parents (177,269), parental depression (126), large family size (177) and fear of stigma and discrimination (273,274).

- Medicine-related factors

The second most common barrier to adherence in patients with epilepsy were medicine-related factors as reported in six studies (126,177,270,271,273,274). Three of these studies showed that fear of side effects was associated with poor adherence (177,270,271). In addition, Shah et al. found that patients and their parents with low beliefs on the necessity of medicine were more likely to have poor adherence to medicines (OR 1.08-1.57) (126). Two studies showed that poor adherence to

treatment was associated with multidrug administration (177,271), bad taste and large pill size (273,274).

- Patient-related factors

Patient-related factors such as forgetting were shown in four studies to result in non-adherence (177,270,273,274). Among these studies, one study showed that the use of medicine reminders, such as an alarm watch, is associated with good adherence (270).

Table 3-7 Studies reporting barriers and facilitators to medicines adherence in patients with epilepsy. For barriers and facilitators numbers are reported as % or significant association (if no numbers given numbers not reported in study).

Study	Design	Tools used	Barriers identified	Facilitators identified
Modi et al. 2008, United States (269)	Cohort study, 35 participants, aged 2 to 12 years.	Questionnaire completed by parents: child's age, gender, socioeconomic status, parent's age, occupation, and composition of family. Effect of these on adherence assessed. Adherence rate assessed by EMDs.	· Children of divorced parents. · Low socioeconomic status.	· Children of married parents. · High socioeconomic status.
Shah et al. 2013, United Kingdom (126)	Cohort study, 100 participants, aged 0.9 to 16 years.	Beliefs about Medicines Questionnaire (BMQ) scale completed by children and parents (table 3.1). Adherence rate assessed by EMDs, self-report, and medicine plasma level.	· Older age (OR 1.03-1.4). · Parent depressed (OR 1.16-11.41). · Lower belief on medicine necessity (OR 1.08-1.57).	Did not report facilitators.
Nazziwa et al. 2014, Uganda (270)**.**	Cross-sectional study, 122 participants, aged 6 months to 16 years.	Questionnaire completed by children-open-ended questions to explore barriers and facilitators. Adherence rate assessed by self-report, and medicine plasma level.	· Caregivers having a job (did not have time to care for children). · Lack of money. · Forgetting. · Fear of side effects.	· Having a primary caregiver other than the mother. · Medicine reminder such as an alarm watch.
Gaber et al. 2014, Saudi Arabia (177)	Cohort study, 116 participants, aged 13 to 18 years.	Beliefs about Medicines Questionnaire (BMQ) and Morisky Medication adherence Scale (MMAS) completed by	· Forgetting. · Fear of side effects. · High number of medicines.	Did not report facilitators.

Study	Design	Tools used	Barriers identified	Facilitators identified
		adolescents (table 3.1). Demographic information obtained. Adherence rate assessed by EMDs, self-report.	· Divorced parents. · Large family size. · Stronger concern about medicine consequences.	
Malik et al. 2015, Pakistan (271)**.**	Cross-sectional study, 120 participants, aged ≤ 18 years.	Questionnaire completed by caregivers and professionals. Open-ended questions identified barriers and facilitators. Adherence rate assessed by self-report.	· Fear of side effects. · Lack of continuous supply of antiepileptic drugs because family did not have enough money. · Lower socioeconomic status. · Multi-drug. · Caregivers and children have poor knowledge of adherence and therapy.	· Monotherapy. · Caregivers and children have good knowledge of adherence and therapy. · Good socioeconomic status.
Paschal et al. 2016, United States (272)	Cross-sectional study, 146 participants, aged 1 to 12 years.	Questionnaire completed by parents-open-ended questions related to adherence, missed doses, missed appointment, seizure frequency, socioeconomic status, and health literacy. Adherence rate assessed by self-report.	· Inadequate parent health literacy · Lack of money. · Older children. · Children without health insurance.	Did not report facilitators.
Ramsey et al. 2017, United States (273)	Cohort study, 48 participants, aged 2 to 12 years.	Questionnaire completed by caregivers and children-open-ended questions identified barriers to adherence. Adherence rate assessed by EMDs.	· Taste of medicine. · Forgetting. · Child refusal. · Difficulty getting to pharmacy. · Fear of stigma and discrimination. · Difficulty swallowing medicines.	Did not report facilitators.

Study	Design	Tools used	Barriers identified	Facilitators identified
Smith et al. 2018, United States (190)	Cohort study, 48 participants, aged 13 to 17 years.	Paediatric Epilepsy Medication Self-Management Questionnaire scale completed by adolescents and Paediatric Epilepsy Side Effects Questionnaire scale completed by adolescents (table 3.1). Parental Environment Questionnaire scale completed by parents (table 3.1). Adherence rate assessed by EMDs.	· Family conflict. · Lower socioeconomic status. · Experienced with side effects. · Long treatment duration.	· Less family conflicts. · Higher socioeconomic status.
Gutierrez-colina et al. 2018, United States (274)	Cohort study, 77 participants, aged 5 to 25 years.	Questionnaire completed by caregivers and adolescents- open-ended questions identified barriers to adherence. Adherence rate assessed by EMDs.	· Taste of medicine. · Forgetting. · Child refusal. · Difficulty getting to pharmacy. · Fear of stigma and discrimination. · Difficulty swallowing medicines.	Did not report facilitators.
Alsous et al. 2018, Jordan(275)	Cross-sectional study, 63 participants, aged 1.5 to 18 years.	Beliefs about Medicines Questionnaire (BMQ) scale completed by parents (table 3.1). Adherence rate assessed by self-report.	· More concern about side effects. · Low beliefs of medicine necessity.	Did not report facilitators.

G. Studies conducted with patients with different diseases

As shown in Table 3-8, six studies identified barriers and facilitators to medicines adherence in patients with different diseases (85,92,162,276–278).

Medicine-related factors were the most common barriers to medicines adherence including fear of side effects (85), bad taste of medicine (85,92) and difficulty with inhaler medicine devices (277). Venables et al. reported that patients who were taking medicines with bad taste or with high dose frequencies were more likely to refuse their medicines and have poor adherence ($p<0.001$) (92).

Table 3-8 Studies reporting barriers and facilitators to medicines adherence in patients with different diseases. For barriers and facilitators numbers are reported as % or significant association (if no numbers given numbers not reported in study).

Study	Design	Tools used	Barriers identified	Facilitators identified
Fischer et al. 2010, United States (162)	Cohort study, 9417 children with various diseases, aged 0 to 18 years.	E-prescribing data of patients included information on prescribing clinician, patient, prescription date, dosage form, medicine name and insurance plan. Adherence rate assessed by MPR calculation.	· Medicines were prescribed by general physician (not paediatrician). Poor adherence was common for newly prescribed medicines.	Did not report facilitators.
Elliott et al. 2013, United Kingdom (85)	Cohort study, 18 children with asthma, heart disease, diabetes, and epilepsy, aged 10 to 17 years.	Questionnaires completed by professionals, children, and caregivers about issues around medicine-taking in children. Adherence rate not assessed.	· Forgetting. · Interference with routine.	· Reminder device. · Having routine related to medicine administration.
Bryson et al. 2014, United Kingdom (276)	Cohort study, 70 children with various diseases, aged 3 to 11 years.	Questionnaires completed by children, professionals, and caregivers about issues around medicine-related factors. Adherence rate assessed by MPR calculation. 82% of children who took ≤ two different medicines each week were adherent. 73% of children who took ≥ three medicines each week were non-adherent.	· Taste of medicine especially in younger children. · Complexity of the medicines' regimen.	· Medicines with good taste. · Simple medicines regimen.

Study	Design	Tools used	Barriers identified	Facilitators identified
Venables et al. 2015, United Kingdom (92)	Cohort study, 57 children aged 12-18 years and 221 carers/parents of children with various diseases and administered oral formulations.	13-item questionnaire completed by children and parents with questions to explore barriers to adherence. Adherence rate assessed by self-report.	· Bad taste (p<0.001) · Volume or quantity of medicine (p<0.001). · Texture of medicine (p = 0.017). · Difficulty with swallowing. · Smell and colour of medicine.	Did not report facilitators.
Venables et al. 2015, United Kingdom (278)	Cohort study, 27 healthcare providers.	Focus groups to discuss barriers to medicine adherence (oral formulations barriers). Information recorded during sessions. Adherence rate not assessed.	· Bad taste. · Texture of medicine. · Difficulty with swallowing. · Smell and colour of medicine.	Did not report facilitators.
Venables et al. 2016, United Kingdom (277)	Cohort study, 29 children diagnosed with different diseases and administered non-oral formulations, aged 0 to 17 years.	13-item questionnaire completed by children and parents with questions to explore barriers to adherence. Adherence rate assessed by self-report.	· Difficulty with spacer for inhaled devices in patients with asthma 38%. · Disliking parenteral formulations 38%. · Greasy texture of topical medicines. · Large dose of nasal medicines. · Difficulty with an ocular ointment.	Did not report facilitators.

H. Sickle cell disease

As shown in Table 3-9, five studies identified barriers and facilitators to medicines adherence in patients with sickle cell disease (180,191,279–281).

Patient-related factors were the most common barriers to medicines adherence. Three studies reported that forgetting or lack of time are reasons for non-adherence to medicines (191,279,280). In addition, three studies reported that patients using medicine reminders such as receiving daily text messages and established daily routines related to medicine taking were more likely to have good adherence (191,280,281). Klitzman et al. reported that having an established routine related to medicine taking and family support were associated with good adherence ($p<0.05$) (281).

Table 3-9 Studies reporting barriers and facilitators to medicines adherence in patients with sickle cell disease. For barriers and facilitators numbers are reported as % or significant association (if no numbers given numbers not reported in study).

Study	Design	Tools used	Barriers identified	Facilitators identified
Modi et al. 2009, United States(191)	Cross-sectional study, 71 participants, aged 6 to 18 years.	Disease Management and Barriers Interview-Sickle Cell Disease scale completed by adolescents and caregivers (table 3.1). Adherence rate assessed by self-report.	· Fear of stigma 57%. · Multiple medicines 43%. · Forgetting 29%. · Treatment discomfort 29%. · Lack of time 29%.	· Medicine reminder 38%. · Physician emphasis 25%.
Inoue et al. 2016, United States (279)	Cohort study, 19 participants, aged 2 to 21 years.	Questionnaire completed by caregivers or patients about disease knowledge, barriers to adherence, and beliefs about treatment. Adherence rate assessed by EMDs.	· Absence of medicine delivery to the home 74%. · Forgetting 68%.	Did not report facilitators.
Badawy et al. 2016, United States (280)	Cross-sectional study, 80 participants, aged 12 to 22 years.	Questionnaire completed by patients-4 items of questions were about daily medicines and barriers to adherence. Adherence rate assessed by self-report.	· Forgetting 67%. · Lack of time 23%. · Being overwhelmed 23%.	· Medicine reminder 94%. · Disease education 89%. · Medicine education 88%.
Badawy et al. 2017, United States (180)	Cross-sectional study, 34 participants, aged 12 to 22 years.	Brief Medication Questionnaire (BMQ) scale completed by children and parents (table 3.1). Adherence rate assessed by self-report.	· Worse pain (p=0.02). · Fatigue (p=0.05). · Depression (p=0.05).	Did not report facilitators.

Study	Design	Tools used	Barriers identified	Facilitators identified
Klitzman et al. 2018, United States (281)	Cross-sectional study, 85 participants, aged 8 to 18 years.	Questionnaire completed by patients and parents to assess family communication, child routines, family problem-solving, and demographic information. Adherence rate assessed by self-report.	Did not report barriers	· Established routine related to medicine administration ($p<0.05$). · Family support ($p<0.05$).

I. Cystic Fibrosis

As shown in Table 3-10, four studies identified barriers and facilitators to medicines adherence in patients with cystic fibrosis diseases (178,282–284).

- Medicine-related factors

The most common barriers to medicines adherence in patients with cystic fibrosis were medicine-related factors. Low beliefs on the necessity of medicine were reported to be associated with poor adherence (178,283,284). In addition, two studies reported that high beliefs on the necessity of medicine were associated with good adherence (178,284).

- Patient-related factors

The second most common barriers to medicines adherence in patients with cystic fibrosis were patient-related factors. Two studies reported that lack of time and forgetting were reasons for non-adherence to medicine (282,284). Sawicki et al. reported that having a routine related to medicines administration was associated with good adherence (284).

Table 3-10 Studies reporting barriers and facilitators to medicines adherence in patients with cystic fibrosis diseases. For barriers and facilitators numbers are reported as % or significant association (if no numbers given numbers not reported in study).

Study	Design	Tools used	Barriers identified	Facilitators identified
Bregnballe et al. 2011, Denmark (282)	Cohort study, 146 participants, aged 14 to 25 years.	Questionnaire completed by participants and parents to explore reasons for non-adherence, and family status. Adherence rate assessed by self-report.	· Forgetting 35%. · Lack of time 35%. · Too tired to take medicine 22%.	Did not report facilitators.
Goodfellow et al. 2015, United Kingdom (178)	Cross-sectional study, 100 participants, aged ≤ 18 years.	Beliefs about Medicines Questionnaire (BMQ) scale completed by parents (table 3.1). Adherence rate assessed by self-report and MPR calculation.	· Older age. · More concern about side effects. · Low beliefs of medicine necessity.	· High beliefs of medicine necessity.
Hilliard et al. 2015, United States (283)	Randomised controlled trial, 128 participants, aged 16 and older.	Questionnaire completed by participants assessing: medicine beliefs, motivation, self-efficacy, and perceived importance. Adherence rate assessed by MPR calculation.	· High depressive symptoms. · Low beliefs of medicine necessity. · Less self-efficacy. · Less motivation.	· High severity of disease.
Sawicki et al. 2015, United States (284)	Cohort study, 18 participants, aged 16 to 21 years.	Questionnaire completed by participants focused on: readiness of self-care, living with disease as an adult, barriers, and facilitators to adherence. Adherence rate assessed by self-report.	· Lack of time. · Being too busy. · Fear of stigma and discrimination. · Low beliefs of medicine necessity.	· High beliefs of medicine necessity. · Good relationship with care provider. · Being treated as adult. · Having routine related to medicine administration.

J. Diabetes

As shown in Table 3-11, four studies identified barriers and facilitators to medicines adherence in patients with diabetes (95,182,285,286).

Patient related factors were the most common barriers to medicines adherence. Three studies reported that lack of family support was associated with poor adherence (95,182,285). In addition, good family support was associated with good adherence (95,182).

Table 3-11 Studies reporting barriers and facilitators to medicines adherence in patients with diabetes. For barriers and facilitators numbers are reported as % or significant association (if no numbers given numbers not reported in study).

Study	Design	Tools used	Barriers identified	Facilitators identified
Saletsky et al. 2014, United States (285)	Cohort study, 137 type 2 diabetes diagnosed children, aged 10 to 17 years.	Questionnaire completed by children and parents. Open-ended questions to assess diabetes self-care, parent-youth conflict, and its' effect on adherence. Adherence rate assessed by pill count.	· Parents using more controlling style to their child towards diabetes. · Lack of family support.	· Adolescents with high responsibility about diabetes treatments.
Lancaster et al. 2015, United States (182)	Cohort study, 53 type 1 diabetes diagnosed children, aged 8 to 18 years.	Diabetes Family Responsibility Questionnaire (DFRQ) completed by children and parents (table 3.1). Adherence rate assessed by glucose plasma level.	· Lack of family support. · Child-parent disagreement regarding treatment responsibility.	· Child-parent agreement regarding treatment responsibility. · Family support.
Katz et al. 2016, United States (286)	Cohort study, 699 type 2 diabetes diagnosed children, aged 10 to 17 years.	At each consultation visit, study staff discussed and evaluated adherence and factors that may affect adherence with the participant. Adherence rate assessed by pill count.	· Depression symptoms (p<0.05).	Did not report facilitators.
Venditti et al. 2018, United States (95)**.**	Cohort study, 525 type 2 diabetes diagnosed children, aged 10 to 17 years.	Questionnaire completed by caregivers and professionals. Open-ended questions identified barriers and facilitators. Adherence rate assessed by pill count.	· Forgetting. · Being outside home. · Interference with activity. · Pill burden. · Lack of family support.	· Family help and support. · Uses routine or schedules. · Reminder device. · Caregivers and children have good knowledge of adherence and therapy.

K. Tuberculosis

As shown in Table 3-12, four studies identified barriers and facilitators to medicines adherence in patients with tuberculosis (287–290).

Medicine-related factors were the most common barriers to medicines adherence. Several factors related to medicine were reported to cause poor adherence such as experienced side effects (p<0.05) (287), fear of side effects (288), dosing errors and complexity of the medicine regimen (290).

Table 3-12 Studies reporting barriers and facilitators to medicines adherence in patients with tuberculosis. For barriers and facilitators numbers are reported as % or significant association (if no numbers given numbers not reported in study).

Study	Design	Tools used	Barriers identified	Facilitators identified
Chang et al. 2014, United States (287)	Cohort study, 1587 children, aged 0 to 18 years.	Questionnaire completed by children and parents. Factors associated with failure to adherence including side effects, sex, age, and reasons for missing doses assessed. Adherence rate assessed by pill count.	· Aged 15-18 years (p<0.05). · Development of hepatitis (p<0.05). · Experienced side effects (p<0.05).	Did not report facilitators.
Yusuf et al. 2015, Ethiopia (288)	Cross-sectional study, 126 children, aged < 16 years.	Study based on retrospective data conducted by reviewing patient medical chart and patient's registration book. Adherence rate assessed by MPR calculation.	· Fear of side effects 28.6% of participants. · Feeling better 16.48% of participants. · Forgetting 4.39% of participants. · Weak physician-patient communication.	· Caregivers and children have good knowledge of adherence and therapy. · Good physician-patient communication. · High quality of service.
Lopez-Varela et al. 2016, Mozambique (289)	Cohort study, 50 children, aged < 3 years.	Clinical data obtained at every clinical visit. Other socio-demographic data obtained by patient medical records. Adherence rate assessed by MPR calculation.	· Malnutrition (p<0.05). · History of migrant mother (p<0.05).	Did not report facilitators.
Chiang et al. 2017, Peru (290)	Cohort study, 53 healthcare providers and parents of children aged 0 to 19 years.	Questionnaire completed by healthcare providers and parents to identify barriers to treatment. Adherence rate assessed by self-report.	· Dosing errors. · Time, preparation, and administration of medicines. · Providers concern that isoniazid resistance may result from isoniazid preventive therapy.	Did not report facilitators.

L. Chronic rheumatic diseases

As shown in Table 3-13, three studies identified barriers and facilitators to medicines adherence in patients with chronic rheumatic disease (291–293).

Patient-related factors were the most common barriers to medicines adherence. Several factors related to patients were reported to cause poor adherence such as forgetting (291,292), children being responsible for medicines management (293) and children refusing to take medicine (291,292). In addition, other factors were associated with good adherence such as using medicine reminders (291) and caregivers being responsible for medicines management (p<0.0015) (293).

Table 3-13 Studies reporting barriers and facilitators to medicines adherence in patients with chronic rheumatic disease. For barriers and facilitators numbers are reported as % or significant association (if no numbers given numbers not reported in study).

Study	Design	Tools used	Barriers identified	Facilitators identified
Erica et al. 2011, United States (291)	Cross-sectional study, 52 adolescents with chronic rheumatic disease, aged 13 to 20 years.	Questionnaire completed by adolescents to explore reasons for missing medicines. Adherence rate assessed by self-report.	· Forgetting 54%. · Running out of medicine 10%. · Child refused the medicine 10%.	· Using medicines reminder 80%.
Pelajo et al. 2012, United States and Brazil (292)	Cross-sectional study conducted in two sites, 76 children with arthritis, 50 in Rio de Janeiro and 27 in Boston aged 1 to 17 years.	Questionnaire completed by children > 12 years and parents to identify barriers to adherence. Participants given list of barriers to adherence and asked to tick factors they have faced. Adherence rate assessed by self-report.	· Child refused the medicine 50% in Boston. · Fear of side effects 25% in Boston and 16% in Rio de Janeiro. · Forgetting 25% in Boston 21% in Rio de Janeiro. · Inability to go to hospital 26% in Rio de Janeiro. · Medicine not available in pharmacies 21% in Rio de Janeiro.	Did not report facilitators.
Keppeke et al. 2018, Brazil (293)	Cross-sectional study, 90 children with chronic rheumatic disease, with mean age 14.1 years.	Questionnaire completed by caregivers and children aged >10 years to collect sociodemographic information such as, caregivers' education level, age, family composition, and responsibility for medicines administration. Adherence rate assessed by self-report.	· Older children (p<0.0001). · Older caregivers (p=0.011). · Caregivers with lower education level (p=0.031). · High number of patients per caregiver (p=0.004). · Child was responsible for medicine management (p<0.0015). · Caregivers have depression (p=0.028).	· Caregiver together with the child were responsible for medicine management (p<0.0015). · Younger children (p<0.0001). · Younger caregivers (p=0.011).

M. Multiple Sclerosis

As shown in Table 3-14, three studies identified barriers and facilitators to medicines adherence in patients with multiple sclerosis (294–296).

- Medicine related factors

The most common barriers to medicines adherence in patients with multiple sclerosis were medicine-related factors. Several factors related to medicines have been reported to cause poor adherence such as experienced side effects (294,296), intolerance to injections and lack of treatment efficacy (294).

- Patient related factors

Other barriers to medicines adherence in these patients were patient-related factors. Two studies reported that forgetting was a reason for non-adherence to medicines (295,296). Using medicines reminders such as a phone alarm was associated with good adherence (296).

Table 3-14 Studies reporting barriers and facilitators to medicines adherence in patients with multiple sclerosis. For barriers and facilitators numbers are reported as % or significant association (if no numbers given numbers not reported in study).

Study	Design	Tools used	Barriers identified	Facilitators identified
Thannhauser et al. 2009, Canada (294)	Cohort study, 17 adolescents, mean age 15.8 years.	Questionnaire completed by adolescents to explore reasons for discontinuing treatment. Adherence rate assessed by self-report.	· Intolerance to injections 37.5%. · Experienced side effects 37.5%. · Lack of treatment efficacy 12.5%.	Did not report facilitators.
Lulua et al. 2014, United States (295)	Cross-sectional study, 30 participants, mean age 15.8 years.	Questionnaire completed by adolescents and parents to explore reasons for discontinuing treatment. Adherence rate assessed by self-report.	· Forgetting 50 % of patients. · Children wanted to ignore their disease (p=0.008).	Did not report facilitators.
Yeh et al. 2018, United States (296)	Cohort study, 28 participants, aged 10 to 18 years.	Questionnaire completed by children. Open-ended questions identified barriers and facilitators to adherence. Adherence rate assessed by self-report.	· Forgetting. · Experienced with fatigue. · Experienced with side effects.	· Using medicines reminder. · Parent support.

N. Cancer

As shown in Table 3-15, two studies identified barriers and facilitators to medicines adherence in patients with cancer (297,298).

- Patient-related factors

Factors related to patients were reported to cause poor adherence such as forgetting (297,298), patients refusing to take medicine (297), and patients being away from home (298).

- Medicine-related factors

Factors related to medicines were also reported to cause poor adherence such as bad taste, difficulty swallowing (298), experienced side effects and fear of potential side effects (297).

Table 3-15 Studies reporting barriers and facilitators to medicines adherence in patients with cancer. For barriers and facilitators numbers are reported as % or significant association (if no numbers given numbers not reported in study).

Study	Design	Tools used	Barriers identified	Facilitators identified
Lehrnbecher et al. 2008, Germany (297)	Cohort study, 216 children with cancer, aged 1 month to 27 years.	Questionnaire completed by children and parent evaluated factors with potential impact on adherence: knowledge, side effects, efficacy of treatment, personal belief and medical care. Adherence rate assessed by self-report.	· Forgetting 25.9%. · Patient refused to take medicine 25.5%. · Experience of side effects 11.1%. · Fear of potential side effects 2.8%. · Inadequate supply of medicine 1.4%.	Did not report facilitators.
Hullmann et al. 2015, United states (298)	Cohort study, 103 children with cancer, aged 13 to 19 years.	Questionnaire completed by children and parents evaluated factors with potential impact on adherence: self-efficacy, side effects and medicine related factors. Adherence rate assessed by self-report.	· Forgetting 37.9%. · Not being at home 11.7 %. · Hard to swallow pills 10.7%. · Hating the taste 9.7%. · Not feeling well 6.8%.	Did not report facilitators.

O. (GH) deficiency

As shown in Table 3-16, two studies identified barriers and facilitators to medicines adherence in patients with growth hormone deficiency (299,300).

GH treatment is expensive, and its' cost has an effect on adherence, especially when the medicine is not free. Moheseni et al. in Iran reported that GH cost is the most common cause of non-adherence (300). A long duration of GH injections has also been reported to be associated with poor adherence (p=0.001) (299), because patients may become exhausted from long-term injections or dissatisfied with treatment results (300).

Table 3-16 Studies that reported barriers and facilitators to medicines adherence in patients with GH deficiency. For barriers and facilitators numbers are reported as % or significant association (if no numbers given numbers not reported in study).

Study	Design	Tools used	Barriers identified	Facilitators identified
De Pedro et al. 2016, Spain (299)	Cohort study, 158 children, aged 4 to 16 years.	Questionnaire completed by children and parents about: duration of treatment, socio-economic status, level of education, and parental employment status. Adherence rate assessed by self-report.	· Long treatment duration (*P*=0.001) · Lower mother's education level (*P*=0.007).	Did not report facilitators.
Mohseni et al. 2017, Iran (300)	Cross-sectional study, 169 children, aged 2 to 12 years.	Questionnaire completed by children and parents. Participants given a list of barriers to adherence and asked to tick factors they have faced. Adherence rate assessed by self-report.	· Cost (65.7% child, 55.6% adolescent). · Inaccessibility to growth hormone distributing pharmacy (64.7% child, 38.9% adolescent). · Growth hormone shortage (64.7% child, 38.9% adolescent) · Exhausted from long-term injections (54.3% child, 48.6% adolescent). · Concern about long-term complications (54.3% child, 51.4% adolescent). · Dissatisfaction with treatment results (37.1% child, 32.4% adolescent). · Being away from home (34.4% child, 18.9% adolescent). · Forgetting (22.9% child, 18.9% adolescent).	Did not report facilitators.

P. Thalassemia

Table 3-17 shows two studies which identified barriers and facilitators to medicines adherence in patients with thalassemia (129,301).

Patient related factors were the most common barriers to medicines adherence. Factors such as being aged over 16 years ($p<0.05$) (129,301), low parent education level ($p<0.05$) and large family size ($p=0.01$) (129) were significantly associated with poor adherence.

Table 3-17 Studies reporting barriers and facilitators to medicines adherence in patients with thalassemia. For barriers and facilitators numbers are reported as % or significant association (if no numbers given numbers not reported in study).

Study	Design	Tools used	Barriers identified	Facilitators identified
Al-Kloub et al. 2014, Jordan (301)	Cross-sectional study, 36 adolescents, aged 12 to 19 years.	Questionnaire completed by adolescents to explore sociodemographic information, disease knowledge, psychosocial impairment, and its' effect on treatment adherence. Adherence rate assessed by self-report and medicine plasma level.	· Psychosocial impairment was significantly associated with low adherence rate (p<0.05). · Older age over 16 years was significantly associated with low adherence rate (p<0.05).	Did not report facilitators.
Al-Kloub et al. 2014, Jordan (129)	Cross-sectional study, 164 adolescents, aged 12 to 19 years.	Questionnaire completed by adolescents to explore sociodemographic information, disease knowledge, psychosocial impairment, and its' effect on treatment adherence. Adherence rate assessed by self-report, medical record and medicine plasma level.	· Older age over 16 years (p<0.05). · Low parent education level (p =0.04). · Large family size (p=0.01). · Presence of sibling with thalassemia (p=0.02).	Did not report facilitators.

Q. Other diseases

As shown in Table 3-18, the four remaining studies identified barriers and facilitators to medicines adherence in patients with other different diseases (163,302–304).

Medicine-related factors were the most common barriers to medicines adherence. Two studies reported that experience of side effects was associated with poor adherence (303,304). Multidrug treatment and high dose frequencies (303) were also reported to cause poor adherence. In addition, factors such as good taste (302), fewer daily doses, fewer pills and using a medicines combination (302–304) were reported to result in good adherence. Healthcare professional and system-related factors included healthcare professionals providing sufficient information to patients about the disease and its treatment (302) and frequent consultation visits (163), both were reported to cause good adherence.

Table 3-18 Studies reporting barriers and facilitators to medicines adherence in patients with other diseases. For barriers and facilitators numbers are reported as % or significant association (if no numbers given numbers not reported in study).

Study	Design	Tools used	Barriers identified	Facilitators identified
Salazar et al.2012, United States(302)	Cross-sectional study, 246 caregivers of children taking antibiotics, aged 0 to 18 years.	Questionnaire completed by caregivers. Participants given list of facilitators to adherence and asked to tick factors they have faced. Adherence rate not assessed.	Did not report barriers.	· Physician explanation of indication 85%. · Physician explanation of medicine 75%. · Physician explanation of side effects 72%. · Less daily dosing 42%. · Short duration 37%. · Good taste of medicine 20%.
Ariceta et al. 2015, Spain (303)	Cohort study, 34 cystinosis diagnosed children. Age not reported.	Questionnaire completed by children and parents - 21 multiple choice questions covering: knowledge of disease, adherence to treatment, and measures to improve adherence. Adherence rate assessed by self-report.	· Patients complained of unpleasant smell (side effect of cystamine) 44%. · Multidrug 44% · High number of daily doses 35%. · Gastrointestinal side effects 24%.	· Dose reminder or alarms 65%. · Fewer pills, less frequency doses, or reduced pill size 60%. · Additional education about the disease 42%.
Joyce et al. 2016, United States (163)	Cohort study, 8710 patients with high cholesterol level, Aged 8 to 20.	Study based on medical records of patients to determine predictors of adherence to medicines. Adherence rate assessed by MPR calculation.	· Older adolescents. · Obesity patients. · ≤2 inpatient visits in last year. · ≤5 outpatient visits in last year.	· Younger adolescents. · 3+ inpatient visits in last year. · 6+ out-patient visits in last year. · Using statin combination product.
Leischow et al. 2016, United States (304)	Cohort study, 312 participants used bupropion to quit smoking. Aged 14 to 17 years.	Questionnaire completed by adolescents about symptoms of smoking withdrawal, adherence to medicine and abstinence. Adherence rate assessed by self-report and pill count.	· Race other than white/Caucasian. · Experience of side effects of medicines.	Did not report facilitators.

3.4 Discussion

Our search for a systematic review of barriers and facilitators to medicines adherence in children identified only the TABS review that was done in August 2008 and published in 2013 (85). This review was a critical evidence synthesis of research to examine reasons for non-adherence to medicines in children with chronic diseases (85). It analysed 197 studies identifying barriers and facilitators to medicines adherence in children (85). More than 70% of these studies were conducted in the US, and less than 10% were conducted in the UK (85). About 50% of these studies focused on patients with asthma, whereas the others focused on patients with HIV, arthritis, diabetes, epilepsy, kidney diseases and other diseases (85). The review found that factors potentially affecting adherence in children were related to the medicine, patient, condition and patient healthcare provider relationships (85). Specifically, this review showed that the most common barriers to adherence included parents' fear of side effects, forgetting, lack of family support, medicine responsibility among adolescents, regimen complexity and perceptions regarding the necessity of medicine (85). Adherence rates were positively correlated with income when patients paid for their medicine. Although providing clear information about a disease and its treatment was thought essential, provision of such information did not guarantee good medicines adherence. Moreover, regimen complexity was associated with poor adherence, but reducing dosing frequency did not always increase adherence rate (85).

We performed a systematic review to update the TABS work and to identify the barriers and facilitators to medicines adherence in children in studies published since then. Most studies (75%) in our review were conducted in HEDCs similar to those in the TABs review including the US (76), the UK (11), and Canada (6) (over 70% of the included studies in TABs were from the US, and fewer than ten percent from the UK). Only 25% of the studies were conducted in LEDCs, including Uganda (9), Ethiopia (7) and Kenya (3) (no such information was reported in the TABs). The studies included in this review included 50% focusing on patients with HIV or asthma, 30% on patients with kidney disease, epilepsy, psychiatric disorders or IBD, and the remaining 20% focussing on patients with other diseases including sickle cell disease, diabetes and cystic fibrosis. Our review identified studies of more diseases than those identified by the TABS review including GH deficiency, thalassemia, multiple sclerosis, psychiatric disorders and cancer. Our review included eight studies identifying only facilitators to adherence, 86 studies identified only barriers to adherence and the remaining 83 studies identified both barriers and facilitators to medicines adherence. The TABs study did not specify which studies reported barriers only, facilitators only, or both together.

3.4.1 Barriers to medicines adherence in children

Our findings are consistent with that of the TABS review about most common barriers and facilitators to medicines adherence in children. Here

we will discuss barriers to medicines adherence in children found in our review according to the WHO classification.

A. Patient-related factors

The patient-related factor that is the most commonly reported barrier to medicines adherence was forgetting. Reasons such as, 'just forget' , 'interferes with activity' and 'wasn't home' were the causes of poor adherence in patients with HIV, IBD, kidney diseases, asthma, cystic fibrosis, chronic rheumatic disease and diabetes (95,164,170,189,192,243,254,284,291). This finding shows that everyday life activities have a large impact on whether patients take their medicines or not (189). We could infer that caregivers and children do not have a systematic procedure related to their medicines taking (243). Moreover, a study that assessed potential barriers to medicines adherence in HIV-infected children showed that 41% of children and 33% of caregivers reported that forgetting was the main reason for non-adherence (61). This finding suggests that even in severe diseases, forgetting affects the rate of medicines adherence.

Another patient–related factor that is considered to be a barrier to medicines adherence is the patient's age. Younger children with HIV and asthma tended to have lower rates of medicines adherence than older children (69,199,240,249). Older children with HIV or asthma tended to have better awareness and appreciation of the negative effects of poor medicines adherence, especially if their disease status was disclosed to

them (199,240). This may suggest that when children aged 11 years and older are informed about their condition, they tend to become more responsible; therefore, their adherence rate is higher than younger children (69,199,240). This is probably due to the fact that younger children are fully dependent on their parents to take their medicines because they do not have the cognitive understanding or physical capacity to take their medicines by themselves (69). In addition, younger children who are usually reminded by their parents to take their medicines may forget about their doses when their parents or caregivers are absent or busy (199).

By contrast several studies have reported that adolescents with HIV, asthma, chronic rheumatic disease, psychiatric disorder, thalassemia and kidney diseases tend to have lower adherence rates than younger children because taking medicines is a responsibility that is likely to have been transferred from parents to children (129,160,176,181,194,197,246,253,293). There are a few sociological explanations for this finding. First, is that parents who were responsible for their adolescent's treatment may be in conflict with their child's desire to develop competence and independence (197). Another possible reason is that adolescents who are given full responsibility may not believe they need medicines to control their disease or perhaps they are not yet ready for this responsibility (129,194). Moreover young children are dependent on their parents for taking their medicine, and since parents carry this

responsibility many of them ensure to set alarms or visual reminders (181).

B. Socioeconomic-related factors

Fear of stigma and discrimination is a social-related factor that is reported to result in poor adherence. Some conditions, such as HIV disease are particularly linked to social stigma. Galea et al. reported that children with HIV hid their medicine when going out with friends (73). This pattern suggests that being around others could cause children stress, and it increases their likelihood of not taking their medicines as they feel the need to act just like their peers (73,74). In relation to this, MacCarthy et al. reported that school attendance limits patients' privacy, resulting in poor medicines adherence (74). When children attend school, they spend less time with their family at home and they may feel ashamed to take their medicines in front of their peers (74).

Another socioeconomic-related factor considered to be a barrier to medicines adherence is non-disclosure of the children's health status. Studies have shown that children with HIV who are unaware of their condition are more likely to have poor adherence to antiretroviral therapy (61,73,93,196,198). There are two possible reasons for this pattern. First, patients who were aware of their condition were more health aware and believed their medicines to be helpful (196). Second, patients who were unaware of their condition refused to take their medicines as they

did not understand the rationale behind the treatment while they felt apparently healthy (196).

Some of the most important reasons for medicines non-adherence in patients with HIV, asthma, psychiatric disorder, IBD and diabetes include family conflict, stability, parental marital status, family size, and stress for children and parents (210,211,224,241,247,264,268,285). Low family support and a lack of adult support tends to be a barrier to medicines adherence, as the children/adolescents feel uncared for and thus they do not see the need for adherence (211,224,285). In addition, suboptimal relationships with caregivers may affect a child's adherence and attendance to appointments, a pattern more common in older children (210,247,268).

Children who live in a single parent household tend to have less family support, which may contribute to low medicines adherence rates (264). According to Chan et al., adherence may also be poor in larger families as there are more matters to attend to, reducing the time spent to care for an ill child in the family (241).

C. Medicine-related factors

Complexity of drug regimens (such as high dosing frequency or administering multiple drugs) has been associated with poor medicines adherence in patients with HIV, IBD, asthma, kidney diseases, epilepsy (70,79,122,167,170,177,210,236,270). When the number of medicines prescribed increased or when changes in administration schedule were

made, the possibility that medicines or doses were missed increased, leading to poor adherence (70,79,177,236).

Long duration of treatment has been reported to cause poor adherence in patients with HIV, psychiatric disorders, epilepsy, asthma, IBD, kidney diseases and growth hormone deficiency (81,162,168,190,202,299). For example, where medicines are administered over a long period, adherence may significantly decline over time (168,299). Adherence drops when patients do not perceive therapeutic effectiveness, and their motivation to take medicines decreases (168,299). In addition, the fear of a lack of efficacy of certain medicines can affect adherence, especially with regard to chronic diseases, such as HIV and multiple sclerosis, where medicines are prescribed to control the disease and do not make the patients feel better (197,294).

Medicines are administered in various ways. The oral route is preferred and is the most frequently used route of medicine administration in children (92). However, the bad taste of some medicines has been seen to negatively affect the adherence of patients with HIV, psychiatric disorders and kidney diseases (70,85,92,193,208,254,259). Bad-tasting medicines discouraged younger children to willingly take their prescribed medicine, increasing non-adherence (70,85,92,193,208,254,259).

Moreover, fear of the unknown adverse effects of medicines has been reported as a reason for discontinuing daily medicines in patients with

HIV, asthma, epilepsy, chronic rheumatic disease, tuberculosis and psychiatric disorders (70,85,193,196,197,240,254,270,288,292). For example, when an asthmatic child begins to feel better, some parents stop administering daily inhaled steroids, believing this will prevent the medicine's side effects (173,240). However, this behaviour may worsen the condition which the patient is suffering from.

Poor adherence has also been reported in children with HIV, psychiatric disorders, multiple sclerosis and kidney disease who have experienced the side effects of medicines (171,198,254,262,296). For example, children have been shown to often struggle with Lopinavir/Ritonavir syrup, which can cause vomiting. This side effect disrupts the dosing if the medicine is not re-administered after vomiting (198). This side effect reduces adherence because other barriers may arise; for instance, children may develop a negative perspective towards taking medicines if they feel it will make them feel worse (198).

D. Condition related factors

Studies with patients with HIV and asthma have shown that when the symptoms of the disease are few or had disappeared, the absence of symptoms became a barrier for patients to follow their treatment regimen as patients did not see the need to continue taking their medicine and thus their adherence decreased (61,195,240).

Disease severity and rate of progression may affect medicines adherence in different ways. For example, when the severity of HIV is high,

medicines adherence may decrease if patients lose trust in their treatments, or because parents prefer nonmedical options such as the use of holy water (religious practices) (61,69,70,195). This behaviour has been attributed to reduced trust in healthcare providers and the effectiveness of the treatments given (61,69,70,195). By contrast, some studies have reported that low severity of HIV and asthma is associated with poor adherence (68,70,173,196,240). There are two possible reasons for this pattern: first, when disease severity decreases, patients tend to stop taking medicines because they think they are no longer necessary (68,173,240). Second, high severity of a disease motivates patients to take medicines as prescribed to avoid condition complications (70,196).

E. Healthcare professional- and system-related factors

These factors have been seen to particularly influence patients with asthma (87,88,236,238,240). Several studies have shown that inadequate communication between healthcare providers and their patients or their parents can contribute to poor adherence (87,88,236,238,240). In some cases, the parents did not have the same views about their children's condition as their healthcare provider. For example, the parents did not always view asthma as a chronic disease that requires constant administration of medicine, nor did they necessarily believe that inhaled corticosteroids are safe (240). In addition, a healthcare provider's failure to explain the side effects and

benefits of medicines, failure to demonstrate how to use inhaler devices or failure to explain the need for a complex medicine regimen may contributes to non-adherence (238,242).

3.4.2 Facilitators to medicines adherence

In contrast to the above-mentioned barriers to medicines adherence, numerous factors contribute to high adherence rates. These factors include integrating taking medicines into daily routines or using medicines reminders to avoid forgetfulness. In addition, the practices that effectively prevent forgetting include taking medicines at the same time each day (e.g., before a meal), marking a calendar, setting an alarm clock, or using note reminders (70,87,91,122,189,193,241,243).

Other factors that have been associated with high rates of adherence in patients with HIV, asthma, kidney disease and psychiatric disorders involve a higher level of caregivers and parental education (175,196,240,255,258). Educated parents or caregivers had a better understanding and knowledge about certain diseases and treatment, which in turn helped them to improve the adherence rates of their children (196,240).

Factors that promote good relationships between patients (and their parents) and healthcare providers have also been associated with high rates of adherence in patients with HIV, tuberculosis and epilepsy (193,271,288,302). These factors included discussing with the patients and their parents the different formulations of medicines (e.g., some patients prefer syrup formulation with a good taste over tablets) (193,302). Other important matters, such as the safety of medicines,

treatment rationale and benefits of adherence, are also associated with high rates of medicines adherence (193,271,288).

3.4.3 HEDC vs LEDC

One hundred and twenty six studies were conducted in HEDCs including the US (76), UK (11), and Canada (6), and only forty six studies were conducted in LEDCs, including Uganda (9), Ethiopia (7) and Kenya (3). Forgetting was a common barrier to adherence in both HEDC and LEDC (95,164,170,189,192,243,254,284,291) and measures taken to avoid forgetting to take medicines include the use of reminders, such as notes on the refrigerator and the use of an alarm clock; these efforts were associated with good adherence in both HEDC and LEDC (87,122,241,243). Medicines related-factors such as experienced and fear of side effects, complexity of drug regimens and bad taste of medicines were associated with poor adherence in both HEDCs and LEDCs (70,79,210,236,254,259,270,85,92,122,167,170,177,193,208).

In LEDCs poor adherence has been reported to be due to low socioeconomic status and limited access to healthcare facilities, such as long distances from medical centres (74,86,196,199,203). Arage et al. reported that patients who needed to travel more than 10 kilometres were 2.3 times more likely to show poor adherence to medicines compared with patients who had to travel less distance (196). This mainly

refers to families with a low income and who live in LEDC such as Ethiopia (196).

Two studies conducted in Iran (LEDC) revealed an association between high medicine costs and poor adherence of patients with asthma and GH deficiency and without health insurance (240,300). In some cases, these patients tried to reduce the cost of medicines by decreasing their dosage and/or the frequency of a recommended treatment (240,300). Moreover, lack of knowledge about the disease and its treatment in patients with HIV, asthma, kidney diseases, tuberculosis and epilepsy has been reported to be associated with poor understanding regarding medicines regimens and poor adherence (61,70,71,73,170,221,242,270,271,288). Many of the studies that support this idea were conducted in LEDCs, where the level of education is often low (70,71,73,221,270,271,288). Given the low level of education in LEDCs, medicines adherence is also low as parents may be unaware of the impact of following medicine prescriptions on their children's overall health (71,221).

In contrast, countries such as the US and the UK generally provide high-quality education, which helps facilitate good communication among healthcare professionals, patients and parents. Such communication helps to ensure that the patients are more aware of their condition and that parents gain a wider knowledge about the treatments given and their impact on their children; as a result, adherence rates may increase (62,87,233,253).

3.4.4 Limitations

All titles and abstracts of the search results should have been screened according to the inclusion criteria by two researchers. Due to the limited resources of our department, one researcher (Aldosari M) screened all titles and abstracts, but only 5% of titles and abstracts were assessed independently by another researcher from our group (Abramson J). The quality of all included studies should also have been assessed independently by two researchers. Given the high numbers of included studies and the limited resources of our department, one researcher (Aldosari M) quality assessed all of the included studies but, only 5% of the included studies were quality assessed independently by another researcher from our group (Abramson J). In addition, conference abstracts and the grey literature were not searched therefore it is possible that studies have been missed.

3.5 Conclusion

This systematic review identified the barriers and facilitators to medicines adherence in children reported in the literature in the last 12 years. We found that children faced many different barriers to medicines adherence which varied with different diseases and that no single facilitator could improve medicines adherence. Rates of adherence are influenced by children's or caregiver's beliefs about the treatment. Forgetfulness and fear of side effects were the most common barriers to medicines adherence. The

range of barriers to adherence included family conflict, weak patient-provider relationships, stigma and discrimination, drug regimen complexity, and lack of support from families. The most frequent facilitators of medicines adherence included using reminders to avoid forgetfulness, high parental education levels and good patient-provider relationships. To achieve optimal adherence, healthcare providers need to be aware of these barriers and to consider the most appropriate facilitators to encourage patients to take their medicines as prescribed.

Chapter 4: Exploratory study on the barriers and facilitators of medicines adherence in a Saudi Arabia children's hospital

4.1 Introduction

We have already completed a systematic review on the barriers and facilitators of medicines adherence in children (**Chapter 3**). This systematic review highlighted that forgetfulness and fear of side effects were the most common barriers to medicines adherence. The most frequent facilitators of medicines adherence included using reminders to avoid forgetfulness, high parental education levels and good patient-provider relationships.

Most of the included studies in our systematic review focussed on patients with a limited number of specific diseases. Just one of these studies was conducted in Saudi Arabia and explored barriers of medicines adherence in children with epilepsy (177). This study reported that forgetfulness, fear from side effects, high numbers of medicines, divorced parents, lack of family support and strong concerns about medicine consequences were the most common barriers of medicines adherence in children with epilepsy in Saudi (177). It focused only on barriers and did not explore facilitators of adherence.

This chapter describes the first study to explore both barriers and facilitators of medicines adherence in children with any chronic disease in Saudi Arabia to our knowledge. Saudi is my home country which is the reason why we wished to conduct a study there in order to fill the gap in knowledge by exploring medicines adherence in children with any chronic disease.

4.1.1 Aims

This study aims were to:

- Measure medicines adherence in children with chronic diseases attending the King Fahad Medical City (KFMC) in Saudi Arabia.
- Explore the barriers and facilitators to medicines adherence in these children.

4.2 Method

Both the Institutional Review Board (IRB) in the KFMC and the Head of Pharmacy in the KFMC approved our research protocol to conduct this study **(Appendix 1)**.

This study was conducted between 24th July 2019 and 10th October 2019 at King Fahad Medical City (KFMC), a tertiary hospital and one of the largest medical facilities in Saudi Arabia, containing 246 beds for children.

4.2.1 Inclusion criteria

- Paediatric patients ≤ 18 years receiving long-term medicines who were inpatients or attending outpatient clinics at the KFMC Hospital.
    - If a child was too young to complete the study questionnaires, then their parent would assist the child by completing the questionnaires in the child's own words i.e. reading questions out to the child and writing the answers down.
- Parents of children taking long-term medicines who were too young to provide their own opinions on the questionnaires.

4.2.2 Exclusion criteria

- Patients over 18 years old.
- Patients/ Parents who were too distressed/ ill to approach.
- Patients/ Parents who did not speak English or Arabic.

4.2.3 Recruitment

The researcher (MA) worked under the supervision of the hospital pharmacy supervisor during the data collection in KFMC. Participants were recruited from the waiting area at the outpatient pharmacy and from the paediatric in-patient wards in the hospital. Participant information sheets and consent forms were available in English and Arabic **(Appendix 2)**.

The researcher (MA) asked the pharmacists in the waiting area of the outpatient pharmacy and the nurses in the paediatric in-patient wards which families would be suitable to be approached in terms of age of the patient, medicines prescribed and ability to speak English or Arabic. We received approval from the IRB in KFMC to access the pharmacy refill records for each patient. The researcher checked if the patient was taking long-term medicines from pharmacy refill records.

After eligibility for inclusion in the study was confirmed, the patients and their parents or guardians were asked to participate in the study. They were provided with written and verbal information about the study in age-appropriate language by the researcher (English and Arabic).

In all cases, written informed consent was obtained from the parent/legal guardian or the child if ≥16 years of age. The patient or parent were asked to answer all questions in the Beliefs about Medicines Questionnaire (BMQ) and our own designed questionnaire form **(Appendices 3 and 4)** which are explained below. The participants' personal information was recorded on the consent forms only, and the researcher coded the questionnaires with a number corresponding to each participant's consent form.

From the pharmacy refill records for each patient we could establish the total number of days' supply of medicines dispensed and the number of days that the patient should have been taking the medicines. This information allowed us to calculate the Medication Possession Ratio (MPR) to assess medicines adherence (as described in more detail on page 184).

The completed questionnaires and consent forms were stored separately in locked facilities in the KFMC during the data collection period in Saudi Arabia. Data were entered on University password-protected computers. Data were analysed using SPSS version 26.

4.2.4 Justification of the questionnaires

Most of the studies included in our systematic review used purpose designed questionnaires to explore barriers and facilitators of medicines adherence in children and studied only a single specific disease **(Chapter 3)**. We also found that sixteen studies used validated questionnaires e.g. the Morisky, and the Paediatric Epilepsy Medication Self-Management Questionnaire Scales. These were used only in studies involving children with epilepsy

(177,273). The Diabetes Family Responsibility Questionnaire was used only in studies with children with diabetes (182), the Medication Adherence Rate Scale (MARS) was used only in studies with children with asthma and epilepsy (123,126), and the Medical Adherence Measure was used only in studies with children with inflammatory bowel disease and organ transplantation (164,169).

Only one of the validated questionnaires was used in studies in children with several different chronic diseases. This validated questionnaire was the Beliefs about Medicines Questionnaire (BMQ) (42).

A. Beliefs about Medicines Questionnaire (BMQ)

The BMQ was originally developed and validated by Professor Robert Horne and colleagues to use in adult patients, and parents and guardians of children with chronic diseases (42). A 2017 review shows that this questionnaire has been used successfully in studies about medicines adherence across a broad range of clinical conditions in adults, including asthma, HIV, diabetes, liver transplant, inflammatory bowel disease, cardiovascular disease, mental disorders, haemophilia, hypertension, and patients after stroke events (305). The BMQ questionnaire was also used by eight studies identified by our own systematic review **(Chapter 3)** including studies in children with asthma, inflammatory bowel disease, attention deficit hyperactivity disorder, epilepsy, and cystic fibrosis (68,81,126,173–176,178). An Arabic translation of the BMQ has also been

validated for use in children and their parents (306). We therefore used the BMQ in our study using the English and Arabic translations.

The BMQ **(Appendix 3)** aims to assess patient's concerns and beliefs about medicines (42,307). It consists of 18 questions and is divided into two sections, the BMQ-General (8 questions) which assesses beliefs about medicines in general and the BMQ-Specific (10 questions) which assesses beliefs about medicines prescribed for personal use (42,307). The two sections can be used separately or in combination (42,307). As our objective was to explore barriers and facilitators of children's adherence to their prescribed medicines, we used the BMQ-Specific questionnaire only. This was also the case with all nine studies in our systematic review that used the BMQ (68,81,126,173–178). Four of these studies utilised the BMQ-Specific only for the parents because they included children aged under 7 years of age (68,173,175,178), three studies utilised the BMQ-Specific only for adolescents (81,176,177), and only one study utilised the BMQ-Specific for both parents and children aged over 6 years (126,174).

The BMQ-Specific questionnaire consists of ten questions: five on people's concerns about taking medicines and five on people's beliefs about medicine necessity (42). The questions involving concerns assess patients' concerns about taking the medicines prescribed (e.g., "I sometimes worry about the long-term effect of my medicines"). The questions involving necessity assess patients' beliefs in the necessity of taking the medicines prescribed (e.g. "my life would be impossible without my medicines") (42). All items

are rated on a five-point scale ranging from 5 = strongly agree to 1 = strongly disagree (i.e., the overall score range is from 5-25 for each section). A score of 15 to 25 is defined as high concern or high necessity. A differential score between necessity and concern is calculated by subtracting the results of the concern scores from those of the necessity scores. Therefore, a negative score indicates stronger concerns about the consequences of the medicine than beliefs in the necessity of taking the medicine. By contrast, a positive differential score indicates stronger beliefs in the necessity of taking the medicine (42).

By also measuring adherence using our separate purpose designed questionnaire (described below) and in addition, by using the Medication Possession Ratio (MPR) (calculated as described below), we assessed the relationship between adherence rates and beliefs in the necessity of children's medicines and concerns about consequences.

B. Purpose-designed questionnaire

The BMQ only assesses participant's beliefs about medicines in terms of necessity and concerns. Our aim was to explore all factors that affect medicines adherence in children. To achieve this aim, we therefore designed our own questionnaire to use in addition to the BMQ to explore other barriers and facilitators of medicines adherence in children.

From our systematic review **(Chapter 3)**, we found that most of the included studies used questionnaires that were designed for each individual study to identify the barriers and facilitators of medicines adherence in

children. Taking these findings into account, we developed our purpose-designed questionnaire **(Appendix 4)** by including questions modified from various previous studies to make it suitable for children with different diseases and their parents.

Our purpose-designed questionnaire consists of:

- *Most common barriers and facilitators to medicines adherence*

The first question consisted of lists of ten barriers and seven facilitators of medicines adherence. The lists included the most frequent barriers and facilitators of medicines adherence that were reported in our systematic review. The children, children with parent's help when needed or parents when their children were too young were asked to either tick (✓) the "agree" box if they had encountered this barrier or facilitator or tick the "disagree" box if they had not.

The participants' answers to this part of the questionnaire enabled us to report the percentage of participants who have faced each barrier or facilitator and to identify the most common barriers and facilitators in our participant population in a similar way to those reported in previous studies (70,164,167,192,196,197,240,254,288).

- *Measures of adherence*

From our systematic review on measuring medicines adherence in children **(Chapter 2)** we found that there is no known ideal method to measure adherence but that it is more reliable to use two or more adherence

measures together. We therefore used self-report through our questionnaire and also the MPR method to measure medicines adherence in our participants.

Our systematic review on measuring medicines adherence **(Chapter 2)** showed that a single question (i.e., How do you rate your medicine taking in the last month from 0% to 100%?) was used by six studies to measure adherence in children (116–118,120,122,129). We therefore used this question as a self-report tool to estimate patients' adherence rates in our own questionnaire.

The participants were asked:

'Plot on the line from 0% (none) to 100% (all) how many of the prescribed doses of medicines you/your child managed to take in the last four weeks'.

The MPR is the most common measure of medicines adherence using prescription refill records. It measures the percentage of time a patient has access to their medicines. The MPR is calculated by dividing the total number of days' supply of medicines dispensed by the number of days that the patient should have been taking the medicines and multiplying this by 100.

The MPR equals 100, representing the highest adherence, when the total days' supply is equal to the number of days between two prescription refill times.

We therefore used two methods to measure the medicine adherence rate, the MPR and self-report methods. Both provided the medicine adherence rate as a percentage which allowed us to compare the two results.

The remaining questions explored the areas listed below **(Appendix 4)**. Our systematic review of the barriers and facilitators to medicines adherence identified previous studies that used similar questions. We modified the questions from those studies to be suitable for different diseases.

a) Forgetfulness

As our systematic review **(Chapter 3)** suggested that forgetfulness is one of the most common barriers to adherence, one question elucidated participants' own thoughts about why they might forget to take their medicine and how they could manage this barrier (85,93,195).

b) Side effects of medicines

Two questions explored whether the children/parents worry about or have experienced any side effects from taking medicines in order to determine whether this concern affects medicines adherence. All medicines have possible side effects, and we wanted to know the most frequent side effects that may cause children to stop taking their medicine (62,85,89).

c) Responsibility for medicines adherence

One question asked who is responsible for administering the medicines and explored how this affects medicines adherence. The transition age of children as they become responsible for their own actions is an important issue in assessing medicines adherence (176). We wanted to compare the adherence rates of children whose parents were responsible for administering their medicines to adherence rates of children who are responsible for administering their medicines (85,195,244,254).

d) Fear of stigma or discrimination

One question was about whether the child/family experience any concerns about taking medicines in front of others. In particular, we wanted to assess whether stigma affects medicines adherence in children (85,93,193).

e) Problems with regimen

Two questions were about the medicines regimen and how it affects adherence. For children, there are different dosage forms and different methods of administration e.g. a liquid formulation is the preferred and most frequently used form for many children (76). Each medicine regimen has different forms and different dosage frequencies. We wanted to explore whether the child had difficulties with their medicine regimen and how it affected adherence (85,89,165,238).

f) Participants' thoughts that may improve adherence

One question asked for thoughts and suggestions that the children and their families may have to help improve medicines adherence in children. With this question, we intended to gather ideas from the children and their family which would help with this.

Both questionnaires (BMQ and our own designed questionnaire) were tested by the researcher (MA) and the Chief Investigator (Dr Sharon Conroy) in the Derby Children's Hospital before the study started.

4.2.5 Thematic analysis

Three questions in our purpose designed questionnaire were open ended (Q2, Q6 and Q10) **(Appendix 4)**. The participants' answers to these questions (qualitative data) were analysed using thematic analysis (308,309).

Thematic analysis is one of the most commonly used analysis methods for qualitative research (308,310). According to Braun and Clarke, thematic analysis identifies, organises and links participants' answers into themes within a data set. It also interprets different aspects of the research topic (310). This analysis allows a researcher to identify participants' answers in relation to a specific topic, and it can identify numerous topics in a data set (308,310). Many researchers use this method for its accessibility and flexibility (it can be used for interviews and questionnaires) (308,310);

however, this flexibility can make it difficult for a researcher to decide what aspect of their data to focus on (310). Therefore, a researcher should be aware of how to generate themes that serve to focus on the issues being studied (310). We decided to use thematic analysis because its flexibility allowed us to analyse the answers to the open questions and also extract defined themes from the participants' answers (308,310).

In this study, to undertake the thematic analysis manually, Braun and Clarke's six-phases framework was followed (310). This framework is one of the most commonly used methods to conduct thematic analysis and provides a clear step-by-step process:

1- Familiarisation

I read the participants' answers text, generally looking through the participants' answers to get familiar with it.

2- Generating initial codes

I highlighted sections of participants' answers (phrases or words) and wrote codes to describe their content (examples are shown in Table. 4-1). At this stage, I collated all the participants' answers into groups identified by code.

Table 4-1 Examples of coding

Question	Participants' answers	codes
can you think of anything that could help you to remember?	1- We set a phone alarm to remind us of the time of doses. 2- I use phone alarm.	Setting an alarm
can you think of anything that could help you to remember?	1- Writing notes. 2- I use notes.	Writing notes

3- Searching for themes

I looked over the codes that had been created, identified patterns among them, and started to generate themes. In this method, themes are generally intended to be broader than codes. Most codes became themes in their own right. Sometimes however, I combined several codes into a single theme. Table 4-2 shows examples of turning codes into themes.

Table 4-2 examples of turning codes into themes

Codes	Themes
• Setting an alarm • Writing notes	Using reminders.
• Multidrug • Many doses	Many doses each day.
• Medicine tastes bad • Painful injection • Difficulty with inhaler device	Medicine difficult to take due to size, poor taste/smell/pain/device.
• Family help/support	Family support.

4- Reviewing themes

After generating themes for all the participants' answers, I re-read each answer and the initial code and chosen theme for each question to ensure the selected themes were appropriate.

5- Defining and naming themes

I identified more precisely what each theme is about and described how it helps us understand the data.

6- Producing the report

In this final phase, I wrote the analysis and provided examples of the participants' answers that related to each theme.

Therefore, by applying Braun and Clarke's six-phases framework, I have been able to identify, analyse, and generate themes.

As a reliability measure, all the participants' answers, codes and themes generated were checked and agreed between the Chief Investigator and the researcher.

4.2.6 Statistical analysis

To express the adherence rate as a binary variable, the defined cut-off value was 80% (as used in several previous studies) of the continuous data for the two adherence assessment methods (68,160,161,178,292). Patients at 80% and above were defined as adherent, patients below as non-adherent. For statistical analysis, data was analysed descriptively to determine the agreement between the two assessment methods for the adherence rate (the Questionnaire and the MPR). Kappa (κ) testing was conducted to compare the adherence rates measured by the two methods. The strength of agreement between the two methods was described as poor if $\kappa < 0.2$, fair if $0.2 < \kappa \leq 0.4$, moderate if $0.4 < \kappa \leq 0.6$, substantial if $0.6 < \kappa \leq 0.8$, and almost perfect if $0.8 < \kappa \leq 1$ (311,312).

We also used chi-square testing to assess the correlation of medicine adherence rates (good adherence ≥ 80% and poor < 80%) with child age, child sex, parents' education level, and child's/parents' beliefs in the necessity and their concerns about consequences of their medicines (assessed by the BMQ-Specific).

4.2.7 Sample size and justification

The estimated sample size was 96 patients. We calculated this sample size with the help of a University of Nottingham statistician using nQuery Sample Size Software. It was computed based on the precision approach that we would need a sample size of 96 to estimate the proportion adhering with a

good level of precision, which was defined as a 95% confidence interval width of 0.1, assuming the rate of adherence is no less than 50%. If the proportion of adherence were higher, the precision would be better (width higher than 0.1).

The sample size of 96 also provided 90% power to detect a kappa of 0.35 or higher. In the chi-squared analysis, this sample size of 96 would also provide 80% power to detect a difference in adherence proportions between two groups (e.g. male/female) of ≥ 18% (e.g. 80% vs 98%).

4.3 Results

4.3.1 Demographic and clinical characteristics

In total, 100 children were recruited to the study. Thirty-nine children answered questions alone, 35 children answered questions with the help of their parents and 26 parents answered questions for their children. Twenty-nine participants did not answer every question. This is described below for each section. **Appendix 5** shows a summary table with the gender, age, disease, medicines, adherence rates and BMQ results for each participant.

Previous studies used the mean or median age as a cut-off point to compare two different age groups (older and younger age group) (129,178,233). The mean age of the participants in our study was 9.35 ± 4.50 years (range: 1-18) and the median was ten years. Ten years was chosen based on the median as the cut-off point to compare the two age groups.

Fifty-two children (52%) were ≥10 years of age (26 male, 26 females) (27 with parents with low education level and 25 with parents with high education level) and 48 (48%) were under 10 years of age (30 male and 18 female) (21 with parents with low education level and 27 with parents with high education level). Most of the children were males (56%). Slightly more than half of the children's parents (52%) had a university education and 48% had a secondary education or less. One-fifth of the study population (19%) had epilepsy, 17% had asthma and 14% were diabetic children (Table 4-3).

Table 4-3 Demographic and clinical characteristics of the study population (n = 100)

Age (mean ± SD), (median)	(9.35±4.50), (10)
≥10 years	52 (52%)
<10 years	48 (48%)
Gender	
Male	56 (56%)
Female	44 (44%)
Level of Parent Education	
Secondary or less	48 (48%)
University	52 (52%)
Disease	
Epilepsy	19 (19%)
Asthma	17 (17%)
Diabetes	14 (14%)
Growth Hormone Deficiency	8 (8%)
Heart Disease	7 (7%)
End-Stage Renal disease	6 (6%)
Anaemia	5 (5%)
Leukemia	4 (4%)
Psychiatric Disorder	3 (3%)
Gastrointestinal Disorder	3 (3%)
Sickle Cell Anaemia	3 (3%)
Cystic Fibrosis	3 (3%)
Hypothyroidism	3 (3%)
Hypertension	2 (2%)
Hyperactivity	1 (1%)

Haemophilia B	1 (1%)
Lupus Erythematous	1 (1%)

4.3.2 Barriers to medicines adherence

The answers to the first part of our purpose designed questionnaire are summarised in Table 4-4. The most frequently perceived barrier of medicines adherence was '*I worry about possible side effects*' as reported by 79 (79%) of the participants. This was followed by '*I forget to take my medicine*' reported by 62 (62%) and '*I worry about what other people would think of me if they knew I took medicine*' reported by 62 (62%).

Forty-seven participants ticked "not certain" for Q2 '*My medicine tasted bad'* (Table 4-4). Thirteen of these participants were taking non-oral medicines. Eight patients with GH deficiency, two with diabetes and one with haemophilia B were taking injections only; one with a GI disorder was taking medicines via a feeding tube; and one with cancer was having their medicines administered intravenously. The remaining 34 participants were taking oral medicines.

Twenty-six participants ticked on "agree" for '*I don't know enough about the illness and treatment'.* Twenty-one of these participants were with parents with a secondary-level education.

Fourteen participants ticked on "agree" for '*I don't have enough family support'.* Twelve of these participants were belonged to the older age group.

Table 4-4 Barriers to Medicines adherence as perceived by the study population.

	Agree n (n%)	**Disagree** n (n%)	**Not Certain** n (n%)	**Not answered** n (n%)
Q.1: *I forget to take my medicine.*	62 (62%)	36 (36%)	1 (1%)	1 (1%)
Q.2: *My medicine tastes bad.*	24 (24%)	29 (29%)	47 (47%)	0
Q.3: *I worry about possible side effects.*	79 (79%)	19 (19%)	1 (1%)	1 (1%)
Q.4: *I don't have enough family support.*	14 (14%)	85 (85%)	0	1 (1%)
Q.5: *I don't know enough about the illness and treatment.*	26 (26%)	74 (74%)	0	0
Q.6: *The medicine makes me feel sick.*	19 (19%)	76 (76%)	5 (5%)	0
Q.7: *We weren't given enough information about the illness and treatment.*	19 (19%)	79 (79%)	2 (2%)	0
Q.8: *I have to take lots of medicine or many doses per day***.**	57 (57%)	40 (40%)	3 (3%)	0
Q.9: *I worry about what other people would think of me if they knew I took medicine.*	62 (62%)	37 (37%)	1 (1%)	0
Q.10: *I don't need to take my medicine as my symptoms have gone.*	25 (25%)	73 (73%)	2 (2%)	0

4.3.3 Facilitators to medicines adherence

All questions exploring perceived facilitators to medicines adherence were answered by all participants except Q4 which was answered by 97 participants (Table 4-5).

The highest perceived facilitator of medicines adherence, as reported by 96 (96%), was '*I have good family support'*. In addition, 81 (81%) agreed that '*I use a medicine reminder or routine about my medicine*', and 80 (80%) agreed that '*We were given enough information about my illness and the importance of treatment*'. Seventy-five percent of the participants ticked on "not certain" for Q7 *'My doctor gives me medicine which taste ok'* and thirteen of them were on non-oral medicines as described previously (Table 4-5). The remaining 34 participants were taking oral medicines.

Fifteen participants ticked on "disagree" for '*I have good knowledge about my disease and treatment'.* Thirteen of these participants were with parents with a secondary-education level.

Table 4-5 Facilitators to medicines adherence as perceived by the study population

	Agree n(n%)	**Disagree** n(n%)	**Not certain** n(n%)	**Not answered** n(n%)
Q.1: *I use a medicine reminder or routine about my medicine (e.g. taking medicine before school).*	81 (81%)	19 (19%)	0	0
Q.2: *We were given enough information about my illness and the importance of treatment.*	80 (80%)	18 (18%)	2(2%)	0
Q.3: *I have good family support.*	96 (96%)	4 (4%)	0	0
Q.4: *I have good knowledge about my disease and treatment.*	76 (76%)	15 (15%)	6 (6%)	3(3%)
Q.5: *The doctor has prescribed medicine which can be taken once or twice a day.*	37 (37%)	41 (41%)	22 (22%)	0
Q.6: *My medicine schedule is quite simple.*	33 (33%)	48 (48%)	19 (19%)	0
Q.7: *My doctor gives me medicine which taste ok.*	4 (4%)	21 (21%)	75 (75%)	0

4.3.4 Adherence rates

Fifty-six patients took two medicines, 27 patients took one medicine, 14 patients took three medicines and only three patients took four medicines **(Appendix 5)**.

All patients taking more than one medicine reported the same adherence rate to each medicine. In addition, the MPR percentages were the same for each medicine.

Twenty-six parents reported the adherence rate for their children and 74 children reported their own adherence rate. Adherence rates reported by parents were higher than those reported by children. The mean percentage of medicines adherence as reported by parents was 97.12, while the mean percentage as reported by children was 95.13.

The mean percentage of medicines adherence as reported by the study population overall was higher than the mean percentage of medicines adherence measured by the MPR (Table 4-6).

Table 4-6 Medicines adherence, as reported by the study population and measured by the MPR

Medicines adherence	[Min-Max]	Mean ±SD
Self-reported Adherence	70-100	95.41±8.63
Medicine Possession ratio (MPR)	50-100	92.40±12.00

A score of ≥80% adherence was considered the cut-off for good medicines adherence. Based on the MPR 85 participants had good medicines adherence, while 15 participants had poor adherence. Based on the self-report 91 participants had good medicines adherence, while nine participants had poor adherence.

Two children (7.4% of children who took a single medicine) who took a single medicine displayed poor adherence (by MPR and self-report), while among children who took multiple medicines, seven children (9% of children who took multiple medicines) (self-report) and 13 children (18% of children who took multiple medicines) (MPR) displayed poor adherence.

According to both adherence measures, 85 participants displayed good medicines adherence and nine participants displayed poor medicines adherence (Table 4-7). For six participants (four males and two females), the two measures showed conflicting medicines adherence ratings with good adherence being self-reported but the MPR showing poor adherence. These included two patients with asthma, one with end-stage renal disease, one with diabetes, one with epilepsy and one with anaemia.

The Kappa test (κ) was run to determine whether there was an agreement between the two medicines adherence measures (self-reported vs. MPR). There was substantial agreement between the two medicine adherence measures, $\kappa = 0.718$, $p<0.001$. The confidence interval gives us 95% confidence that the true kappa falls between 0.509 and 0.928; in other

words, the agreement between the two methods was between moderate and almost perfect (Table 4-7).

Table 4-7 Self-reported vs. MPR level of agreement of medicines adherence.

		Medicine Possession ratio (MPR)		Total	*P*-value	95% Confidence Interval
		Poor adherence <80%	Good Adherence ≥80%			
Self-reported adherence	<80%	9	0	9	<0.001***	0.509-0.928
	≥80%	6	85	91		
Total		15	85	100		

***p≤0.001, **κ** = 0.718

Most of the children had good medicines adherence (≥ 80%) across all diseases except asthma, where eight (47%) showed poor adherence by MPR and five of them (29.5%) showed poor adherence by MPR and self-report.

Two of five patients with anaemia showed poor adherence when measured by MPR and one of them showed poor adherence when measured by self-report and MPR.

One of three patients with sickle cell anaemia showed poor adherence when measured by MPR and self-report.

Five of six children with end-stage renal disease had good adherence by MPR, and all of them had good adherence by self-report.

Children with diabetes, cancer, heart disease, and growth hormone (GH) deficiency had complete medicines adherence. Further details of adherence are displayed in Table 4-8.

Table 4-8. Distribution of children's adherence to medicines by disease

	Poor adherence by MPR (<80%) n (n%)	Good Adherence by MPR (≥80%) n (n%)	Poor adherence by self-report (<80%) n (n%)	Good Adherence by self-report (≥80%) n (n%)
Epilepsy	3 (15.8%)	16 (84.2%)	2 (10.5%)	17 (89.5%)
Asthma	8 (47.1%)	9 (52.9%)	5 (29.5%)	12 (70.5%)
Diabetes	0	14 (100%)	0	14 (100%)
Growth Hormone Deficiency	0	8 (100%)	0	8 (100%)
Heart Disease	0	7 (100%)	0	7 (100%)
End-Stage Renal disease	1 (16.7%)	5 (83.3%)	0	6 (100%)
Anaemia	2 (40%)	3 (60%)	1 (20%)	4 (80%)
Leukemia	0	4 (100%)	0	4 (100%)
Psychiatric Disorder	0	3 (100%)	0	3 (100%)
Gastrointestinal Disorder	0	3 (100%)	0	3 (100%)
Sickle Cell Anaemia	1 (33.3%)	2 (66.7%)	1 (33.3%)	2 (66.7%)
Cystic Fibrosis	0	3 (100%)	0	3 (100%)
Hypothyroidism	0	3 (100%)	0	3 (100%)
Hypertension	0	2 (100%)	0	2 (100%)
Hyperactivity	0	1 (100%)	0	1 (100%)
Haemophilia B	0	1 (100%)	0	1 (100%)
Lupus Erythematous	0	1 (100%)	0	1 (100%)

4.3.5 Statistical analysis

Table 4-9 shows the stratification of the study participants' characteristics and their adherence to medicines as assessed by MPR. The only statistically significant association was that children whose parents had a university-level education had good adherence measured by the MPR compared with children whose parents had a secondary-level education or less. Forty-nine children whose parents had a university-level education showed good adherence compared to only 36 children of parents with a secondary-level education or less ($p = 0.007$). There was no statistically significant association between age and gender with the MPR. However, a non-significant result does not mean that there is no association. Our study was only powered to detect a difference of more than 18% in the adherence rates of the two exposure groups. The findings suggest that children who were adherent to medicines were younger than non-adherent children. Eighty-seven per cent of children aged < 10 years had good adherence to medicines, while almost 83% of children aged ≥ 10 years had good medicines adherence. Eighty-six per cent of females had good adherence to medicines, while 84% of males had good adherence to medicines.

Table 4-9 Stratification of the study participants' characteristics and children's adherence to medicine (MPR)

	Medicine Possession Ratio (MPR)		**p-value**
	Good Adherence ≥80% n=85 n(n%)	**Poor Adherence <80% n=15 n(n%)**	
Age ¥			
<10 years	42 (87.5%)	6 (12.5%)	0.501
≥10 years	43 (82.9%)	9 (17.7%)	
Gender ¥			
Male	47 (84%)	9 (16%)	0.735
Female	38 (86.3%)	6 (13.7%)	
Level of Education ¥			
Secondary or less	36 (75%)	12 (25%)	
University	49 (94.2%)	3 (5.8%)	**0.007****

¥: Chi-square test; **p ≤0.01.

Table 4-10 shows the stratification of the study participants' characteristics and their adherence to their medicines as assessed by self-report. Again, only the children with parents with university-level education were significantly associated with good adherence when compared with children with parents with secondary-level education or less ($p = 0.01$).

Again, there was no statistically significant association between age and gender with the reported adherence. The findings suggest similar results to those measured by the MPR (Table 4-9); younger children, females and children of parents with a university-level education had a higher adherence rate. Forty five children aged <10 years had good adherence to medicines (21 parents reported their children's adherence rate and 24 children reported their own adherence rate), while forty six children aged ≥10 years reported good medicines adherence (four parents reported their children's adherence rate and 42 children reported their own adherence rate).

Table 4-10. Stratification of the study participants' characteristics and self-report adherence to medicine

	Self-report adherence rate		p-value
	Good adherence ≥80% n=91 n(n%)	**Poor Adherence <80% n=9 n(n%)**	
Age ¥			
< 10 years	45 (93.8%)	3 (6.3%)	0.356
≥ 10 years	46 (88.5%)	6 (11.5%)	
Gender ¥			
Male	50 (89.3%)	6 (10.7)	0.499
Female	41 (93.2%)	3 (6.8%)	
Level of Education ¥			
Secondary or less	40 (83.3%)	8 (16.7%)	
University	51 (98.1%)	1 (1.9%)	**0.01****

¥: Chi-square test, **p ≤0.01.

4.3.6 Barriers and facilitators to medicines adherence

Questions Q2 to Q10 in the second part of our purpose designed questionnaire **(Appendix 4)** explored barriers and facilitators to medicines adherence in more detail. Four of these questions were open-ended questions (Q2a, Q2b, Q6 and Q10a) and the free text answers will be discussed later in the thematic analysis section. **Appendix 5** shows a summary table with the gender, age, disease, medicines, adherence rates and BMQ results for each participant.

The responses to these questions are summarised in Table 4-11. Most were answered by 99 participants, except Q5, which was answered by 97 participants and Q10, which was answered by 95 participants

Three questions about the barriers to medicines adherence from the first part of the questionnaire (Table 4-4 (Q1, Q8 and Q9)) were repeated to confirm the participants' answers and to explore further details of these barriers. Only one question, which was about forgetfulness, received different answers to the same question in the first and second parts (Table 4-4 and Table 4-11). Forty-five per cent of patients reported forgetting to take their medicines in the second part of the questionnaire, a lower percentage than that reported in the first part (Table 4-4 (Q1)) which was 62%. This difference may have occurred because an answer of Yes to Q2 in the second part of the questionnaire would require the patient to answer an open-ended question. This open-ended question was at the end of the

questionnaire. Because participants often wanted to complete the questionnaire quickly, some patients may have answered No to finish more quickly. It has been reported that response rates are lower for longer questionnaires (313).

The majority (77%) were worried about the side effects of the medicine, despite 76% not having experienced any side effects. One participant who had end-stage renal disease reported that he did not take his medicine because he was worried about the gastro-intestinal side effect of mycophenolate. Also, two participants reported that they did not take their medicines because they had experienced side effects. One experienced dry cough as a side effect of captopril and one experienced weakness and dizziness as side effects of levetiracetam.

Thirty-four children were responsible for measuring and taking their medicines by themselves (31 of these children were aged ≥ 10 years, and three were aged < 10 years old) (Q5). The mean percentage of adherence rates by MPR when the children were responsible for taking their medicines was 94.02% with a range of 63%-100%, while the mean percentage of adherence rates by self-report was 96.2% (all adherence rates were reported by children) with a range of 75%-100%. 78.5% children with diabetes, 64.5% of children with asthma and 50% of children with GH deficiency were responsible for taking their medicines **(Appendix 5)**. All patients with diabetes and GH deficiency showed good adherence rates (by MPR and self-reporting). However, eight patients with asthma showed poor

adherence rates by MPR, and five of the eight reported poor adherence rates (for four of these patients, their parents were responsible for administering the medicine and all of them showed poor adherence by the MPR and self-report). Nineteen of the children responsible for measuring and taking their own medicine had parents with a university-level education, and all of them showed good adherence rates by MPR and self-reporting, while the other 15 children had parents with a secondary-level or less education; six of the 15 showed poor adherence by MPR and four of the 15 reported poor adherence rates (None of these were analysed statistically because the sample size was small).

The mean adherence rate by MPR when the parents were responsible for measuring and administering medicine to their children was 90.78%, with a range of 50%-100%, while the mean percentage of self-reported adherence rates was 94.6% (26 parents reported the adherence rates and 40 children reported the adherence rates) with a range of 70%-100%.

Most participants who used medicines reminders had good adherence rates (60 participants by self-report and 58 by MPR).

Table 4-11 Questions about barriers and facilitators to medicines adherence

	Yes n (n%)	No n (n%)	Not answered n (n%)
2. Do you ever forget to take your medicine?	45 (45%)	54 (54%)	1(1%)
a. If so can you think of anything that makes this happen?	41 (41%)	0	4 (4%)
b. Can you think of anything that could help you to remember?	52 (52%)	0	0
3. Do you worry about side effects of any of your medicine?	77 (77%)	22 (22%)	1 (1%)
a. Does this ever put you off taking your medicines?	1 (1%)	98 (98%)	1 (1%)
b. If yes please tell us which medicines and give us an example of side effects that worry you.			
4. Have you experienced side effects of any medicine?	24 (24%)	75 (75%)	1 (1%)
a. Did this ever put you off taking the medicines?	2 (2%)	97 (97%)	1 (1%)
b. If yes please write the name of the medicines causing side effects and what side effects they were.			
5. Do you measure and take your medicine by yourself?	34 (34%)	63 (63%)	3 (3%)
6. Is there anything that makes it harder for you to take your medicine?	62 (62%)	37 (17%)	1 (1%)
7. Do you ever feel concerned about taking your medicine when other people are around?	59 (59%)	40 (43%)	1 (1%)

a. Does this ever put you off taking them?	12 (12%)	87 (87%)	1 (1%)
8. Do you have any worries about the number of medicine doses that you need to take or the time of the doses?	53 (53%)	46 (46%)	1 (1%)
a. Does this ever put you off taking your medicines?	2 (2%)	97 (97%)	1 (1%)
9. Do you have any worries about the size of tablets that you need to take or the taste of your medicine?	35 (35%)	64 (64%)	1 (1%)
a. Does this ever put you off taking your medicine?	0	34 (34%)	1 (1%)
b. If yes can you please give us an example?			
10. Have you tried or do you use any methods to help you with medicine taking?	60 (60%)	35 (35%)	5 (5%)
a. If yes, please describe them and how well they work.			

4.3.7 Thematic analysis

Further information on barriers and facilitators to medicines adherence was explored in the study participants' answers to open-ended questions in the second part of the questionnaire and shown in Table 4-11 (Q 2, Q6 and Q10). Questions 2a (answered by 41 participants) and Q6 (answered by 62 participants) explored barriers to medicines adherence and Q2b (answered by 52 participants) and Q10a (answered by 60 participants) explored facilitators of medicines adherence.

The participants' answers about the barriers to medicines adherence were grouped into seven themes and the answers regarding the facilitators of medicines adherence were grouped into six themes (Table 4-12).

Table 4-12 Barriers and facilitators themes.

Barriers themes	**Facilitators themes**
Many doses each day	Using reminder
Changes in usual routine	Established routine
Feeling better so not needing medicines	Masking poor taste/pain of medicine/big tablet
Fear of stigma	Family support
Medicine difficult to take due to size, poor taste/smell/pain/device	More acceptable medicinal product/ device provided
Fear of side effects	Medicines organiser
Being busy	

A. Barriers to medicines adherence

The study participants' answers about the barriers to medicines adherence (Q2a and Q6 in Table 4-11) were grouped into seven themes and 17 codes as shown in Table 4-13.

Table 4-13 Barriers to medicines adherence as reported by study participants

Barriers themes	n	Codes (n)
1. Many doses each day	**50**	• Many doses each day (n= 24) • Many doses each day and multiple medicines (n=18) • Night doses (n=5) • Multiple medicines (n=3)
2. Changes in usual routine	**33**	• Changes in usual routine (n=17) • Not at home (n=11) • Forget at weekends (n=3) • Holiday/Travelling (n=2)
3. Medicine difficult to take due to poor taste/smell/pain/device	**18**	• Poor taste (n=12) • Painful injection (n=4) • Difficulty with inhaler devices (n=2)
4. Fear of side effects	**12**	• Fear of side effects (n=12)
5. Being busy	**7**	• Busy (n=5) • Rushing (n=2)
6. Feeling better so not needing medicines	**3**	• Feeling better so not needing medicines (n=3)
7. Fear of stigma	**2**	• Embarrassed to take medicine in front of others (n=1) • Hates people knowing (n=1)

Theme 1: Many doses each day

This was the strongest theme reported by many participants (n = 50). This theme was reported by 36 children and 14 parents. This theme describes aspects of the dose frequency, which may affect medicine taking or

potentially hinder adherence. Fifty of the participants reported that many doses, multiple drugs or night doses made it hard for them to give or take their medicines.

'My medicines doses are too many because I need to take them every six hours, and sometimes I missed the night doses when I was sleeping' (Child: 16-year-old boy, asthma, Q6).

'I have to take many doses every day' (Child: 14-year-old boy, heart disease, Q6).

'Our child needs many doses every day, which may cause some doses to be forgotten sometimes' (Mother: four-year-old girl, epilepsy, Q2a).

Theme 2: Change in daily routine

This theme describes how a change in daily routine may lead to forgetting, which affects medicine adherence (n = 33). This theme was reported by 17 parents and 16 children.

'During the holiday time, I did not give my child her medicines as much as I should. We travel a lot, so our schedule was changing every day and sometimes we missed one or more doses' (Mother: five-year-old girl, anaemia, Q6).

'Change in routine' (Mother: three-year-old boy, anaemia Q2a).

'On weekends, we may go out and forgot to take the medicines with us' (Mother: five-year-old girl, epilepsy, Q2a).

Theme 3: Medicine difficult to take due to poor taste/smell/pain/device

This theme describes the effects of poor taste of medicines, pain caused by injections and difficulty with inhaler devices on medicine adherence (n = 18). This theme was reported by seven children and 11 parents. All the participants who reported that the bad taste of the medicine made it hard for them to take their medicine belonged to the younger group (aged < 10 years old). Some participants who reported poor taste showed poor adherence (five by MPR and three of them by self-report also).

> *'Some of her medicines taste badly, so we mix them with good flavoured juice' (Mother: seven-year-old girl, epilepsy, Q10a).*

> *'I take an insulin injection twice daily, and it is painful' (Child: 16-year-old boy, diabetes, Q6).*

> *'I have to take 3 puffs of salbutamol every 4 hours/Difficulty with inhalers devices' (Child: 14-year-old boy, asthma, Q6).*

Theme 4: Fear of side effects

Some participants (n = 12) linked adherence with their concern about the expected side effects of the medicine. This theme describes that the participants' fear of side effects made it hard for them to take their medicine. This theme was reported by three children aged ≥ 10 years old and nine parents.

'I fear of steroids side effects' (Child: 17-years-old girl, asthma, Q6).

'I have some concerns about the long effect of his medicine' (Mother: five- year-old boy, GH deficiency, Q6).

'Possible side effects of his medicines' (Mother: one-year-old boy, cancer, Q6).

Theme 5: Being busy

This theme describes the effect of children's or parents' preoccupation with other life matters on their medicine adherence (n = 7). This theme was reported only by parents.

'Busy with other children' (Mother: five-year-old boy, diabetes, Q2a).

'Rushing in morning' (Mother: seven-year-old boy, diabetes, Q2a).

Theme 6: Feeling better so not needing medicines

This theme describes that some of the participants felt their condition had improved, so they no longer needed to take their medicine (n = 3). This theme was reported by one child and two parents.

"Sometimes, I felt that, I did not need to take my inhaler when asthma symptoms disappeared" (Child:15 years old girl, asthma, Q6).

'The biggest thing that made it hard to give him medicines was that when he felt better, he thought that he didn't need his medicines anymore' (Mother: 10-year-old boy, asthma, Q6).

'Sometimes he refused to take his medicines because he thought that he felt better and didn't need the medicines' (Mother: nine-year-old boy, asthma, Q6).

Theme 7: Fear of stigma

This theme describes that some children fear being stigmatised because of their medicine, and this may affect their adherence (n = 2). Both participants who reported that a fear of being stigmatised made it hard for them to take their medicine were female.

'She hates people knowing about her medicines' (Mother: eight-year-old girl, epilepsy, Q6).

'Sometimes I ashamed to take my inhaler in front of my friends and others' (Child: 15-years-old girl, asthma, Q6).

B. Facilitators of medicines adherence

The answers of the study participants (Q2b, Q10a in Table 4-11) regarding the facilitators of medicines adherence were grouped into six themes: and 14 codes as shown in Table 4-14.

Table 4-14 Facilitators of medicines adherence as reported by study participants

Facilitators themes	n	Codes (n)
1. Using reminders	**56**	• Phone alarm (n=31) • Writing notes (n=14) • Clock alarm (n=11)
2. Established routine	**29**	• Established routine (n=18) • Taking medicine on waking and before sleeping (n=6) • Linking medicine taking with meals (n=5)
3. Masking poor taste/pain of medicine/big tablet	**17**	• Mix with drink (n=9) • Takes with drink (n=2) • Ice helps (n=2) • Mix with yoghurt (n=2) • Change injection site (n=2)
4. Family support	**8**	• Family help/support (n=8)
5. Medicines organiser	**4**	• Pillbox (n=4)
6. More acceptable medicinal product/device provided	**1**	• Pen injection device better (n=1)

Theme 1: Using reminders

Fifty-six of the participants' answers were grouped under the theme of using reminders, such as a phone alarm (n = 31), writing notes (n = 14) and an alarm clock' (n = 11). This theme was reported by 29 children and 27 parents. Most of these participants showed good adherence (55 by self-report and 53 by the MPR).

> *'We set a phone alarm to remind us of the time of doses' (Father: three-year-old boy, epilepsy, Q10a).*
>
> *'I use clock alarm to help me remember' (Child: 10-year-old girl, lupus erythematous, Q2b).*
>
> *'Writing notes to remember my medicines' (Child: 13-year-old girl, asthma, Q10a).*

Theme 2: Established routine

Twenty-nine of the participants' answers were grouped under the theme of established routine. The participants reported that establishing a routine helped them remember to take their medicine. Four of these participants used medicine reminders with an established routine, and all of them showed good adherence by MPR and self-report. This theme was reported by 15 children and 14 parents. All participants who reported that they linked medicine taking with meals were diabetic patients.

'It was easy to remember to take medicine when I link it with the meals times' (Child: 18-year-old boy, diabetes, Q2b).

'I take my medicine when I wake up every morning' (Child: 12-year-old girl, hypothyroidism, Q2b).

'Set phone alarm and establish routine' (Mother: five-year-old girl, epilepsy, Q2b).

Theme 3: Masking poor taste/pain of medicine/big tablet

Seventeen of the participants' answers were grouped under the theme of masking the poor taste/pain of medicine. Thirteen participants reported that they mixed or took their medicine with juice, a drink or yoghurt to make its taste more acceptable. Four participants reported that they put ice on the injection site, or they changed the injection site to relieve injection pain. This theme was reported by one child and 16 parents.

'She did not like her medicine's taste, and we mixed with juice' (Mother: six-year-old boy, epilepsy, Q10a).

'We give her medicine with yoghurt' (Mother: 11-year-old girl, sickle cell anaemia, Q10a).

'We put ice on the injection site to relieve the pain' (Mother: 10-year-old girl, GH deficiency, Q10a).

'Change injection site' (Mother: seven-year-old boy, diabetes, Q10a).

Theme 4: Family support

Eight of the participants' answers were grouped under the theme of family support. The participants reported that family support was important for encouraging children to take their medicine. This theme was reported only by children.

> *'When I was first diagnosed, I had difficult times that I could not have overcome without my family's support and help' (Child: 16-year-old boy, end-stage renal disease, Q6).*
>
> *'My family reminds me to take my medicine if I forgot it' (Child: 14-year-old girl, anaemia, Q2b).*
>
> *'My mother reminds me to take my medicine' (Child: 13-year-old girl, GORD, Q2b).*

Theme 5: Medicines organiser

Four of the participants' answers were grouped under the theme of medicines organiser. The participants reported that the use of an organisational tool, such as a pillbox, helped them organise multiple medicines by day and dose. This theme was reported by three children and one parent.

> *'With a pillbox, it became easy for us to organise our multiple medicines and doses' (Mother: 10-year-old girl, cancer, Q10a).*
>
> *'I use a pillbox' (Child: 13-year-old girl, epilepsy, Q10a).*

Theme 6: More acceptable medicinal product/device provided

Only one participant reported that using a more acceptable medicinal device helped her with medicine taking.

> *'My doctor changed my insulin needle to new pen injection device which is less painful' (Child: 15-year-old girl, diabetes, Q10a).*

4.3.8 Beliefs about Medicines Questionnaire (BMQ)

All questions were answered by all 100 participants except Q3 and Q7 answered by 99 participants and Q5 and Q6 answered by 98 participants.

On the **necessity** scale (Q1, Q3, Q4, Q7 and Q10), Table 4-15 shows that 82 participants agreed or strongly agreed that, '*My health at present depends on my medicine*'. Also, 81 participants agreed or strongly agreed that, '*My medication protects me from becoming worse*'.

On the **concern** scale (Q2, Q5, Q6, Q8 and Q9), 76 participants agreed or strongly agreed that, '*I sometimes worry about the long-term effects of my medication'.* Furthermore, 61 participants agreed or strongly agreed that, '*I sometimes worry about becoming too dependent on my medication*'. More than two-thirds of the participants disagreed or strongly disagreed that, '*My medication is mystery to me* (Table 4-15).

Table 4-15 Beliefs about Medicines among Saudi participants.

	Strongly Agree	Agree	Uncertain	Disagree	Strongly Disagree
Q.1: *My health at present depends on my medicine*	34	48	8	7	3
Q.2: *Having to take medication worries me*	8	36	21	33	2
Q.3: *My life would be impossible without my medication*	27	28	20	20	4
Q.4: *Without my medication I would be very ill*	26	37	17	16	4
Q.5: *I sometimes worry about the long-term effects of my medication*	18	58	6	14	2
Q.6: *My medication is a mystery to me*	2	12	18	58	8
Q.7: *My health in the future will depend on my medication*	18	38	24	16	3
Q.8: *My medication disrupts my life*	5	29	19	41	6
Q.9: *I sometimes worry about becoming too dependent on my medication*	7	54	10	28	1
Q.10: *My medication protects me from becoming worse*	38	43	13	6	0

Twenty-six parents and 74 children answered the BMQ. The mean necessity score of the parents was 19 and the mean concerns score was 13.6. The mean necessity score of the children was 17.2 and the mean concerns score was 15.45. Children appeared to have less necessity beliefs and more concern beliefs than parents (Table 4-16).

Children with parents with secondary-level education or less appeared to have less necessity beliefs and more concern beliefs than children with parents with university-level education level (Table 4-16).

Table 4-16 Mean BMQ necessity and concerns scales in different groups.

	Mean BMQ necessity score	**Mean BMQ concern score**
Children Parents	17.2 19	15.45 13.6
Older children Younger children	17.48 18.15	16.27 15.79
Children with parents with university-level education Children with parents with secondary-level education	18.31 17.33	15.73 16.38

The mean necessity score of all the study population was 18 and the mean concerns score was 15. A positive mean necessity-concerns differential of 3 was calculated. Most of the participants (74%) had a higher necessity than concern score and 26% had a higher concern than necessity score (Table 4-17).

The participant who had the highest positive differential score reported 100% adherence rate by MPR and self-report and the participant who had the highest negative differential score reported 75% adherence rate and had 67% adherence rate by MPR.

Table 4-17. Mean BMQ necessity and concerns scales

	n	**[Min-Max]**	**Mean ± SD**
BMQ Necessity Scale (mean ±SD)	100	[7-25]	18.00±4.25
BMQ Concerns Scale (mean ±SD)	100	[5-25]	15.00±3.4
Necessity-Concerns differential	100	[(- 6) – (12)]	3
Positive or equal differential	74 (74%)	-	-
Negative differential	26 (26%)	-	-

Table 4-18 shows that patients' necessity beliefs about medicines exceeded their concerns in 67 participants with good adherence as assessed by MPR and seven participants with poor adherence. Eight patients with strong concern belief scores had poor adherence, six of them with asthma, one with epilepsy and one with diabetes.

The chi-square test showed a statistically significant association between the BMQ differential score and the MPR ($p = 0.009$). This suggests a positive relationship between good medicines adherence and a positive BMQ differential score, where participants have greater belief in the necessity of taking medicines than concern about the medicines.

Table 4-18. Correlation between BMQ differential scores and MPR adherence

		Medication Possession Ratio		**Total**	**P-value**
		Good adherence ≥80% n (n%)	**Poor adherence <80% n (n%)**		
BMQ differential scores ¥	Higher necessity belief score (0* or positive differential)	67 (90.5%)	7 (9.5%)	74	**0.009****
	Higher concern belief score (Negative differential)	18 (69.2%)	8 (30.8%)	26	
Total		85	15	100	

¥: Chi-square test. ** p ≤0.01. * four participants had zero differential score.

Table 4-19 shows that medicine necessity beliefs exceeded concerns in 70 participants with good adherence to medicines as assessed by self-report and four participants with poor adherence. Five patients with higher concern belief scores had poor adherence, four with asthma and one with epilepsy.

The chi-square test showed a statistically significant association between the BMQ differential score and the reported adherence rate ($p = 0.034$). This means there is a relationship between medicines adherence rates measured by self-report and the BMQ differential score.

Table 4-19. Correlation between BMQ differential scores and self-reported adherence

		Self-report adherence rate		**Total**	**P-value**
		Good adherence ≥80% n (n%)	**Poor adherence <80% n (n%)**		
BMQ differential scores ¥	Higher necessity belief score (0 or positive differential)	70 (94.6%)	4 (5.4%)	74	**0.034***
	Higher concern belief score (Negative differential)	21 (80.8%)	5 (19.2%)	26	
Total		91	9	100	

¥: Chi-square test. * $p \leq 0.05$.

4.4 Discussion

As stated at the beginning of this chapter, from our systematic review **(Chapter 3)** we found only one study conducted in Saudi Arabia that explored the barriers to medicines adherence in children with epilepsy (177).

The current study is the first to measure medicines adherence and to explore the barriers and facilitators in children with a variety of chronic diseases in Saudi Arabia. It demonstrated a substantial agreement between the two adherence measurement methods (self-report and the MPR).

Furthermore, this study found a statistically significant association between the BMQ differential score and adherence rates. This suggests a positive relationship between good medicines adherence and a positive BMQ differential score, indicating that participants with a greater belief in the necessity of taking a medicine than concerns about the medicine are more likely to be adherent.

We also found a statistically significant association between good adherence rates and the children of parents with a university-level education.

No statistically significant associations between adherence rates and age and gender were found.

Additionally, this study identified that many doses each day, changes in daily routine, medicines being difficult to take due to large tablet size, poor

taste/smell, causing on pain on administration or difficult to use devices and fear of side effects were the most common barriers to medicines adherence.

Using reminders, established routine for taking medicines, measures to address poor taste, pain caused by administration or taking big tablets and family support were the most common facilitators for medicines adherence in children.

4.4.1 Adherence rates

Patients with ≥ 80% adherence were defined as having good adherence and patients below that level as having poor adherence. This study showed that most participants displayed good medicines adherence using the two medicines adherence measures, self-reporting (95%) and the MPR (92%). This result is consistent with previous studies conducted in the UK, the USA, India, Sweden, Saudi Arabia and Thailand in which mean adherence rates were ≥ 80% among children with chronic diseases, including asthma, ADHD, epilepsy and HIV (81,87,177,230,246,249).

This study also showed a substantial agreement between adherence measured by participants' self-reports and the MPR ($\kappa = 0.718$). Similar to this result, Muller et al. conducted a study in South Africa with children with HIV and reported that there were no significant differences between adherence rates measured by self-report and MPR ($p > 0.1$) (120). However, in the current study, adherence rates measured by self-report were slightly higher than those measured by the MPR, which is similar to

previous studies conducted among children with thalassemia and chronic kidney disease (129,253). The high self-reported adherence rate may be the result of participants' tending to provide socially desirable responses (314).

In the current study the mean percentage of medicines adherence as reported by parents was slightly higher than the mean percentage reported by children. Parents appear to overestimate their children's adherence to medicines, possibly to avoid being accused of failing to give their children their medicines as prescribed (31,37,118). In addition, in Goodfellow et al.'s (178) study with children with cystic fibrosis, they noted that the parents reported higher adherence rates than the children. They justified this by proposing that the parents may have thought their children had taken their medicine when they had not (178).

Both methods were found to be inexpensive and easy to use, but they do not guarantee medicines' taking/administration as highlighted in previous studies (120,129,132).

The free education system in Saudi Arabia has encouraged Saudi people to continue their studies and obtain a high level of education (315,316). In addition, the Saudi government gives stipend to postgraduate students to help them with the cost of living (315). In this study, half of the children's parents had a university degree, which reflects the support available from the Saudi Arabia government for encouraging people to continue their

education. The adherence rate (measured by MPR and self-report) was significantly (p<0.05) associated with the level of parental education, meaning that good adherence was positively associated with a high parental education level. This result is consistent with reports in previous studies conducted with children in Jordan, Iran, US and Brazil (129,233,240,253,293). This finding suggests that parents with higher education levels are more likely to understand the necessity of adherence and the effects that poor adherence can potentially have on their child (240).

4.4.2 Barriers to medicines adherence

Many barriers to medicines adherence were identified from the quantitative and qualitative analyses in the current study.

The quantitative results of this study reported that the top four perceived barriers to medicines adherence amongst children with chronic diseases in Saudi Arabia were '*I worry about possible side effects*' as reported by 79 (79%) of the participants followed by '*I forget to take my medicine*' reported by 62 (62%). '*I worry about what other people would think of me if they knew I took medicine*' was reported by 62 (62%) of patients and '*I take lots of medicine or many doses per day*' reported by 57 (57%). Previous studies conducted in patients with IBD, epilepsy, asthma and HIV support these findings (167,177,196,240). For example, Gabr et al. found the primary reasons for poor adherence in patients with epilepsy in Saudi Arabia were a fear of side effects, forgetfulness and high numbers of medicines (177).

The qualitative results of this study reported that the most common barriers to medicines adherence were many doses each day, changes in daily routine, medicines being difficult to take due to large tablet size, poor taste/smell, causing on pain on administration or difficult to use devices and fear of side effects. Each barrier is discussed separately below.

In this study, multiple drugs, doses and night doses were the most common reported barrier. These findings are supported by previous research (122,162,177,210,236,240,245). A study conducted in the USA with children with HIV reported that complexity of medicine regimen was significantly associated with poor adherence (p<0.05) (210). Two studies conducted in Australia and Iran with children with asthma found that taking many medicines at different times of the day may affect adherence to timing of the medicines' administration, which could result in missed or delayed doses (122,240). Having to take multiple medicines a day or the same medicine multiple times a day is a barrier to many patients (122,240). In the current study, evening doses are seen as a separate barrier as children normally go to sleep earlier than most adults so taking their medicines at a late hour could affect their adherence.

In this study, the answers reported by children and parents revealed that changing a daily routine (being outside the home, holidays/travelling) was the most common cause of forgetfulness. Likewise, previous studies showed that reasons such as 'interferes with activity' and 'wasn't home' caused

poor adherence in patients with HIV, IBD, kidney diseases, asthma, cystic fibrosis, chronic rheumatic disease and diabetes (95,164,170,189,192,243,254,284,291). Everyday life activities have a large impact on whether patients take their medicines as prescribed (189). We could infer that parents, or perhaps even children, do not always follow a daily routine when taking medicine (243).

The third most common barrier that reported by the participants in the current study was 'medicine difficult to take due to poor taste/smell/pain/device' (n = 18). Taste-masking is a major barrier to the development of medicines as oral liquid formulations (317). The bad taste of some medicines has been associated with poor medicines adherence in patients with ADHD, psychiatric disorders and kidney diseases (85,92,254,259). In the current study, some participants who reported poor taste showed poor adherence (three by self-report and five by MPR). Venables et al. found that the bad taste of medicine was significantly associated with medicine refusal in children and poor adherence ($p<0.001$) (92). Some evidence indicates that mixing the medicine with drinks or food to make the taste more acceptable may reduce the delivered dose and affect the effect of medicine (92).

Fear of medicine side effects was the fourth most common barrier reported by 12 participants in the current study. Eight of them showed poor adherence by MPR and five of them showed poor adherence by self-report. Likewise, previous studies have shown that a fear of unknown, adverse side

effects is the reported reason for discontinuing daily medicine for patients with HIV, asthma, epilepsy, chronic rheumatic disease, tuberculosis and psychiatric disorders (70,85,193,196,197,240,254,270,288,292). This fear may greatly impact medicine adherence, especially if the patient believes it is not necessary to take their medicine (173,240).

In our study, the BMQ was used to assess patients' and parents' beliefs about the necessity of medicines and concerns about their long-term use. Substantial evidence from children suffering a wide range of chronic diseases and their parents demonstrates that these beliefs have a major impact on adherence to medicines (68,81,126,173–176,178). Our study's results revealed that most participants perceived the necessity of medicines outweighs concerns about their long-term use. Significantly, there was higher adherence among those with lower concern about their medicines use and with stronger beliefs in the necessity of medicines. Patients with negative necessity-concern differential scores were less adherent compared to patients with positive scores. These results are supported by several studies conducted in Saudi Arabia, the USA and Sweden among children with asthma, epilepsy and ADHD that found statistically significant associations between the BMQ differential score and the reported adherence rate (81,174,177). For example, Gabr et al. conducted a study involving children with epilepsy in Saudi Arabia using the BMQ and reported that patients who believed that medicines do more harm than good were less likely to adhere to their medicines ($p<0.05$) (177).

Overall, these results suggest that the BMQ differential score is a robust indicator of medicines adherence and shows that adherence in children may be influenced by their beliefs about their medicines.

Our results showed that most children had good medicines adherence (≥80%) across all diseases except asthma, in which 47% of children showed poor adherence by MPR and 30% showed poor adherence by self-report. Klok et al. measured adherence rates by EMD and found that 41% of asthmatic children demonstrated poor medicines adherence (68). Koster et al. measured adherence rate by self-report and concluded that 43% of children with asthma had poor medicines adherence (243).

The low adherence rates of children with asthma could be explained by differences in asthma severity. Low severity of asthma together with low patients' beliefs about the necessity of taking medicines and greater concern about medicines have been associated with poor medicines adherence (68,173,174). In our study, all patients with asthma who reported poor adherence had greater concerns about the medicines than their beliefs about the necessity of taking them. Several studies conducted with children with asthma and IBD found that children who experienced a reduction of symptoms may not take their medicines in order to avoid expected side effects (90,239,267).

Our study suggested that when children were given full responsibility to take their medicines, they displayed a slightly higher adherence rate (94% by MPR, 96% by self-report) than children whose parents were responsible

(90% by MPR, 94% by self-report). Several studies similarly reported that when children with HIV and asthma were responsible for taking their medicines, they showed a higher adherence rate than children whose parents were responsible for administering the medicines to their children (69,196,199,240,249). This could be because when children are responsible for taking their medicines, they sense their importance and rely on themselves to take them, even in the absence of their parents (196,199). The transition of the responsibility to take medicines from parents to children is an important area and there are some points that it is suggested should be taken into account (61). Children must be aware of the importance of their medicines and how to use them (318). In addition, during this transition, it is recommended that parents and children have a discussion with their healthcare providers regarding medicines adherence and any factors that might affect adherence (61,318). If a child is not yet ready to take full responsibility, it is preferable for their parents to continue to support them until it is confirmed that the child has the ability to take responsibility for himself (61).

4.4.3 Facilitators of medicines adherence

Our study found that the most common perceived facilitator of medicines adherence, as reported by 96 (96%), was '*I have good family support'*. In addition, 81 (81%) agreed that '*I use a medicine reminder or routine about my medicine*', and 80 (80%) agreed that '*We were given enough information about my illness and the importance of treatment*'. As this study

only focused with children, having good family support was the highest rated facilitator as many children rely on their parents for help with their medicines' administration.

Additionally, as our systematic review **(Chapter 3)** suggested that forgetfulness is one of the most common barriers to adherence, setting reminders or a routine is a way to overcome this barrier, as it seems to highly be an effective facilitator. In our study most participants who used medicines reminders had good adherence (by MPR and self-report). Moreover, patients who are more aware of why they are taking their medicines and what effects they may experience if they do not take their prescribed medicines are more likely to have good adherence.

The qualitative results of this study revealed the most commonly reported facilitator for medicines adherence was '*using reminders*' such as setting alarms on phone or clock and making notes, which agrees with findings from previous studies conducted with children with HIV, asthma, kidney disease, solid organ transplant and chronic diseases (70,85,87,91,122,189,193,241,243) and using these tools was associated with good adherence (87,122,241,243). Using a phone or clock alarm was the most common technique among the current study's participants to avoid forgetfulness, as it provides patients (or patients' parents) with automatic reminders to take their medicine.

Another facilitator to medicines adherence reported by participants was established routine with the dose times. Twenty-nine participants reported that integrating medicine into daily routines (e.g., meals, morning, and bedtime) and taking medicine at a specific time each day helped them to avoid forgetfulness. Similarly, previous studies reported that using a scheduled routine corresponded to good adherence (70,87,91,122,189,193,241,243). Some participants in our study however, reported that having an established, scheduled routine is challenging when away from home and or when there are changes in daily routines.

Medicines administered to children have different tastes and smells. Children may be hesitant to take bad-tasting medicines, or they may vomit or spit out the dose, resulting in an inappropriate use of medicines, because the child is not receiving the full dose. A bad drug taste has been extensively reported as a factor associated with poor medicines adherence (170,193,197,198,208,213,215,254). In this study, 13 participants' answers were grouped under the '*Masking poor taste'* (e.g., mixing medicine with water or juice, taking it with yoghurt or water). Masking the taste of medicines and parent counselling about a medicine's flavour could have a positive impact on adherence. El Rachidi et al. reported that techniques like using flavours and oral syringes for drug administration can conceal or minimise an unpleasant taste (58).

4.4.4 Implications for practice

Healthcare providers who are interested in medicine adherence should consider the difficulties faced by with children and their parents. Finding ways to flexibly address the various causes of non-adherence and empower children and their parents to honestly disclose their medicine adherence are essential.

Children may have important opinions about their medicine; therefore, it is critical that healthcare providers address and include children when discussing matters related to medicines.

The adherence measures of MPR and self-report used in this study were in substantial agreement, which suggests that both are reliable. Calculation of the MPR requires sufficient time and information from the patients' records. Self-report is inexpensive and easy to use. Doctors could assess their patients' medicine adherence in a short time by using a single question self-report.

Children's and parents' beliefs about the necessity of medicine and their concerns about their use significantly impact their medicine adherence. To improve medicine adherence, healthcare professionals in Saudi Arabia can help develop patients' and parents' beliefs by explaining the importance of the medicine and addressing their concerns at each medical or pharmacy appointment.

The BMQ differential score is a robust indicator of medicines adherence and suggests that adherence in children may be influenced by their beliefs regarding their medicines. It was easy for participants (parents and children) to answer the BMQ because of the options of available answers and answering the BMQ did not take a long time (from two to five minutes). These advantages may make the BMQ easy to use during medical appointments, while patients wait to meet with their healthcare providers. Alternatively, it may be better to send it to patients' homes before appointments so that they can bring it with them already answered.

4.4.5 Limitations

There were some limitations to this study. We had sufficient statistical power to detect only quite large differences in adherence rates between exposure groups (e.g. differences greater than 18% of adherence rates between two different groups). Therefore, smaller differences would have been missed in this study. A larger sample size would be needed in future studies to detect smaller differences.

In this study, we could not conduct statistical comparisons between sub-groups (e.g. the medicine-taking responsibility of the child vs his/her parents) because the sub-group sample sizes were too small. However, we compared the adherence rates between these sub-groups by looking at the percentages of adherent children in each group and found some

differences between them. In future research, it would be interesting to conduct such comparisons by increasing the sample sizes.

Neither adherence measure guaranteed that the patients actually took their medicines. For all patients who took more than one medicine they reported the same adherence rate to each medicine. Additionally, the MPR percentages were the same for each medicine. Some patients may have a different adherence rate for each medicine. Hence, further research is required to discover a method that can accurately measure medicines adherence in children and guarantee that patients took their medicine.

In addition, while some patients refused to participate in our study, we did not document their numbers. We have no way to discern why they refused or whether they may be different from our sample in terms of adherence. In a future study, it would be useful to document the numbers of patients who refuse to participate and to explore their reasons for refusal if possible.

4.5 Conclusions

This study found good agreement between the two adherence measurements MPR and self-report. Parental education level and BMQ differential scores were found to be factors that were significantly associated with medicines adherence.

The study has shown for most participants a positive necessity–concern differential, which indicates that these participants cared more about the necessity of administering medicines than the anticipated harm.

The most common barriers to medicines adherence identified were many doses each day, changes in daily routine, medicine difficult to take due to poor taste/smell/pain/device and fear of side effects and the most common facilitators were using reminders, established routine for taking medicines, masking poor taste/pain of medicine/big tablet and family support.

This study was the first such study in children with chronic diseases in Saudi Arabia and its' findings will add to the understanding of the barriers to and facilitators of medicines adherence.

Chapter 5: Exploratory study on the barriers and facilitators of medicines adherence in a UK children's hospital

5.1 Introduction

Our systematic review **(Chapter 3)** showed that twelve studies had been conducted in the United Kingdom (85,87,277,278,92,126,178,219,228,238,261,276) to explore the barriers and facilitators to medicines adherence in children, seven of which were conducted with patients with specific diseases: two with patients with HIV (219,228), two with patients with asthma (87,238), one with patients with psychiatric diseases (261), one with patients with epilepsy (126) and one with patients with cystic fibrosis (178). Only five studies were conducted with patients with diverse diseases (85,92,276–278). Four of the five studies with patients with diverse diseases did not address all barriers and facilitators to medicines adherence in children: three explored only formulation factors affecting adherence (92,276,278) and one explored only barriers to administering non-oral formulations in a paediatric population (277).

Only one study addressed all barriers and facilitators to medicines adherence in children with diverse diseases (85). This study focused mainly on parental reporting rather than child reporting and excluded younger children and the parents of older children from discussions. It examined the barriers and facilitators of adherence only in four specific diseases including diabetes, asthma, epilepsy, and heart disease (85) and was conducted over ten years ago. This study suggested that future research should include the parents of older patients and also younger patients in the discussion (85).

In our study, we proposed to take this work further by measuring medicines adherence and examining the barriers to and facilitators of medicines adherence in children by including all parents and all children in the discussions. We also recruited children with a wider variety of long-term conditions than had previously been studied.

5.1.1 Aims

Our study aims were to:

- Measure medicines adherence in children with chronic diseases attending the Derbyshire Children's Hospital in the UK.
- Explore the barriers and facilitators to medicines adherence in these children.

5.2 Method

The study was approved by the NHS Health Research Authority (HRA) and Health and Care Research Wales (HCRW). It was also approved by the Research and Development (R&D) Department of the University Hospitals of Derby and Burton NHS Trust and was conducted in the Derbyshire Children's Hospital in the UK **(Appendix 6)**.

As part of the approval processes the researcher completed a Research Integrity Comprehensive course (standalone online learning course) **(Appendix 7)**.

This study was conducted between 1 December 2019 and 18 January 2020 at the Derbyshire Children's Hospital, which provides healthcare for 94,000 children annually (319).

5.2.1 Inclusion criteria

- Paediatric patients ≤ 18 years receiving long-term medicines who were inpatients or attending outpatient clinics at the Derbyshire Children's Hospital.
    - If a child was too young to complete the questionnaires but was willing to take part then their parent would assist the child by completing the questionnaires in the child's own words i.e. reading questions out to the child and writing the answers down.
- Parents of children taking long-term medicines who were too young to provide their own opinions on the questionnaires.

5.2.2 Exclusion criteria

- Patients over 18 years old.
- Patients/ Parents who were too distressed/ ill to approach.
- Patients/ Parents who did not speak English or Arabic.

5.2.3 Recruitment

Participants were recruited from the waiting area of the outpatients' clinics and from paediatric inpatient wards in the Derbyshire Children's Hospital.

The researcher asked the nurses in the waiting area of the outpatients clinics and in the paediatric inpatient wards about which families would be suitable to approach in terms of the age of the patients, the medicines prescribed and the ability to speak English or Arabic.

In compliance with the requirements of the NHS Health Research Authority to recruit participants, the researcher needed to be introduced to participants by a member of Trust staff. The researcher was therefore introduced to the participants by the clinic or ward nurses, the Chief Investigator (Sharon Conroy, Paediatric Pharmacist) or a nurse from our research group (Coral Smith) (also employed by the Trust). Participant information sheets and consent forms were available in English and Arabic **(Appendix 3)**.

After eligibility for inclusion in the study was confirmed by the Trust staff and the researcher had been introduced to the family, the patients and their parents or guardians were asked to participate in the study. They were provided with written and verbal information about the study in age-appropriate language by the researcher (MA).

In all cases, informed consent was obtained from the parent/legal guardian or the child if ≥16 years of age. The patients and parents were asked to answer the questions in the BMQ and our own designed questionnaire form **(Appendices 3 and 4)**. The participants' personal information was recorded on the consent forms only, and the researcher coded the completed questionnaires with a number corresponding to each

participant's consent form. Some participants expressed a preference to complete the questionnaires at home and for these participants, a stamped addressed envelope was provided to post the questionnaires back.

We sought and received approval from the HRA, HCRW and the Trust R&D department) to view the patient's Summary Care Records in order to find information on prescription refills so that we could calculate the Medication Possession Ratio (MPR). The researcher and the Chief Investigator viewed the initial patient's Summary Care Records and found unfortunately that the information available in this was not enough to calculate the MPR. Therefore, the adherence rates in this study were assessed by self-report only.

The questionnaires and consent forms were stored separately in locked facilities in the University Medical School. Data were entered on University password-protected computers and analysed using SPSS version 26.

5.2.4 Justification of the questionnaires

We used the same questionnaires as previously described and justified in the Saudi study in **Chapter 4** (BMQ and our designed questionnaire).

5.2.5 Thematic analysis

As mentioned in **Chapter 4**, Braun and Clarke's six-phases framework was followed to conduct thematic analysis of the free text data obtained from the questionnaires by grouping into codes and themes (310).

As a reliability measure, all the participants' answers, codes and themes generated were checked and agreed between the Chief Investigator and the researcher.

5.2.6 Statistical analysis

As described in **Chapter 4**.

5.2.7 Sample size and justification

As described in **Chapter 4**.

5.3 Results

5.3.1 Demographic and clinical characteristics

In total, 108 families were asked to join the study. Five parents did not consent to participate, with two of them saying that they did not have time and the other three not providing a reason. Four participants agreed to answer the questionnaires at home and post them back in the envelope provided, however only one of these participants returned their questionnaires to us.

One hundred children/parents therefore participated in the study. Forty-four children answered the questions themselves, 29 answered the questions with the help of their parents and 27 parents answered the questions for their children. Nine participants did not answer every question. This is described below for each section.

Appendix 8 shows a summary table with the gender, age, disease, medicines, adherence rates and BMQ results for each participant.

As explained in the last chapter, previous studies used the mean or median age as a cut-off point to compare two different age groups (older and younger age groups) (129,178,233). The mean age of the participants in our study was 10.03 ± 4.85 years (range: 1-18 years), and the median age was ten years. Therefore, ten years was chosen as the cut-off point to compare the two age groups. Fifty-six children (56%) were ≥ ten years of age and 44 (44%) were under 10 years of age. Fifty-three (53%) of the children were female. Slightly more than half of the children's parents (54%) had a university or college education, and 46% had a secondary education. One-fifth of the study population (22%) had asthma, 12% had epilepsy and 10% had acne (Table 5-1).

Table 5-1 Demographic and clinical characteristics of the study population (n = 100)

Age (mean ± SD), (median)	(10.03±4.85), (10)
≥10 years	56 (56%)
<10 years	44 (44%)
Gender	
Male	47 (47%)
Female	53 (53%)
Level of Education	
Secondary	46 (46%)
University or college degree	54 (54%)
Disease	
Asthma	22 (22%)
Epilepsy	12 (12%)
Acne	10 (10%)

Constipation	7 (7%)
Attention Deficit Hyperactivity Disorder	6 (6%)
Gastroesophageal reflux disease (GORD)	5 (5%)
End-Stage Renal disease	5 (5%)
Eczema	3(3%)
Autism	3 (3%)
Heart disease	3 (3%)
Diabetes	3 (3%)
Anaemia	3 (3%)
Inflammatory Bowel Disease	2 (2%)
Bronchitis	2 (2%)
Cystic Fibrosis	1 (1%)
Hypothyroidism	1 (1%)
Growth Hormone deficiency	1 (1%)
Cystic fibrosis	1 (1%)
Extreme Prematurity	1 (1%)
Migraine	1 (1%)
Nocturnal enuresis	1 (1%)
Thalassemia	1 (1%)
Pseudohypoaldosteronism	1 (1%)
Chronic urticaria	1 (1%)
Psoriasis	1 (1%)
Scleroderma	1 (1%)
Juvenile dermatomyositis	1 (1%)
Chronic bullous disease of childhood	1 (1%)

5.3.2 Most common barriers to medicines adherence

The answers to the first part of our purpose designed questionnaire are summarised in Table 5-2. All questions exploring perceived barriers to medicines adherence were answered by all participants except Q8 which was answered by 99 participants.

The most frequently perceived barrier of medicines adherence was '*I forget to take my medicine'* as reported by 52 (52%) of the participants. This was followed by '*I worry about possible side effects'* reported by 50 (50%) and '*I have to take lots of medicine or many doses per day'* reported by 50 (50%) (Table 5-2).

Forty-seven participants ticked "agree" for '*My medicine tasted bad'*. Thirty-nine of these participants were belonged to the younger age group. Twelve participants ticked "not certain" for '*My medicine tasted bad'* (Table 5-2). Five of these participants were taking non-oral medicines; three participants with diabetes and one with GH deficiency were taking injections only, while one participant with GORD was taking medicines via a feeding tube (percutaneous endoscopic gastrostomy (PEG) tube). The other seven participants were taking oral medicines.

Twenty-one participants ticked on "agree" for Q7 '*I don't know enough about the illness and treatment'.* Nineteen of these participants were with parents with a secondary-level education.

Table 5-2 Barriers to Medicines adherence as perceived by the study population

	Agree n (n%)	**Disagree** n (n%)	**Not Certain** n (n%)	**Not answered** n (n%)
Q.1: *I forget to take my medicine.*	52 (52%)	46 (46%)	2 (1%)	0
Q.2: *My medicine tastes bad.*	47(47%)	41 (41%)	12 (12%) *	0
Q.3: *I worry about possible side effects.*	50 (50%)	45 (45%)	5 (5%)	0
Q.4: *I don't have enough family support.*	8 (8%)	91 (91%)	1 (1%)	0
Q.5: *I don't know enough about the illness and treatment.*	21 (21%)	71 (71%)	8 (8%)	0
Q.6: *The medicine makes me feel sick.*	12 (12%)	78 (78%)	10 (10%)	0
Q.7: *We weren't given enough information about the illness and treatment.*	10 (10%)	88 (88%)	2 (2%)	0
Q.8: *I have to take lots of medicine or many doses per day***.**	50 (50%)	43 (43%)	6 (6%)	1 (1%)
Q.9: *I worry about what other people would think of me if they knew I took medicine.*	24 (24%)	68 (68%)	8 (8%)	0
Q.10: *I don't need to take my medicine as my symptoms have gone.*	6 (6%)	87 (87%)	7 (7%)	0

* Five of these participants were taking non-oral medicines.

5.3.3 Most common facilitators to medicines adherence

All questions exploring perceived facilitators to medicines adherence were answered by all participants (Table 5-3).

The highest perceived facilitator of medicines adherence, as reported by 94 (94%), was '*I have good family support'*. In addition, 88 (88%) agreed that '*My medicine schedule is quite simple'*, and 85 (85%) agreed that '*The doctor has prescribed medicine which can be taken once or twice a day*' (Table 5-3).

Thirteen participants ticked on "disagree" for '*I have good knowledge about my disease and treatment'.* All these participants were with parents with a secondary-education level.

Twenty-eight participants ticked on "disagree" for '*My doctor gives me medicine which taste ok'.* Twenty-five of these participants were belonged to the younger age group.

Table 5-3 Facilitators to medicines adherence as perceived by the study population

	Agree n (n%)	**Disagree** n (n%)	**Not certain** n (n%)	**Not answered** n (n%)
Q.1: *I use a medicine reminder or routine about my medicine (e.g. taking medicine before school).*	60 (60%)	40 (40%)	0	0
Q.2: *We were given enough information about my illness and the importance of treatment.*	82 (82%)	13 (13%)	2(2%)	0
Q.3: *I have good family support.*	94 (94%)	4 (4%)	2 (2%)	0
Q.4: *I have good knowledge about my disease and treatment.*	75 (75%)	13 (13%)	12 (12%)	0
Q.5: *The doctor has prescribed medicine which can be taken once or twice a day.*	85 (85%)	11 (11%)	4 (4%)	0
Q.6: *My medicine schedule is quite simple.*	88 (33%)	10 (48%)	2 (2%)	0
Q.7: *My doctor gives me medicine which taste ok.*	56 (56%)	28 (28%)	16 (16%)	0

5.3.4 Adherence rates

Twenty-seven parents reported adherence rates for their children, and 73 children reported their own adherence rates. The adherence rates reported by parents (89.62%) were almost the same as those reported by children (89.02%).

Forty-four patients took one medicine, 37 took two medicines, 18 took three medicines and one patient took five medicines **(Appendix 6)**. Most participants who took more than one medicine reported the same adherence rate to each medicine.

Only 14 participants who took more than one medicine reported different adherence rates for each medicine; their adherence rates for the different medicines differed only slightly (Table 5-4). This group included seven participants (two with epilepsy, one with asthma, one with ADHD, one with acne, one with heart disease and one with end-stage renal disease), who reported (in their answers to Q4a) that the side effects they experienced deterred them from taking some of their medicines (Table 5-4).

Among the other seven participants reporting different adherence rates for their different medicines (six with asthma and one with acne), five participants with asthma reported (in their answers to Q8a) that their complex medicine regimens, which involved many doses and night doses, put them off from taking their medicines. Additionally, one participant with asthma and one participant with acne reported (in their answers to Q9a)

that the size of the tablet or the taste of the medicine put them off from taking their medicines.

Table 5-4 Adherence rate for 14 participants who took more than one medicine and reported different adherence rates.

Age	Disease	Medicines	Adherence rate (self-report) (P=Parents, C=Child)
3	Asthma	Salbutamol, Budesonide, Cetirizine	60,75,75 (P) (poor adherence)
15	Heart disease	Atenolol, furosemide	80,90 (C) (good adherence)
12	Epilepsy	Sodium valproate, Carbamazepine	100,85 (C) (good adherence)
9	Asthma	Symbicort, Azithromycin	60,70 (C) (poor adherence)
8	Asthma	Salbutamol, Seretide	90,100 (C) (good adherence)
18	Acne	Doxycycline, Steroid cream	40,70 (C) (poor adherence)
17	End-stage renal disease	Lisinopril, Prednisolone, Azathioprine	90,100,100 (C) (good adherence)
14	ADHD	Atomoxetine, Sertraline	90, 80 (C) (good adherence)
14	Asthma	Salbutamol, Montelukast	90,85 (C) (good adherence)
4	Asthma	Salbutamol, Seretide, Montelukast	80,100,90 (P) (good adherence)
8	Asthma	Salbutamol, Seretide, Montelukast	85,100,90 (C) (good adherence)
7	Asthma	Salbutamol, Desloratadine	80,90 (C) (good adherence)
6	Epilepsy	Sodium Valproate, Clobazam	100, 80 (P) (good adherence)
16	Acne	Doxycycline, Budesonide	90,100 (C) (good adherence)

The mean percentage of medicines adherence reported by the study population overall was 89.31% (range: 47-100). A score of ≥80% adherence was considered the cut-off for good medicines adherence as reported in several studies (68,160,161,178,292). Overall, 82 participants exhibited good medicines adherence, while 18 participants had poor medicines adherence based on their self-reported scores (Table 5-5).

Table 5-5. Self-reported adherence rates

	Participants n (n%)
Poor adherence <80%	18 (18%)
Good Adherence ≥80%	82 (82%)
Total	100 (100%)

Four participants with asthma, four with acne, two with constipation, two with GORD, two with epilepsy, one with ADHD, one with heart disease, one with psoriasis and one with diabetes showed poor adherence. Further details are shown in (table 5-6).

Table 5-6 Distribution of children's adherence to medicines by disease

	Poor adherence (<80%) n (n%) *	Good Adherence (≥80%) n (n%)*
Asthma	4 (18.1%)	18 (81.9%)
Epilepsy	2 (16.6%)	10 (83.3%)
Acne	4 (40%)	6 (60%)
Constipation	2 (28.5%)	5 (71.5%)
ADHD	1 (16.6%)	5 (83.3%)
GORD	2 (40%)	3 (60%)
End-Stage Renal disease	0	5 (100%)
Autism	0	3 (100%)
Heart disease	1 (33.3%)	2 (66.7%)
Diabetes	1 (33.3%)	2 (66.7%)
Eczema	0	3 (100%)
Anaemia	0	3 (100%)
IBD	0	2 (100%)
Bronchitis	0	2 (100%)
Cystic Fibrosis	0	1 (100%)
Hypothyroidism	0	1 (100%)
GH deficiency	0	1 (100%)
Cystic fibrosis	0	1 (100%)
Extreme Prematurity	0	1 (100%)
Migraine	0	1 (100%)
Nocturnal enuresis	0	1 (100%)
Thalassemia	0	1 (100%)
Pseudohypoaldosteronism	0	1 (100%)
Psoriasis	1 (100%)	0
Chronic urticaria	0	1 (100%)
Scleroderma	0	1 (100%)
Juvenile dermatomyositis	0	1 (100%)
Chronic bullous disease of childhood	0	1 (100%)

*(n%) refers here to the percentage of children with each disease.

5.3.5 Statistical analysis

Table 5-7 shows the stratification of some of the study participants' characteristics that affect their adherence to medicines. Almost 80% of children aged <10 years and almost 84% of children aged ≥10 years had good medicines adherence. Eighty-three per cent of females and almost 81% of males had good adherence to medicines. More children of parents with a university-level education adhered to their medicine compared to those with parents with a secondary education. There was no statistically significant association between age and gender (p>0.05) with the adherence rates. Only parental university-education was significantly associated with good adherence when compared with parental secondary-level education (p=0.014). However, a non-significant result does not mean that there is no association. Our study was only powered to detect a difference of more than 18% in the adherence rates of the two exposure groups.

Table 5-7 Stratification of the study participants' characteristics and children's adherence to medicine

	Self-report adherence rate		p-value
	Good adherence ≥80% n=82 n(n%)	**Poor Adherence <80% n=18 n(n%)**	
Age ¥			
< 10 years	35 (79.5%)	9 (20.5%)	0.571
≥ 10 years	47 (83.9%)	9 (16.1%)	
Gender ¥			
Male	38 (80.9%)	9 (19.1%)	0.778
Female	44 (83%)	9 (17%)	
Level of Education ¥			
Secondary	33 (71.7%)	13 (28.3%)	**0.014***
University	49 (90.7%)	5 (9.3%)	

¥: Chi-square test, *p≤0.05.

5.3.6 Barriers and facilitators to medicines adherence

Questions Q2 to Q10 in the second part of our purpose-designed questionnaire explored further barriers and facilitators to medicines adherence. Four of these questions were open-ended questions (Q2a, Q2b, Q6 and Q10a) and the free text answers will be discussed later in the thematic analysis section.

These questions are summarised in Table 5-8. Most questions were answered by each of the 100 participants, except Q4 and Q6, which were answered by 99 participants and Q3a, Q7 and Q10 which were answered by 98 participants.

Table 5-8 shows the percentages of participants who answered Yes or No and their answers to some open-ended questions (Q2, Q6 and Q10).

Three questions about the barriers to medicines adherence already discussed in the first part of the questionnaire (Table 5-2) (Q1, Q8 and Q9) were repeated in the second part (Table 5-8) (Q2, Q3 and Q7) to confirm the participants' answers and to explore further details about these barriers. No participants gave different answers to these questions in the different sections.

The children reported forgetting their medicine (Q2) more than parents. Seventy-four per cent of children reported that they sometimes forgot to take their medicine, while 43% of parents reported that they sometimes forgot to give their children medicine.

Thirty-nine children were responsible for measuring and taking their medicine by themselves (Q5). Thirty-eight of them were aged ≥ 10 years and one aged < 10-years-old. The mean reported adherence rates when the children were responsible for measuring and administering their own medicines was 90.7%, with a range of 60%-100% (all adherence rates were reported by the children). Seven of the children responsible for measuring and administering their own medicine reported poor adherence. Three had acne, two had asthma, one had constipation and one had diabetes. Twenty-five of the children responsible for measuring and taking their own medicine had parents with a university-level education, 24 of them reported good adherence and one reported poor adherence. The other 14 children had parents with a secondary-level education; six of them reported poor adherence.

The mean adherence rate when the parents were responsible for measuring and administering medicines to their children was 88.4% with a range of 47%-100% (adherence rate were reported by 34 children and 27 parents). Eleven of the children whose parents were responsible for measuring and administering their medicine reported poor adherence. Two of them had asthma, two had epilepsy, two had GORD, one had heart disease, one had constipation, one had ADHD, one had acne and one had psoriasis.

Two participants reported that they stopped taking their medicines because of the tablet size or medicine taste. One participant with asthma reported

that he did not take montelukast because of the large size of the tablet. Another participant with acne reported that he did not take doxycycline because of the bad taste of the medicine.

Table 5-8 Questions about barriers and facilitators to medicines adherence

	Yes n (n%)	No n (n%)	Not answered n (n%)
2. Do you ever forget to take your medicine?	52 (52%)	48 (48%)	0
a. If so can you think of anything that makes this happen?	43 (43%)	57 (57%)	0
b. Can you think of anything that could help you to remember?	45 (45%)	55 (55%)	0
3. Do you worry about side effects of any of your medicine?	50 (50%)	50 (50%)	0
a. Does this ever put you off taking your medicines?	0	98 (98%)	2 (2%)
b. If yes please tell us which medicines and give us an example of side effects that worry you.			
4. Have you experienced side effects of any medicine?	24 (24%)	75 (75%)	1 (1%)
a. Did this ever put you off taking the medicines?	8 (8%)	91 (91%)	1 (1%)
b. If yes please write the name of the medicines causing side effects and what side effects they were.			
5. Do you measure and take your medicine by yourself?	39 (39%)	61 (61%)	0
6. Is there anything that makes it harder for you to take your medicine?	69 (69%)	30 (30%)	1 (1%)
7. Do you ever feel concerned about taking your medicine when other people are around?	14 (14%)	84 (84%)	2 (2%)
a. Does this ever put you off taking them?	0	98 (98%)	2 (2%)

8. Do you have any worries about the number of medicine doses that you need to take or the time of the doses?	52 (52%)	48 (48%)	0
a. Does this ever put you off taking your medicines?	4 (4%)	96 (96%)	0
9. Do you have any worries about the size of tablets that you need to take or the taste of your medicine?	18 (18%)	82 (82%)	0
a. Does this ever put you off taking your medicine?	2 (2%)	98 (98%)	0
b. If yes can you please give us an example?			
10. Have you tried or do you use any methods to help you with medicine taking?	52 (52%)	46 (46%)	2 (2%)
a. If yes, please describe them and how well they work.			

Half of the participants (50%) were worried about the side effects of the medicine, despite 75% not having experienced any side effects. Eight participants reported that experienced side effects put them off taking their medicines. For example, one participant who had psoriasis reported that he did not take adalimumab because he experienced migraines as a side effect. Additionally, one participant who had epilepsy reported that he did not take carbamazepine because he experienced weight gain and motor tics as side effects. Further details are shown in Table 5-9. These participants provided no further information about whether they refused to take the medicine or if it had been agreed with the doctor that it would no longer be prescribed.

Table 5-9 Examples of experienced side effects.

Age	Disease	Medicine	Experienced side effects
8	Asthma	Salbutamol	Hallucination
6	Epilepsy	Clobazam	Very tired
14	ADHD	Sertraline	Feel sick and loss of appetite
17	End stage renal disease	Prednisolone	Tiredness
15	Psoriasis	Adalimumab	Migraine
18	Acne	Doxycycline	Sickness
12	Epilepsy	Carbamazepine	Weight gain and motor tics
15	Heart disease	Atenolol	Fatigue

5.3.7 Thematic analysis

Further information on barriers and facilitators to medicines adherence was explored in the study participants' answers to the open-ended questions in the second part of our questionnaire (Table 5-8) (Q 2, Q6 and Q10). Questions 2a and Q6 explored barriers to medicines adherence and Q2b and Q10a explored facilitators of medicines adherence. The participants' answers about the barriers to medicines adherence were grouped into ten themes and the answers regarding the facilitators of medicines adherence were grouped into seven themes (Table 5-10).

Table 5-10 Barriers and facilitators themes.

Barriers themes	**Facilitators themes**
many doses each day	using reminder
changes in usual routine	established routine
feeling better so not needing medicines	masking poor taste/pain of medicine/big tablet
fear of stigma	family support
medicine difficult to take due to size, poor taste/smell/pain/device	more acceptable medicinal product/ device provided
fear of side effects	medicines organiser
feeling ill or tired	more acceptable medicine route of administration
complex manipulations needed	
autism symptoms and understanding	
being busy	

A. Barriers to medicines adherence

The study participants' answers about the barriers to medicines adherence (Q2a and Q6 in Table 8) were grouped into ten themes and 21 codes as shown in Table 5-11.

Table 5-11 Barriers to medicines adherence as reported by study participants

Barriers themes	n	Codes (n)
1. Medicine difficult to take due to size/ poor taste/smell/pain/device	**40**	• Poor taste (n = 15) • Big tablet (n = 13) • Difficulty with inhaler devices (n =7) • Painful injection (n = 5)
2. Many doses each day	**36**	• Many doses each day (n = 19) • Multiple medicines (n = 14) • Night doses (n = 3)
3. Changes in usual routine	**27**	• Changes in usual routine (n = 10) • Not at home (n = 9) • Holiday/Travelling (n = 6) • Forget at weekends N = 2)
4. Being busy	**20**	• Busy (n = 13) • Rushing (n = 7)
5. Feeling ill or tired	**6**	• Tired (n = 4) • Feeling sick (n = 2)
6. Fear of side effects	**5**	• Fear of side effects (n = 5)
7. Fear of stigma	**2**	• Embarrassed to take medicine in front of others (n =1) • Bullying with inhaler use (n =1)
8. Feeling better so not needing medicines	**1**	• Symptoms disappeared (n = 1)
9. Complex manipulations needed	**1**	• Dilution & small volume measurement (n = 1)
10. Autism symptoms and understanding	**1**	• Autism symptoms and understanding (n = 1)

Theme 1: Medicine difficult to take due to size/poor taste/smell/pain/device

This was the most commonly mentioned theme reported by forty participants. This theme describes the effects of poor taste, tablet size, pain caused by the injection of medicine and difficulty with inhaler devices on medicines adherence. This theme was reported by 21 children and 19 parents.

All of the participants who reported that the bad taste of a medicine made it hard for them to take belonged to the younger group (<10 years old), except one child who was aged ≥10 years old. Out of this group, five participants had end-stage renal disease, three had epilepsy, three had GORD, two had acne, two had constipation and the remaining had other diseases.

All participants who reported that the big size of a tablet or capsule was a barrier to taking their medicine belonged to the older group (≥ 10 years old), except three children aged < 10 years old.

Five parents and two children reported that difficulty with inhaler devices made it harder for them to administer or take their medicine.

Four children and one parent reported that pain caused by the injection of medicine made it harder for them to administer or take their medicine.

> *'Sometimes, he refuses to take the medicine because of its taste' (Mother: eight-year-old boy, anaemia, Q6).*

'It is difficult to swallow a big pill' (Child: 11-year-old girl, epilepsy, Q6).

'It is not easy to use inhalers' (Child: 11-year-old boy, asthma, Q6).

'Thought of sting when injecting' (Child: 15-year-old girl, psoriasis, Q6).

Theme 2: Many doses each day

This theme describes aspects of the dose frequency, which may affect medicine taking or potentially hinder adherence. Thirty-six of the participants reported that many doses, multiple drugs or night doses made it hard for them to give or take their medicines. This theme was reported by 23 children and 13 parents. Out of this group, nine participants had asthma, seven epilepsy, four acne, three end-stage renal disease, two diabetes and 11 other diseases.

'Baby was on Nifedipine, which needed dilution + small volume measuring + also Ranitidine, both 3 times daily, which was much harder' (Mother: one-year-old boy, extremely premature, Q6).

'I might not wake up for the night doses' (Child: 14-year-old girl, asthma, Q6).

'He takes more than one medicine several times every day' (Mother: three-year-old boy, asthma, Q6).

Theme 3: Change in usual routine

This theme describes how a change in daily routine may lead to forgetting, which affects medicine adherence (n = 27). This theme was reported by 16 parents and 11 children.

> *'I forget to take my medicines when I have to go out somewhere' (*Child: 17-year-old girl, acne, Q2a).
>
> *'Sometimes, I'm out of the house and don't get back until after my scheduled time to take them so I end up forgetting' (Child: 18-year-old girl, diabetes, Q2a).*
>
> *'Change of routine, e.g. weekend/holidays' (Mother: three-year-old boy, asthma, Q2a).*
>
> *'It was Christmas and we were out of routine' (Child: 14-year-old boy, acne, Q2a).*

Theme 4: Being busy

This theme describes the effect of children's or parents' preoccupation with other life matters on their medicine adherence (n = 20). This theme was reported 18 by parents and two children.

> *'Being late for school rushing' (Mother: eight-year-old girl, asthma, Q2a).*
>
> *'Busy evening life' (Child: 18-year-old girl, GH deficiency, Q2a).*

'I forget at school, too busy with friends' (Child: 16-year-old girl, acne, Q2a).

Theme 5: Feeling ill or tired

Six participants reported that feeling ill or tired made it hard for them to administer or take their medicine. This theme was reported by two parents and four children.

'*When she was feeling sick'* (Mother: eight-year-old girl, asthma, Q6).

'*When being tired'* (Child: 12-year-old girl, epilepsy, Q6).

'Overtired' (Child: 15-year-old boy, epilepsy, Q2a).

Theme 6: Fear of side effects

Some participants (n = 6) linked medicine adherence with their concern about the expected side effects of the medicine. This theme describes that the participants' fear of side effects made it hard for them to give or take their medicine. This theme was reported by two children and four parents.

'I worry about possible side effect of lamotrigine' (Mother: seven-year-old boy, epilepsy, Q6)

'*Sometimes, I feel concern about the side effects of medications' (Child: 14-year-old boy, asthma, Q6).*

'My concern is about the effect of medicines on my child' (Mother: Six-year-old girl, asthma, Q6).

Theme 7: Fear of stigma

This theme describes that some children fear being stigmatised because their medicine, and this may affect their medicine adherence (n = 2). Both participants who reported that a fear of being stigmatised made it hard for them to administer or take their medicine were female.

> *'I feel embarrassed to take my medicines in front of others'* (Child: 18-year-old girl, diabetes, Q6).

> *'At school, she was bullied by an older child who was laughing at her while she used her inhaler'* (Mother: eight-year-old girl, asthma, Q6).

Theme 8: Feeling better so not needing medicines

One participant reported that when the symptoms of her condition disappeared, it made it difficult for her to take her medicine because she felt her condition had improved, so she no longer needed to take her medicine (n = 1). This theme was reported by one child.

> *'When symptoms disappeared' (Child: 11-year-old girl, asthma, Q6).*

Theme 9: Complex manipulations needed

One mother reported that she had to perform complex manipulations to her child's medicines in order to give him the required dose.

'Baby was on Nifedipine, which needed dilution + small volume measuring + also Ranitidine, both 3 times daily, which was much harder' (Mother: one-year-old boy, extremely premature, Q6).

Theme 10: Autism symptoms and understanding

One mother reported that her child's autism symptoms and difficulty in understanding the importance of the medicine made it hard for her to give him the medicine.

'Autism symptoms and understanding' (Mother: 11-year-old boy, autism, Q6).

B. Facilitators of medicines adherence

The answers of the study participants (Q2b, Q10a in Table 5-9) regarding the facilitators of medicines adherence were grouped into seven themes and 23 codes as shown in Table 5-12.

Table 5-12 Facilitators of medicines adherence as reported by study participants

Facilitators themes	n	Codes (n)
1. Using reminders	**58**	• Phone alarm (n = 18) • Alarm (n = 16) • Using reminder (n = 10) • Writing notes (n = 10) • Using Alexa reminder (n = 2) • Using chart (n = 1) • Using iPad/iPod reminder (n = 1)
2. Masking poor taste/pain of medicine/ big tablet	**25**	• Mix with drink (n =10) • Mix with yoghurt (n = 4) • Dissolve in drink (n = 3) • Ice helps (n =2) • Takes with drink (n = 2) • Change injection site (n = 1) • Walk around after injections (n = 1) • Take medicine with milk and biscuit (n = 1) • Mix medicine with honey (n = 1)
3. Family support	**11**	• Family help/support (n = 11)
4. Established routine	**9**	• Established routine (n = 7) • Taking medicine on waking or before sleeping (n = 2)
5. Medicine organiser	**4**	• Pillbox (n = 2) • Organiser box (n = 2)
6. More acceptable medicinal product/device provided	**1**	• Administered medicine via syringe (n = 1)
7. More acceptable route of administration.	**1**	• Given medicines via feeding tube (n = 1)

Theme 1: Using reminders

Fifty-eight of the participants' answers were grouped under the theme of using reminders. This theme was reported by 25 children and 33 parents. In addition, this theme was reported by 21 children aged > 10 years and for 37 children aged ≤ 10 years (reported by four children and 33 parents).

> *'Chart to tick every day with rewards' (Mother: five-year-old boy, kidney disease, Q2b).*
>
> *"Writing it on the calendar /reminder on the phone" (Child: 10-year-old girl, asthma, Q2b).*
>
> *"an alarm/reminders or poster" (Child: 16-year-old boy, hyperthyroidism, Q2b).*

Theme 2: Masking poor taste/pain of medicine/big tablet

Twenty-five of the participants' answers were grouped under the theme of masking the poor taste/pain of medicine/big tablet. Twenty-one participants reported that they mixed, dissolve or take their medicine with juice, a drink, honey or yoghurt to make its taste more acceptable. Out of this group, five participants had asthma, three constipation, three anaemia, three end-stage renal disease, two GORD, two epilepsy and three had other diseases.

Four participants reported that they put ice on the injection site, or they changed the injection site to relieve injection pain. This theme was reported by nine children and 16 parents.

> *'I walk around after I injected the insulin'* (Child: 18-year-old girl, diabetes, Q10a).

> *'We crush the tablets into honey due to the taste' (Child: 10-year-old girl, asthma, Q10a).*

> *'Takes a fizzy drink to help make it go down' (Child: 11-year-old girl, asthma, Q10a).*

Theme 3: Family support

Eleven of the participants' answers were grouped under the theme of family support. Family support has many meanings to different people. The participants explained what this meant to them, stating that their family supported them by reminding them what times to take their medicine, helping them to take their medicine, motivating them to take their medicine and rewarding them when they took their medicine as prescribed. This theme was reported by nine children and two parents.

> *'My family help me to take my medicines when I feel sick'* (Child: 16-year-old girl, asthma, Q10a).

'I give him a reward if he takes medicine' (Mother: five-year-old boy, asthma, Q10a).

'By using clock alarm/telling my parents to remind me' (Child: 11-year-old boy, epilepsy, Q2b).

Theme 4: Established routine

Nine of the participants' answers were grouped under the theme of established routine. The participants reported that establishing a routine helped them remember to take their medicine. Three of these participants used medicine reminders with an established routine, and all of them reported good adherence. This theme was reported by two children and seven parents.

'I made medicine taking a part of my routine' (Child: 13-year-old girl, epilepsy, Q2b).

'I take my medicine same time daily' (Child: 10-year-old boy, heart disease, Q2b).

'Phone /start routine' (Mother: five-year-old boy, hyperactivity, Q2b).

Theme 5: Medicines organiser

Four of the participants' answers were grouped under the theme of medicines organiser. The participants reported that the use of an

organisational tool such as a pillbox, helped them organise multiple medicines by day and dose. This theme was reported by four children.

> *'Using an organiser box (pillbox) to organise each day doses' (Child: 14-year-old boy, epilepsy, Q10a).*

> *'I have a box labelled from Monday-Sunday filled with tablets' (Child: 16-year-old boy, hyperthyroidism, Q10a).*

Theme 6: More acceptable medicinal product/device provided

Only one participant reported that using more acceptable medicinal device helped them with medicine taking.

> *'Liquid medication via syringe' (Mother: one-year-old girl, epilepsy, Q10a).*

Theme 7: More acceptable route of administration

Only one participant reported that giving medicines via a more acceptable route of administration helped them with medicine-taking.

> *'We give them via a PEG (feeding tube) – makes it easier – It's less likely to be refluxed back up/out' (Mother: one-year-old boy, extreme prematurity, Q10a)*.

5.3.8 Questionnaire (BMQ)

As described in **Chapter 4**, the BMQ aims to assess patient's worries and beliefs about medicines (42,307). A differential score between necessity and concern is calculated by subtracting the results of the concern scores from those of the necessity scores. Therefore, a negative score indicates stronger concerns about the consequences of the medicine than beliefs in the necessity of taking the medicine. By contrast, a positive differential score indicates stronger beliefs in the necessity of taking the medicine (42). All questions were answered by all 100 participants.

On the **necessity** scale (Q1, Q3, Q4, Q7 and Q10), Table 5-13 shows that 83 participants agreed or strongly agreed that, '*My medication protects me from becoming worse*'. Also, 66 participants agreed or strongly agreed that, '*My health at present depends on my medicine*'.

On the **concern** scale (Q2, Q5, Q6, Q8 and Q9), 45 participants agreed or strongly agreed that, '*I sometimes worry about the long-term effects of my medication*'. Furthermore, 33 participants agreed or strongly agreed that, '*I sometimes worry about becoming too dependent on my medication*'. On the other hand, 44 disagreed/strongly disagreed that, '*I sometimes worry about becoming too dependent on my medication*', which means more participants understood the need for adhering to their medicines and disagreed with being concerned about becoming dependent on them. More than two-thirds of the participants disagreed or strongly disagreed that, '*My medication is mystery to me* (Table 5-13).

Table 5-13 Beliefs about Medicines among participants.

	Strongly Agree	Agree	Uncertain	Disagree	Strongly Disagree
Q.1: *My health at present depends on my medicine*	29	37	22	9	3
Q.2: *Having to take medication worries me*	7	18	13	41	21
Q.3: *My life would be impossible without my medication*	15	26	29	24	6
Q.4: *Without my medication I would be very ill*	20	26	28	18	8
Q.5: *I sometimes worry about the long-term effects of my medication*	16	29	13	26	16
Q.6: *My medication is a mystery to me*	5	13	22	44	16
Q.7: *My health in the future will depend on my medication*	21	30	29	15	5
Q.8: *My medication disrupts my life*	5	19	12	42	22
Q.9: *I sometimes worry about becoming too dependent on my medication*	11	22	23	31	13
Q.10: *My medication protects me from becoming worse*	33	50	15	2	0

Twenty-seven parents and 73 children answered the BMQ. Parents had slightly lower necessity scores and slightly higher concern scores than children (Table 5-14). The children aged ≥ 10 years had slightly higher necessity scores and slightly higher concern scores than children aged <10 years. The children with parents with secondary-level education had slightly lower necessity scores and slightly higher concern scores than children with parents with university-level education (Table 5-14).

Table 5-14 Mean BMQ necessity and concerns scales in different groups.

	Mean BMQ necessity score	**Mean BMQ concern score**
Children	18.33	13.05
Parents	17.44	13.15
Older children	18.27	13.9
Younger children	17.95	12.43
Children with parents with university-level education	18.44	12.7
Children with parents with secondary-level education	17.67	13.63

The mean necessity score of all the study population was 18 and the mean concerns score was 13. A positive mean necessity-concerns differential of 5 was calculated. Most of the participants (81%) had a higher necessity than concern score and 19% had a higher concern than necessity score (Table 5-15).

The participant who had the highest positive differential score reported 100% adherence rate, and the participant who had the highest negative differential score reported a 60% adherence rate.

Table 5-15. Mean BMQ necessity and concerns scales

	n	**[Min-Max]**	**Mean ± SD**
BMQ Necessity Scale	100	8-25	18±4.25
BMQ Concerns Scale	100	5-23	13±4.66
Necessity-Concerns differential	100	[(-7) – (+20)]	5
Positive or equal differential	81 (81%)	-	-
Negative differential	19 (19%)	-	-

Table 5-16 shows that participants' necessity beliefs about medicines exceeded concerns in 74 participants with good adherence and seven participants with poor adherence. Eleven participants with strong concern belief scores (negative differential) reported poor adherence, three of them with asthma, two with constipation, two with GORD, two with acne, one with epilepsy, and one with diabetes.

Eight participants had experienced side effects of their medicines; six of them reported poor adherence rates and had higher concerns than necessity score. The other two participants reported poor adherence rates despite having a higher necessity than concern score.

The chi-square test showed a statistically significant association between the BMQ differential score and the self-reported medicines adherence rate (p = 0.0001). This suggests that there is a relationship between self-reported medicines adherence rates and the BMQ differential score. For example, there seems to be a positive relationship between good medicines adherence and a positive BMQ differential score, by which participants have greater belief in the necessity of taking the medicine than concern about the medicine.

Table 5-16. Correlation between BMQ differential scores and adherence rate

		Self-report adherence rate		Total	P-value
		Good adherence ≥80% n (n%)	**Poor adherence <80% n (n%)**		
BMQ differential scores ¥	Higher necessity belief score (0* or positive differential)	74 (91.4%)	7 (8.6%)	81	**0.0001*** **
	Higher concern belief score (Negative differential	8 (42.1%)	11 (57.9%)	19	
Total		82	18	100	

¥: Chi-square test, ***p ≤0.001. * only two participants had 0 differential score

5.4 Discussion

As mentioned at the beginning of this chapter, from our systematic review **(Chapter 3)**, we found that only one study (the TABS study (85)) explored all barriers and facilitators to medicine adherence in children suffering from a wide diversity of diseases in the UK (85). This study reported that parents appeared to lack confidence in trusting their children to take responsibility for taking medicines, that schools provided good support to optimise medicine use and that the most common barriers to medicine adherence appear to be related to forgetfulness and routine, rather than stigma or side effects (85). It examined the barriers and facilitators of adherence only in four specific diseases including diabetes, asthma, epilepsy, and heart disease (85) and was conducted over ten years ago. This study suggested that future research should include the parents of older patients and also younger patients in the discussion (85).

Our study took this work further by including all parents and all children in the discussion and recruiting children with a wider variety of long-term conditions than have previously been studied.

This study is the first to use the BMQ with children with a diversity of diseases in the UK. Specifically, it revealed that there was a statistically significant association between the BMQ differential score and adherence rates. This suggests a positive relationship between medicines adherence and BMQ differential score, indicating that participants whose beliefs in the

necessity of taking medicines are greater than their concerns about the medicine are more likely to be adherent.

In addition, this study is also the first in the UK to explore the relationship between adherence rates in children and the education level of their parents. Notably, it was found that there was also a statistically significant association between adherence rates and parents having university-level education, but there were no statistically significant associations between good adherence rates, age and gender.

We also identified that medicines being difficult to take due to large tablet size, poor taste/smell, causing on pain on administration or difficult to use devices; requiring many doses each day plus changes in usual routine and being busy were the most common barriers to medicines adherence. In addition, this study identified that using reminders or measures to address poor taste, pain caused by administration or taking big tablets, family support, and following a scheduled routine for taking medicines were the most common facilitators for medicines adherence in children.

5.4.1 Adherence rates

Patients reporting ≥ 80% adherence were defined as having good adherence, and patients below that level were defined as having poor adherence. Most of our participants (89.3%) self-reported good medicines adherence. This result is consistent with previous studies in which the mean adherence rates was ≥80% among children with chronic diseases, including asthma, ADHD, epilepsy and HIV (81,87,177,230,246,249).

In our study, 80% of children aged <10 years reported good adherence to medicines, while 84% of children aged ≥10 years reported good medicines adherence, the difference was very small. Some studies however have found larger differences in adherence rates between younger and older children with HIV and asthma where adherence rates were also measured by self-report (69,199,240,249). The difference in the adherence rates between young and old children may be due to most younger children being fully dependent on their parents to take their medicines as they do not have the cognitive understanding or physical capacity to take their medicines by themselves (69). In addition, younger children who are usually reminded by their parents to take their medicines may forget about their doses when their parents or caregivers are absent or busy (199).

In our study, 54% of the children's parents had a university education, which represents a high level of education. Based on the report from the Office for National Statistics analysis data from July 2017 to September 2017, 42% of the population aged between 21 to 64 years in the UK who were not enrolled in any educational course were university graduates (320), which is a little lower than the percentage found in this study suggesting that our participant parents were quite highly educated overall. Children whose parents had a university education were significantly more likely to have good adherence compared with children whose parents had a secondary-level education (p=0.014), meaning that good adherence may be positively associated with a high parental education level. This result is

consistent with reports in previous studies (129,233,240,253,293). In addition, our study suggested that the mean necessity score for children with parents with a secondary-level education was less than that for children with parents with a university-level education. Also, the mean concerns of children with parents with a secondary-level education was higher than those for children with parents with university-level education.

Most of our participants believed the necessity of medicines outweighed their concerns about long-term use with a statistically significant positive association between the BMQ differential score and the self-reported medicines adherence rate. These results are paralleled by those of several studies conducted in Saudi Arabia, the USA and Sweden among children with asthma, epilepsy and ADHD that also found a statistically significant association between the BMQ differential score and self-reported adherence rates (81,174,177). Overall, these results suggest that the BMQ differential score is a robust indicator of medicines adherence and that adherence in children may be influenced by their beliefs regarding their medicines.

5.4.2 Barriers to medicines adherence

The quantitative results of this study illustrated that the most frequently perceived barrier of medicines adherence was '*I forgot to take my medicine'* as reported by 52 (52%) of the participants. Children reported forgetting their medicine more than parents. Elliott et al. conducted a study with children with chronic disease and also found that children reported

forgetting more than their parents and suggested that parents may have tended to provide the more socially desirable answer (85). Forgetting may have more of an impact with children who depend on themselves to take their medicine. Some children stated that they were more likely to forget their morning dose because they were rushing to school (85). Moreover, a study that assessed 19 potential barriers to medicines adherence in HIV-infected children showed that 41% of children and 33% of caregivers reported that forgetting was the main reason for non-adherence (61). This finding suggests that even in severe diseases, forgetting affects the rate of medicines adherence.

The qualitative results of this study reported that the most common barriers to medicines adherence were medicines being difficult to take due to large tablet size, poor taste/smell, causing on pain on administration or difficult to use devices, many doses each day, changes in usual routine and being busy. Each barrier is discussed separately below.

Most of our participants who reported that the bad taste of the medicine made it hard for them to take belonged to the younger group (<10 years old). This may be because oral liquid formulations are the preferred and most frequently used form for many younger children (76). Previous studies with patients with ADHD, psychiatric disorders and kidney diseases reported that the bad taste of some medicines was associated with poor medicines adherence (85,92,254,259,276). Bryson et al. conducted a study with

children with chronic disease in the UK and reported that good adherence was associated with a positive response to medicine taste and conversely poor adherence was associated with a negative response (276). Some children refuse to take medicines that have a bad taste or may vomit or spit out some of the dose (58). Bad-tasting medicines also discourage younger children from willingly taking their prescribed medicine, increasing non-adherence (85,92,254,259). Some evidence indicates that mixing medicines with drinks or food to make the taste more acceptable may reduce the delivered dose and affect the effect of medicine (92).

In our study, the large size of tablets/capsules was reported as a barrier by 13 participants, most of who were older children. Previous studies with patients with epilepsy and IBD also reported that poor adherence to treatment was associated with a large pill size (266,268,273,274). The ability of children to swallow capsules or tablets depends on the size of these tablets and the age of the child (321). Some patients who have difficulty swallowing large tablets may have to crush the tablet or open the capsule and dissolve it in a drink, which may affect the actual dose of the medicine delivered (322).

In our study, multiple drugs, doses and night doses were the second most common reported barrier. These findings are supported by previous research (122,162,177,236,240,245,276,303). Multidrug treatment or frequent doses are more likely to be forgotten and not taken on time or

missed (276,303). A study conducted with children with chronic diseases found that 82% of children who took two or less different medicines each week were adherent, while 73% of children who took three or more different medicines each week were non-adherent (276). Previous studies conducted with children with chronic disease, epilepsy and asthma reported that when the number of medicines prescribed increases or when changes in the administration schedule are made, the possibility that medicines or doses are missed increases, leading to poor adherence (177,236,276). In general, a simpler regime reduces confusion, is more easily understood, and facilitates adherence (276). In our study, evening doses were seen as a barrier as most of the children were used to taking their medicine before going to sleep, in cases where they returned home late, children often went to sleep, forgetting to take their medicine (85).

Another common reported barrier in the current study was being busy and rushing. This factor was particularly noticed in children who were dependent on their parents to measure and administer their medicine. The findings of some previous studies conducted with children with asthma and HIV were consistent with those of our study, reporting that parents being busy was a barrier to adherence (122,192,199,245). In addition, some participants in the current study reported that their children being busy was a barrier to adherence. The preoccupation of some children with other matters is a factor that could contribute to them forgetting to take their medicine on time (62).

Some of our participants reported that experiencing side effects put them off taking their medicines. Smith et al. reported that poor adherence in children with epilepsy was significantly associated with experiencing side effects (190). In addition, previous studies conducted with children with tuberculosis, ADHD, HIV, IBD, multiple sclerosis and cancer also found that experiencing side effects was a reason for poor adherence (81,226,267,287,296). The experience of side effects may greatly impact medicines adherence, especially if the patient believes it is not necessary to take their medicine (81). Of the eight patients who experienced side effects in our study, six reported poor adherence rates and had a higher concerns than necessity score. Emilsson et al. reported that children with ADHD who experienced fewer side effects, who had a higher necessity score, and who had a lower concern score on the BMQ were more likely to be adherent to medicines (81).

5.4.3 Facilitators of medicines adherence

The quantitative results of our study showed that the highest perceived facilitator of medicines adherence, as reported by 94 (94%), was '*I have good family support'*. Family support has many meanings to different people. The participants in the current study explained what this meant to them, stating that their family supported them by reminding them what times to take their medicine, helping them to take their medicine, motivating them to take their medicine and rewarding them when they took their medicine as prescribed. Previous studies conducted with children with psychiatric disorders, asthma, HIV and sickle cell disease support this finding (86,90,261,281). Klitzman et al. conducted a study with children with sickle cell disease in the USA and reported that family support was associated with good adherence ($p<0.05$) (281). In addition, low family support and a lack of adult support tends to be a barrier to medicines adherence, as the children can feel uncared for and thus not recognise the need for adherence (211,224,285).

The qualitative results of our study revealed the most commonly reported facilitator for medicines adherence was '*using reminders*'. Fifty-eight participants reported that they used tools such as setting an alarm on a phone and writing notes. Such tools have also been reported as facilitators in previous studies (70,87,91,122,189,193,241,243), and have been associated with good adherence (87,122,241,243). Using a phone or clock

alarm was the most common technique among our study participants to avoid forgetfulness, as it provided patients (or patients' parents) with automatic reminders to take their medicines. Although there are many new smartphone reminder applications, the use of either a phone or clock alarm is a more commonly used technique among patients to remember their medicines (323).

A medicine tasting bad has been extensively reported as a factor associated with poor medicines adherence (170,193,197,198,208,213,215,254). As discussed previously in **Chapter 4**, children may be hesitant to take bad-tasting medicines, or they may vomit or spit out the dose, resulting in an inappropriate use of medicines, because the child is not receiving the full dose. In this study, 25 participants' answers were grouped under the 'masking poor taste/pain of medicines/big tablet' (e.g., mixing medicine with water or juice, taking it with yoghurt or water). Masking the taste of medicines and parent counselling about a medicine's flavour may have a positive impact on adherence. Some techniques such as using flavours and oral syringes for drug administration can conceal or minimise an unpleasant taste (58). In the current study one mother reported that using an oral syringe for drug administration helped them with medicine-taking.

5.4.4 Implications for practice

Finding ways to flexibly identify and address the various causes of non-adherence and to empower children and their parents to honestly disclose their challenges with medicines adherence is essential. Healthcare providers should be aware of the importance of talking to both children and their parents when discussing matters related to medicines and not neglect the child.

The bad taste of medicine was reported by some participants in this study as a barrier to adherence. Careful consideration of alternatives available by the healthcare provider (by asking the patient if they prefer a particular flavour if it is available) may be helpful as may lobbying of pharmaceutical companies to carefully consider the taste of medicines.

Although medicines adherence rates in this study was high for most participants, some demonstrated low adherence. Healthcare providers should consider assessing their patients' medicines adherence over a short time period by using a single question self-report.

Children's and parents' beliefs about the necessity of medicines and their concerns about their use significantly impact their medicines adherence. To improve medicines adherence, Healthcare professionals could help to develop patients' and parents' beliefs by explaining the importance of the medicine and addressing their concerns at each medical appointment.

It is useful for healthcare providers to be aware that parents may have low education levels and ensure that they explain the treatment and the importance of adherence in suitable language adjusted to the child and parents' capacity to understand.

The BMQ differential score is a robust indicator of medicines adherence and that adherence in children may be influenced by their beliefs regarding their medicines. It was easy for participants (parents and children) to answer the BMQ because of the options of available answers. In addition, answering the BMQ did not take a long time (from two to five minutes). These advantages may make the BMQ easy to use during medical appointments, while patients wait to meet with their healthcare providers. Alternatively, it may be better to send it to the patient's home before the appointment and for them to bring it already completed.

5.4.5 Limitations

There were some limitations to this study. We had sufficient statistical power to only detect differences greater than 18% adherence between two different groups, therefore, smaller differences would have been missed. A larger sample size would be needed in future studies to detect smaller differences.

We proposed to measure adherence rates by self-report and MPR. The researcher and the Chief Investigator viewed the initial patient's Summary Care Records and found unfortunately that the information available in this

was not enough to calculate the MPR. Therefore, the adherence rates in this study were assessed by self-report only.

We were unable to conduct statistical comparisons between sub-groups (such as medicines taking responsibility of child vs parents) because the sub-group sample sizes were too small. In future research, it would be interesting to conduct such comparisons by increasing sample sizes.

Although we were able to recruit participants with a good variety of conditions (22 different conditions), it was difficult to recruit diabetic patients as they and their parents were too busy filling in pre-appointment forms. Diabetic patients represent a large proportion of children with chronic disease and may have barriers and facilitators of adherence that are somewhat different from others.

In addition, some patients refused to participate in our study. We have no way of knowing if they were different from our sample in terms of adherence.

5.5 Conclusion

In this study, parents' education level and BMQ differential scores were found to be factors that were significantly associated with medicines adherence rates as measured by self-report.

A number of factors such as medicines being difficult to take due to size, poor taste/smell, causing pain or a difficult to use device together with the need for many doses each day, changes in usual routine and being busy were seen to be the most common barriers to medicines adherence.

Using reminders or finding ways measures to address poor taste or big tablets and pain caused by administration together with family support and following a scheduled routine for taking medicines were the most common facilitators for medicines adherence in children.

Involving patients and their parents in discussions about medicines and their importance and trying to alleviate concerns about potential harm may improve children's adherence.

Chapter 6: Barriers to and facilitators of medicines adherence in children with diverse diseases “a comparison”

6.1 Introduction

In **Chapter 3** we described a systematic review of the barriers to and facilitators of medicines adherence in children that we had conducted. We found six studies conducted involving children with diverse diseases. Three of these studies explored only formulation factors affecting adherence (92,276,278), one identified predictors of non-adherence based on an electronic prescription record (162) and one explored only barriers to administering non-oral formulations in a paediatric population (277). Only one study (TABS study) explored all potential barriers to and facilitators of medicines adherence in children with diverse diseases (85).

In addition, we have conducted two new studies to explore the barriers to and facilitators of medicines adherence in children with diverse diseases in Saudi Arabia and the UK **(Chapters 4 and 5)**. The aim of this chapter is to pull together the information from these eight studies and summarise current knowledge about barriers to and facilitators of medicines adherence in children with diverse diseases.

6.2 Methods

6.2.1 Saudi and UK studies (Chapters 4 and 5) – Key differences

In both countries, recruitment was carried out as previously described. In Saudi Arabia however, it was easy to recruit children with different diseases, and there were no obstacles related to any particular disease, whilst in the UK, it was difficult to recruit diabetes patients. This was because they and

their parents were too busy completing pre-appointment information and other study surveys.

Both self-report and MPR were used to measure medicines adherence in children in the Saudi study, while self-report alone was used in the UK study as previously explained. Notably, in the Saudi study, a substantial agreement was found between self-report and MPR data, providing some reassurance that the methods are comparable.

6.2.2 Previous studies conducted with children with diverse diseases

In our systematic review **(Chapter 3)**, we identified six studies that explored barriers to medicines adherence in children with different diseases (85,92,162,276–278); two of these studies also explored facilitators of medicines adherence in children (85,276).

6.2.3 Data analysis

All included studies were analysed and the following data were extracted into a table:

- Name of authors.
- Publication year.
- Country where study was completed.
- Type of study.
- Number and age of participants.

- Type of tools used to explore barriers and facilitators of medicines adherence.
- Type of disease.
- Reported barriers and facilitators.

6.3 Results

6.3.1 Countries

A total of six studies have now been conducted in the UK (80,87,88,90,91, Chapter 5), one in Saudi Arabia **(Chapter 4)** and one study in the US (162).

6.3.2 Most common barriers and facilitators in all studies

As shown in Table 6-1, four studies (including our two studies) explored both barriers to and facilitators of medicines adherence in children with different diseases (87,91, Chapters 4 and 5) and four studies explored only barriers to adherence (92,162,277,278).

Medicine-related factors were the most common barriers to medicines adherence, including the complexity of the medicines regimen (80,87,88, Chapters 4 and 5), fear of side effects (91, Chapters 4 and 5), problems with size and swallowing of medicines (92,278) and bad taste of medicine (80,87,88, Chapters 4 and 5). Venables et al. reported that patients who were taking medicines with bad tastes or high dose frequencies were more likely to refuse their medicines and have poor adherence (p<0.001) (92). Bryson et al. reported that 82% of children who took two or less different

medicines each week were adherent, and 73% of children who took three medicines or more each week were non-adherent (276).

Our own studies found that parental education level and patients' and parents' beliefs about medicines were found to be factors that were significantly associated with medicines adherence **(Chapters 4 and 5)**.

Table 6-1 Studies reporting barriers and facilitators to medicines adherence in patients with diverse diseases. For barriers and facilitators numbers are reported as % or significant association (if no numbers given numbers not reported in study).

Study	Participants	Tools used	Main barriers identified	Main facilitators identified
Fischer et al. 2010, United States (162)	9417 children with various diseases (prescribed antimicrobial, neuropsychiatric, asthma medicines or dermatologic agents), aged 0 to 18 years.	E-prescribing data of patients including prescribing clinician, patient, prescription date, dosage form, medicine name and insurance plan. Adherence rate assessed by MPR calculation (87.3% children were adherent).	· Medicines being prescribed by general physician (not paediatrician). · Poor adherence common for newly prescribed medicines.	Did not report facilitators.
Elliott et al. 2013, United Kingdom (85)	18 children with asthma, heart disease, diabetes, and epilepsy, aged 10 to 17 years.	Questionnaires completed by professionals, children, and caregivers about issues around medicine-taking in children. Adherence rate not assessed.	· Forgetting. · Interference with routine. · Evening doses. · Side effects. · Being tired.	· Reminder device. · Having routine related to medicine administration. · Knowledge about consequences of not using medicine and necessity of it.
Bryson et al. 2014, United Kingdom (276)	70 children with various diseases, aged 3 to 11 years.	Questionnaires completed by children, professionals, and caregivers about issues around medicine-related factors. Adherence rate assessed by MPR calculation. 82% of children who took ≤ two different medicines each week were adherent. 73% of children who took ≥ three medicines each week were non-adherent.	· Taste of medicine especially in younger children. · Complexity of medicines' regimen.	· Medicines with good taste. · Simple medicines regimen.

Study	Participants	Tools used	Main barriers identified	Main facilitators identified
Venables et al. 2015, United Kingdom (92)	57 children aged 12-18 years and 221 carers/parents of children with various diseases and administered oral formulations.	13-item questionnaire completed by children and parents with questions to explore barriers to adherence. Question about medicine refusal conducted to assess adherence. Almost one third of respondents reported medicines refusal.	· Bad taste ($p<0.05$). · Volume or quantity of medicine ($p<0.05$). · Texture of medicine ($p<0.05$). · Socioeconomic status ($p<0.05$). · Difficulty with swallowing. · Smell and colour of medicine. · Highest incidence of poor taste medicines were prednisolone, ranitidine and trimethoprim.	Did not report facilitators.
Venables et al. 2015, United Kingdom (278)	27 healthcare providers asked about barriers to medicine adherence in children.	Focus groups to discuss barriers to medicine adherence (oral formulations barriers). Information recorded during sessions. Adherence rate not assessed.	· Bad taste. · Texture of medicine. · Problems with size and swallowing. · Problems with smell and colour of medicine. · Problems with quantity and volume.	Did not report facilitators.
Venables et al. 2016, United Kingdom (277)	90 children diagnosed with different diseases administered non-oral formulations, aged 0 to 17 years.	13-item questionnaire completed by children and parents with questions to explore barriers to adherence. Question about medicine refusal conducted to assess adherence. 7% of non-oral formulations were refused.	· Difficulty with spacer for inhaled devices in patients with asthma 38%. · Disliking parenteral formulations 38%. · Greasy texture of topical medicines. · Large dose of nasal medicines. · Difficulty with eye ointment.	Did not report facilitators.

Study	Participants	Tools used	Main barriers identified	Main facilitators identified
Aldosari et al. Saudi study. 2019 (unpublished, Chapter 4), Saudi Arabia	100 children/parents diagnosed with different diseases, aged 0 to 18 years.	BMQ. Purpose-designed questionnaire completed by children/parents to explore barriers and facilitators. Adherence rate assessed by self-report (91% were adherent) and MPR (85% were adherent).	· Many doses each day 50%. · Changes in usual routine 33%. · Medicine difficult to take due to poor taste/smell/pain/device 18%. · Fear of side effects 12%. · High concern belief scores (p<0.05).	· Using reminders 56%. · Established routine 29%. · Masking poor taste/pain of medicine/big tablet 17%. · Family support 8%. · Children with parents with a University education level (p<0.05).
Aldosari et al. UK study. 2020 (unpublished, Chapter 5). United kingdom	100 children/parents diagnosed with different diseases, aged 0 to 18 years.	BMQ. Purpose-designed questionnaire completed by children/parents to explore barriers and facilitators. Adherence rate assessed by self-report (82% were adherent).	· Many doses each day 36%. · Changes in usual routine 27%. · Medicine difficult to take due to poor taste/smell/pain/device 40%. · Fear of side effects 5%. · Being busy 20%. · High concern belief scores (p< 0.05).	· Using reminders 58%. · Established routine 9%. · Masking poor taste/pain of medicine/big tablet 25%. · Family support 11%. · Children with parents with a University education level (p<0.05).

6.4 Discussion

This chapter summarises the main findings of the eight studies (two unpublished) conducted to explore medicines adherence with children with diverse diseases (six in the UK, one in the USA and one in Saudi Arabia). All studies explored barriers to adherence, but only four of them explored facilitators.

Medicine-related factors were the most common barriers to medicines adherence in many studies. Poor taste of the medicine was reported as a barrier by five studies (80,87,88, Chapters 4 and 5), problems with the size of medicine and swallowing was reported by four studies (80,88, Chapters 4 and 5) and complex medicines regimen was reported by five studies (92,162,278).

Most of the participants in the three studies who reported that the bad taste of the medicine made it hard for them to take belonged to the younger group (87, Chapters 4 and 5). This may be explained by the fact that younger children are more likely to be prescribed oral liquid formulations, which often have a bad taste that is more difficult to mask (276). Bryson et al. reported that good adherence was associated with a positive response to medicine taste, and conversely, poor adherence was associated with a negative response (276). Venables et al. also found that the bad taste of a medicine was significantly associated with medicine refusal in children and poor adherence ($p<0.001$). They found that the medicines with the highest

incidence of poor taste were prednisolone soluble tablets, ranitidine liquid and trimethoprim liquid (92). In our studies (Chapters 4 and 5), most participants reporting that their medicine had a poor taste did not report which of their medicines tasted poorly. This may have been due to the nature of the question in our designed questionnaire (Chapters 4 and 5), which asked participants to write the name of medicines with a bad taste only if the poor taste of medicine was the reason they avoided or stopped taking their prescribed medicine. However, the reporting of the poor taste of medicines in many studies suggests that despite the availability of medicines with different flavours and different formulations, the poor taste of medicines is still a common barrier to medicines adherence in children. In addition, participants in three studies (80, Chapters 4 and 5) reported manipulating medicines to mask poor taste. Therefore, the taste of medicines should be considered by pharmaceutical companies when producing new formulations in order to improve medicines adherence in children. Furthermore, prescribers are advised to talk with children and parents about whether the child prefers a particular flavour of medicine if a choice is available.

Problems with the size of solid dose medicines and swallowing were reported by participants in four of the studies (80,88, Chapters 4 and 5). Venables et al. reported that problems with the solid dosage forms were related to difficulty swallowing and the size of the medicine (92). Swallowing may depend on the size of the medicine and the age of the child (92). Some

medicines are available in a mini-tablet form, the acceptability of which has been explored in children aged between six months and six years (324). This study found that 46% of children aged two years and 86% of the oldest children were able to swallow the mini-tablets (324). Some patients who have difficulty swallowing large tablets may have to crush the tablet or open the capsule and dissolve it in a drink, which may affect the actual dose of the medicine (80, Chapters 4 and 5). Mixing medicine with foodstuffs may affect the drug bioavailability by increasing the binding capability of the medicine with foodstuff (92). To minimise medicine manipulation, prescribers are advised to consider the age of the child and the size of the tablets when prescribing the medicine.

Complex medicine regimens, such as those involving multiple drugs, doses (80,87,88, Chapters 4 and 5) and night doses (91, Chapters 4 and 5), were also reported as barriers to adherence. In our studies (Chapter 4 and 5), some participants reported that high dose frequencies were a reason they forgot to take their medicines on time. In addition, night doses were seen as a barrier as children tend to go to sleep early and found it difficult to wake up every night to take their medicine (Chapter 4 and 5). Elliott et al. reported that the night dose was the most frequently missed dose among children with chronic diseases (85).

In general, a simpler regime reduces confusion, is more easily understood, and facilitates adherence (276). Bryson et al. reported that a simple

regimen of prescribed medicine was more likely to be adhered to (276). Some participants in our studies (Chapters 4 and 5) who were taking many doses each day (solid formulations) reported that they used an organising box to separate each day's doses and found that useful. Therefore, it is suggested that those who must take many doses daily (solid formulations) use tools to help them to organise their daily doses, such as an organising box. As these boxes are suitable only for solid dosage forms, no participants reported methods of organising liquid formulations. Therefore, future research may look at how to organise complex medicines regimens involving liquid formulations.

Fear of side effects was reported by participants in three studies (91, Chapters 4 and 5). Side effects of medicines may have a large impact on adherence, especially if patients believe that it is acceptable to refrain from taking their medicines in order to avoid side effects (Chapters 4 and 5). Elliot et al. found that knowledge about the consequences of not using medicines as prescribed and the necessity of doing so facilitated medicines adherence in children (85). Venables et al. also reported that parental understanding of the importance of medicines influenced medicines adherence (278).

In our studies (Chapters 4 and 5), we used the BMQ scale to assess patients' beliefs about medicines and determine how they affect children's adherence to medicines. Our studies were the first studies to use the BMQ with children with diverse diseases and to assess the relationship between patient and

parents' beliefs and their adherence. We found a statistically significant association between the BMQ differential score and the adherence rates. There was an increase in the adherence rate among those with low concern about long-term use and with a stronger belief in the necessity of medicines. Patients with negative necessity-concern differential scores were less adherent than patients with positive scores. In addition, we found that six of eight participants who had experienced side effects of their medicines (Chapter 5) reported poor adherence rates and had higher concerns than necessity scores. These findings suggest that healthcare providers can help to strengthen patient and parents' beliefs by explaining the importance of the medicine and addressing their concerns, and thereby improve adherence in children.

Venables et al. reported that parents have an influence on their children's adherence to medicines (278). The nurses interviewed in this study emphasized the need for parental education (278). The studies presented in Chapters 4 and 5 were the first to investigate the relationship between parental education level and the adherence rate of children with diverse diseases statistically (Chapters 4 and 5). In both studies, more than half of the children's parents had a university education, which represents a high level of education. Children whose parents had a university education were significantly more likely to have a good adherence rate than children whose parents had a secondary-level education, meaning that good adherence was positively associated with a high parental education level. Parents with

higher education levels are more likely to understand the vital importance of adherence and the effects that poor adherence can potentially have on their child (240). This result suggests the importance of ensuring that the patient understands the importance of the medicine and the potential effects of poor adherence.

Three studies reported that using reminders or establishing a routine have a positive effect on remembering to take medicine (91, Chapters 4 and 5). Furthermore, some participants in Chapters 4 and 5 reported that they use reminders to take their medicines and they have an established routine to help them remember to take their medicines. All of these participants showed good adherence rates.

6.5 Conclusion

This chapter summarised the most common known barriers to and facilitators of medicines adherence in children with diverse diseases rather than most previous studies which only examined specific diseases. Poor tasting medicines, problems with swallowing medicines, complexity of the medicine regimen and fear of side effects were the most common barriers. The most common facilitators of medicines adherence were using reminders and establishing a routine. Our studies **(Chapters 4 and 5)** confirmed these barriers and facilitators and observed that rates of adherence were significantly associated with the child's and parents' beliefs about medicines. In addition, finding measures to address poor taste or big tablets

and pain caused by administration, together with family support were findings added by our studies **(Chapters 4 and 5)** as facilitators of medicines adherence. Furthermore, children whose parents had a university education had a significantly better adherence rate compared with children whose parents had a secondary-level education. These findings will add to the understanding of the barriers to and facilitators of medicines adherence in children with various diseases.

Chapter 7: General conclusion

7.1 Introduction

Non-adherence to medicines is a complex healthcare issue. Patients may take their medicine at the wrong time, use less or more than the prescribed amounts, or discontinue treatment prematurely (12). Enhancing medicines adherence for chronic conditions may create significant economic and health benefits (7,50).

This PhD project first aimed to measure medicines adherence in children with chronic diseases and to explore barriers to and facilitators of adherence. While there are a number of known medicines adherence measures, no previous systematic review has been conducted to evaluate their relevance and experience in children. We therefore performed a systematic review to identify medicines adherence measures that have been used with children and explores the strengths and weaknesses of those measures.

We also searched for a systematic review in order to establish what is currently known about barriers and facilitators to medicines adherence in children and found a review from the Talking about medicines study (TABS) published seven years ago (85). This review was a critical evidence synthesis of research to examine the factors influencing non-adherence to medicines in children with chronic diseases from 1970 to 2008 (85). We therefore performed a systematic review to update this work and to identify barriers and facilitators to medicines adherence in children reported since this study.

Based on the information obtained from these systematic reviews, we then conducted two studies to measure medicines adherence in children and to explore the barriers and facilitators to medicines adherence in two centres: Saudi Arabia and the UK.

7.2 Key findings

The first systematic review **(Chapter 2)** aimed to identify medicines adherence measures that have been used in children and to explore the strengths and weaknesses of those measures. This review identified 31 articles that met the inclusion criteria. In these articles seven methods to measure adherence were identified: self-report, EMD, dose count, canister weight, plasma level, medical record or pharmacy refill data, daily telephone calls.

Self-reporting was the most commonly used method to assess adherence and was reported to be flexible, inexpensive, and time saving but it was the least accurate and overestimated adherence rates. MEMS was the most accurate method but was also the most expensive. Dose counting was easy to use and inexpensive but adherence was also overestimated with this method. Measuring medication plasma levels was more precise than self-reporting and dose counting but was costly, time consuming and difficult to perform. Pharmacy refill data was more accurate than self-reporting and less accurate than MEMS and medication plasma levels. Mobile phone methods were reported to be very expensive and difficult to perform. Canister weight had the same efficacy as using MEMS and was

less expensive but was only applicable to inhalation devices. Currently, no gold standard method to measure adherence to medicines in children exists as each method has its own advantages and disadvantages.

The second systematic review **(Chapter 3)** aimed to identify barriers and facilitators to medicines adherence in children as reported over the past twelve years. This review identified 177 articles that met the inclusion criteria. Most studies were conducted in the US (76), followed by the UK (12) and Canada (6), with the remaining 83 studies in various other countries. Forgetfulness and fear of side effects were the most common reported barriers to medicine adherence. Others reported barriers included family conflict, weak patient-provider relationships, stigma and discrimination, drug regimen complexity and lack of support from families. Factors reported to facilitate high rates of adherence include linking of medicine taking with daily life routines, using reminders to avoid forgetfulness, a higher level of caregivers and parental education and good communication between healthcare professionals, patients and parents.

The exploratory study **(Chapter 4)**, which aimed to measure medicines adherence in children with chronic diseases attending the KFMC in Saudi Arabia and to explore related barriers and facilitators to medicines adherence, found good agreement between the study's two adherence measurements methods (self-report and the MPR). Additionally, this study found a statistically significant association between the BMQ differential score and adherence rates. There was also a statistically significant

association between adherence rates and the education level of a patients' parents. Furthermore, this study identified that many doses each day, changes in daily routine, medicines being difficult to take due to large tablet size, poor taste/smell, causing on pain on administration or difficult to use devices and fear of side effects were the most common barriers to medicines adherence. Using reminders, having an established routine for taking medicines, measures to address poor taste, pain caused by administration or taking big tablets and family support were the most common facilitators for medicines adherence in children.

The second exploratory study **(Chapter 5)** aimed to measure medicines adherence and to explore the barriers to and facilitators of adherence in children with chronic diseases attending the Derbyshire Children's Hospital in the UK. The findings of this study were similar to those of the Saudi study (Chapter 4) and the differences were only in the order of the most common barriers to and facilitators of medicines adherence. This study found a statistically significant association between the BMQ differential score and adherence rates and between adherence rates and the education level of the patients' parents. In addition, this study found that medicines being difficult to take due to large tablet size, poor taste/smell, causing on pain on administration or difficult to use devices; requiring many doses each day plus changes in usual routine and being busy were the most common barriers to medicines adherence. Furthermore, this study identified that using reminders or measures to address poor taste, pain caused by

administration or taking big tablets, family support, and following a scheduled routine for taking medicines were the most common facilitators for medicines adherence in children.

7.3 Key practice implications

The aforementioned findings from this project add to the understanding of the barriers to and facilitators of medicines adherence in children with various diseases.

- The most common barriers to and facilitators of medicines adherence in children with diverse diseases have been identified which will be useful to healthcare providers to help them when prescribing medicines for children.
- To achieve optimal adherence, healthcare providers need to be aware of the most common barriers for their patients and to consider the most appropriate facilitators to encourage them to take their medicines as prescribed.
- Children's and parents' beliefs about the necessity of medicines and their concerns about their use significantly impact their medicines adherence. To improve medicines adherence, healthcare providers may help develop patients' and parents' beliefs by explaining the importance of each medicine and addressing any concerns or questions they may have.

- Parental education level significantly impacts a child's drug adherence. If possible, healthcare providers should identify parents with low education levels in order to explain treatment and the importance of drug adherence to them in understandable terms.
- The bad taste of a medicine was reported by some participants in both studies **(Chapters 4 and 5)** as a barrier to adherence. Pharmaceutical companies need to carefully consider the taste of medicines when designing new formulations, especially oral liquid formulations. Furthermore, prescribers are advised to talk with children and parents about whether the child prefers a particular flavour of medicine if a choice is available. In addition, techniques such as using oral syringes for drug administration may help to conceal or minimise an unpleasant taste.
- None of the medicines' adherence measures were highly accurate in the assessment of adherence. It is therefore important to use a combination of multiple measures in order to gain a true picture of adherence.

7.4 Limitations

There were some limitations to this work as has been highlighted already in each chapter. This thesis included two systematic reviews **(Chapter 2 and 3)**. The main limitations in these reviews were that all titles and abstracts of the search results should have been screened according to the inclusion criteria by two researchers. The limited resources of our

department, one researcher (Aldosari M) screened all titles and abstracts, but only 5% of titles and abstracts were assessed independently by another researcher from our group. The quality of all included studies should have been assessed independently by two researchers. Given the high numbers of included studies in the **Chapter 3** and the limited resources of our department, one researcher (Aldosari M) quality assessed all of the included studies but, only 5% of the included studies were quality assessed independently by another researcher from our group. Finally, conference abstracts and the grey literature were not searched, so it is possible that studies were missed.

For the two exploratory studies, the main limitations were that we only had sufficient statistical power to detect quite large differences in adherence rates between exposure groups (e.g., differences greater than 18% between the two groups), so smaller differences were not detectable in this study. Also, neither of the adherence measures in this study guarantees that patients took their medicine. Some patients also refused to participate in our study, and it is possible that those who chose not to participate varied from our sample in terms of adherence.

7.5 Challenges

During my PhD, I faced many challenges. As was required at the beginning of a PhD, I needed to learn different skills regarding literature search techniques, methodology, statistical analysis and quality assessment. It

took a lot of effort and time to learn these skills and apply them in my studies. These skills however will help me in my future research.

In the second systematic review **(Chapter 3)**, there were numerous studies that needed to be carefully read, assessed, and have data extracted from them. I learned how to organise many studies, and I gained experience in search techniques, quality assessment and data management and analysis.

In the exploratory studies **(Chapters 4 and 5)**, I also spent a significant time at the two hospitals in order to recruit 100 participants at each centre. During this time, I improved my confidence and communication skills with patients and their parents and with healthcare providers. It became clear to me during this time that most children, parents and healthcare providers are cooperative and helpful in supporting this type of research.

7.6 Future research

Despite the project findings, there are still some areas that require further research:

- The first systematic review **(Chapter 2)** showed that there is not a gold-standard method for measuring children's medicine adherence. Future research should therefore focus on developing a highly accurate assessment tool to measure medicines adherence.
- In the exploratory studies **(Chapter 4 and 5)**, we had sufficient statistical power to detect only quite large differences in adherence rates between groups (e.g. differences greater than 18% of

adherence rates between two different groups). Therefore, smaller differences would have been missed in these studies. A larger sample size would be needed in future studies to detect smaller differences.

- In the exploratory studies **(Chapter 4 and 5)**, we did not conduct statistical comparisons between sub-groups (such as child vs. parents having the responsibility for taking or giving medicine) because the sub-groups' sample sizes were too small. Future research could increase the sample sizes to conduct such comparisons.

7.7 Conclusion

The objectives of this project, to measure medicines adherence in children in the UK and Saudi Arabia and to explore to the barriers and facilitators of that adherence, were achieved. Previous studies covered a limited number of diseases, but in this project, we covered a wider variety of long-term conditions than had previously been studied. We also explored all barriers to and facilitators of medicines adherence in children with diverse diseases in the UK and Saudi Arabia.

This project found a statistically significant association between the BMQ differential score and adherence rates and between the education level of patients' parents and adherence rates in both countries.

The most common barriers in both countries seem to be medicine-related issues and patient-related factors. In addition, this project found that the most common facilitators for children's medicines adherence in both countries were using reminders, concealing a medicine's unappealing

flavour, developing a scheduled routine for taking medicine, and having family support.

The findings of this project will add to the understanding of the barriers to and facilitators of medicines adherence in children with various diseases.

References

1. Lerner BH. From careless consumptives to recalcitrant patients: The historical construction of noncompliance. Soc Sci Med. 1997;45(9):1423–31.
2. Sackett DL, Haynes RB. Compliance with Therapeutic Regimens. Balt MD Johns Hopkins Univ Press. 1976;1–6.
3. Hugtenburg JG, Timmers L, Elders PJM, Vervloet M, van Dijk L. Definitions, variants, and causes of nonadherence with medication: A challenge for tailored interventions. Patient Prefer Adherence. 2013;7:675–82.
4. Aronson JK. Compliance, concordance, adherence. Br J Clin Pharmacol. 2007;63(4):383–4.
5. Foster P, Hudson S. From compliance to concordance: a challenge for contraceptive prescribers. Health Care Anal. 1998 Jun;6(2):123–30.
6. Miller NH, Hill M, Kottke T, Ockene IS. The multilevel compliance challenge: recommendations for a call to action. A statement for healthcare professionals. Circulation. 1997 Feb 18;95(4):1085–90.
7. World Health Organization. Adherence to long-term therapies: evidence for action. Geneva: World Health Organisation. 2003. 1-209 p.
8. Mullen PD. Compliance becomes concordance. BMJ. 1997 Mar 8;314(7082):691–2.
9. Segal JZ. "Compliance" to "concordance": A critical view. J Med

Humanit. 2007;28(2):81–96.

10. Mandal A. The concept of concordance and its relation to leg ulcer management. J Wound Care. 2006 Sep;15(8):339–41.
11. Cramer JA, Roy A, Burrell A, Fairchild CJ, Fuldeore MJ, Ollendorf DA, et al. Medication compliance and persistence: Terminology and definitions. Value Heal. 2008;11(1):44–7.
12. Touchette DR, Shapiro NL. Medication compliance, adherence, and persistence: current status of behavioral and educational interventions to improve outcomes. J Manag Care Pharm. 2008;14(6 Suppl D):2–10.
13. Elliott R. Non-adherence to medicines: not solved but solvable. J Health Serv Res Policy. 2009 Jan;14(1):58–61.
14. Chappell F. Medication adherence in children remains a challenge. Prescriber. 2015;26(12):31–4.
15. Martin L, Williams S, Haskard K, DiMatteo M. The Challenge of Patient Adherence. Bariatr Nurs Surg Patient Care. 2005;7(4):186–186.
16. Jimmy B, Jose J. Patient medication adherence: Measures in daily practice. Oman Med J. 2011;26(3):155–9.
17. Luga A, McGuire M. Adherence and health care costs. Risk Manag Healthc Policy. 2014;7:35–44.
18. Matsui DM. Drug compliance in pediatrics. Clinical and research issues. Pediatr Clin North Am. 1997 Feb;44(1):1–14.

19. Dawood OT, Izham M, Ibrahim M, Palaian S. Medication compliance among children. World J Pediatr. 2010;6(3):200–2.
20. Farmer KC. Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. Clin Ther. 1999;21(6):1074–90.
21. Gandhi K, Vu B-MK, Eshtehardi SS, Wasserman RM, Hilliard ME. Adherence in adolescents with Type 1 diabetes: strategies and considerations for assessment in research and practice. Diabetes Manag (Lond). 2015;5(6):485–98.
22. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. 2005 Aug 4;353(5):487–97.
23. Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: Its importance in cardiovascular outcomes. Circulation. 2009;119(23):3028–35.
24. MacLaughlin EJ, Raehl CL, Treadway AK, Sterling TL, Zoller DP, Bond CA. Assessing medication adherence in the elderly: Which tools to use in clinical practice? Drugs and Aging. 2005;22(3):231–55.
25. Cramer JA. Microelectronic systems for monitoring and enhancing patient compliance with medication regimens. Drugs. 1995 Mar;49(3):321–7.
26. Raehl CL, Bond CA, Woods TW, Patry RA, Sleeper RB. Individualized Drug Use Assessment in the Elderly. Pharmacotherapy. 2002;22(10):1239–48.

27. Stirratt MJ, Dunbar-Jacob J, Crane HM, Simoni JM, Czajkowski S, Hilliard ME, et al. Self-report measures of medication adherence behavior: recommendations on optimal use. Transl Behav Med. 2015;5(4):470–82.

28. Martin S, Elliott-DeSorbo DK, Calabrese S, Wolters PL, Roby G, Brennan T, et al. A Comparison of Adherence Assessment Methods Utilized in the United States: Perspectives of Researchers, HIV-Infected Children, and their Caregivers. AIDS Patient Care STDS. 2009;23(8):593–601.

29. Wiens MO, MacLeod S, Musiime V, Senyonga M, Kizza R, Bakeera-Kitaka S et al. Adherence to Antiretroviral Therapy in HIV-Positive Adolescents in Uganda Assessed by multiple methods. Paediatr Drugs. 2012;14(5):331–5.

30. Vik SA, Maxwell CJ, Hogan DB. Measurement, Correlates, and Health Outcomes of Medication Adherence among Seniors. Ann Pharmacother. 2004;38(2):303–12.

31. Jentzsch NS, Camargos PAM, Colosimo EA, Bousquet J. Monitoring adherence to beclomethasone in asthmatic children and adolescents through four different methods. Allergy Eur J Allergy Clin Immunol. 2009;64(10):1458–62.

32. Cramer JA, Mattson RH, Prevey ML, Scheyer RD, Ouellette VL. How often is medication taken as prescribed? A novel assessment technique. JAMA. 1989 Jun 9;261(22):3273–7.

33. Chan AHY, Harrison J, Black PN, Mitchell EA, Foster JM. Using Electronic Monitoring Devices to Measure Inhaler Adherence: A Practical Guide for Clinicians. J Allergy Clin Immunol Pract. 2015;3(3):335–349.e5.
34. Neal S. LeLeiko, Debra Lobato, Sarah Hagin, Elizabeth McQuaid, Ronald Seifer, Sheryl J. Kopel, Julie Boergers, Jack Nassau, Kristina Suorsa, Jason Shapiro and BB. Rates and Predictors of Oral Medication Adherence in Pediatric IBD Patients. 2013;44(2):319–35.
35. Ho PM, Magid DJ, Shetterly SM, Olson KL, Maddox TM, Peterson PN, et al. Medication nonadherence is associated with a broad range of adverse outcomes in patients with coronary artery disease. Am Heart J. 2008;155(4):772–9.
36. Watanabe JH, Bounthavong M, Chen T. Revisiting the medication possession ratio threshold for adherence in lipid management. Curr Med Res Opin. 2013 Mar;29(3):175–80.
37. Lehmann A, Aslani P, Ahmed R, Celio J, Gauchet A, Bedouch P, et al. Assessing medication adherence: Options to consider. Int J Clin Pharm. 2014;36(1):55–69.
38. Jonikas MA, Mandl KD. Surveillance of medication use: early identification of poor adherence. J Am Med Inform Assoc. 2011;19(4):649–54.
39. Lehane E, McCarthy G. Intentional and unintentional medication non-adherence: A comprehensive framework for clinical research and

practice? A discussion paper. Int J Nurs Stud. 2007;44(8):1468–77.

40. Donovan JL, Blake DR. Patient non-compliance: deviance or reasoned decision-making? Soc Sci Med. 1992 Mar;34(5):507–13.

41. Horne R, Chapman SCE, Parham R, Freemantle N, Forbes A, Cooper V. Understanding patients' adherence-related Beliefs about Medicines prescribed for long-term conditions: A meta-analytic review of the Necessity-Concerns Framework. PLoS One. 2013;8(12).

42. Horne R, Weinman J, Hankins M, Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire : The development and evaluation of a new method for assessing the cognitive representation of medication. Psychol Heal. 1999;14:1–24.

43. Fransen GAJ, Mesters I, Janssen MJR, Knottnerus JA, Muris JWM. Which patient-related factors determine self-perceived patient adherence to prescribed dyspepsia medication? Health Educ Res. 2009;24(5):788–98.

44. Weiner B. An Attributional Theory of Achievement Motivation and Emotion. In: An Attributional Theory of Motivation and Emotion [Internet]. New York, NY: Springer US; 1986. p. 159–90. Available from: http://link.springer.com/10.1007/978-1-4612-4948-1_6

45. Ryan RM, Patrick H, Deci EL, Williams GC, Ryan RM, Patrick H, et al. Facilitating health behaviour change and its maintenance: Interventions based on Self-Determination Theory. Eur Heal Psychol. 2008;10(1):2–6.

46. De Las Cuevas C, Peñate W, Cabrera C. Perceived Health Control: A Promising Step Forward in Our Understanding of Treatment Adherence in Psychiatric Care. J Clin Psychiatry. 2016 Oct;77(10):e1233–9.
47. West LM, Borg Theuma R, Cordina M. Health locus of control: Its relationship with medication adherence and medication wastage. Res Soc Adm Pharm. 2018;14(11):1015–9.
48. Morowatisharifabad MA, Mahmoodabad SS, Baghianimoghadam MH, Tonekaboni N. Relationships between locus of control and adherence to diabetes regimen in a sample of Iranians. Int J Diabetes Dev Ctries. 2010;30(1):27.
49. Horne R, Weinman J, Barber N, Elliott R. Concordance, adherence and compliance in medicine taking. Rep Natl Co-ord Cent NHS Serv Deliv Organ R D. 2005;1–331.
50. Brown MT, Bussell JK. Medication Adherence: WHO Cares? Mayo Clin Proc. 2011;86(4):304–14.
51. Lin J, Sklar GE, Oh VM Sen, Li SC. Factors affecting therapeutic compliance: A review from the patient's perspective. Ther Clin Risk Manag. 2008;4(1):269–86.
52. Kvarnstrom K, Airaksinen M, Liira H. Barriers and facilitators to medication adherence: A qualitative study with general practitioners. BMJ Open. 2018;8(1):6–13.
53. Raynor DKT. Medication literacy is a 2-way street. Mayo Clin Proc.

2008 May;83(5):520–2.

54. Kindig D, Affonso DR, Chudler E, Gaston M, Meade CR, Parker R, et al. Is Health Literacy About Education? Dc. 2000;624–6242.

55. UCL Institute of Heallth Equity. Improving health literacy to reduce health inequalities. Public Heal Engl. 2015;(September).

56. Kalogianni A. Factors affect in patient adherence to medication regimen. Heal Sci J. 2011;5(3):157–8.

57. Lask B. Motivating children and adolescents to improve adherence. J Pediatr. 2003;143(4):430–3.

58. El-Rachidi S, LaRochelle JM, Morgan JA. Pharmacists and Pediatric Medication Adherence: Bridging the Gap. Hosp Pharm. 2017;52(2):105–16.

59. Gardiner P, Dvorkin L. Promoting medication adherence in children. Am Fam Physician. 2006;74(5).

60. Penkower L, Dew MA, Ellis D, Sereika SM, Kitutu JMM, Shapiro R. Psychological distress and adherence to the medical regimen among adolescent renal transplant recipients. Am J Transplant. 2003 Nov;3(11):1418–25.

61. Buchanan AL, Montepiedra G, Sirois PA, Kammerer B, Garvie PA, Storm DS, et al. Barriers to Medication Adherence in HIV-Infected Children and Youth Based on Self- and Caregiver Report. Pediatrics. 2012;129:1244–51.

62. Chandwani S, Koenig LJ, Sill AM, Abramowitz S, Conner LC, D'Angelo

L. Predictors of antiretroviral medication adherence among a diverse cohort of adolescents with HIV. J Adolesc Heal. 2012;51(3):242–51.

63. Lewis LM, Ogedegbe C, Ogedegbe G. Enhancing adherence of antihypertensive regimens in hypertensive African-Americans: current and future prospects. Expert Rev Cardiovasc Ther. 2012 Nov;10(11):1375–80.

64. Kripalani S, LeFevre F, O Phillips C, Williams M, Basaviah P, Baker D. Deficits in Communication and Information Transfer Between Hospital-Based and Primary Care Physicians. JAMA J Am Med Assoc. 2007;297(8):831–41.

65. Sriharsha M AP. Treatment and Disease Related Factors Affecting Non-adherence among Patients on Long Term Therapy of Antidepressants. J Depress Anxiety. 2015;04(02):2–7.

66. Rose LE, Kim MT, Dennison CR, Hill MN. The contexts of adherence for African Americans with high blood pressure. J Adv Nurs. 2000;32(3):587–94.

67. Pagès-Puigdemont N, Mangues MA, Masip M, Gabriele G, Fernández-Maldonado L, Blancafort S, et al. Patients' Perspective of Medication Adherence in Chronic Conditions: A Qualitative Study. Adv Ther. 2016;33(10):1740–54.

68. Klok T, Kaptein AA, Duiverman EJ, Brand PL. Long-term adherence to inhaled corticosteroids in children with asthma: Observational study. Respir Med. 2015;109(9):1114–9.

69. Feyissa A. Magnitude and Associated Factors of Non-Adherence to Highly Active Antiretroviral Therapy among Children in Fiche Hospital , North Shewa , Ethiopia. J Pharm Care Heal Syst. 2017;4(1):1–7.
70. Kendre GM, Gabhale YR, Shah ND, Jadhav VM, Nath K, Manglani M V. Adherence to antiretroviral therapy and factors affecting adherence among paediatric HIV patients. Int J Contemp Pediatr. 2017;4(6):1962–8.
71. Nakigozi G, Makumbi FE, Kigozi G, Nalugoda F, Reynolds SJ, Chang LW, et al. Barriers to Utilization of HIV Care Services Among Adolescents and Young Adults in Rakai , Uganda : the Role of Economic Strengthening. Glob Soc Welf. 2015;2:105–10.
72. Madiba S, Josiah U. Perceived Stigma and Fear of Unintended Disclosure are Barriers in Medication Adherence in Adolescents with Perinatal HIV in Botswana: A Qualitative Study. Biomed Res Int. 2019;2019.
73. Galea JT, Wong M, Mu M, Valle E, Kolevic L, Franke M, et al. Barriers and facilitators to antiretroviral therapy adherence among Peruvian adolescents living with HIV : A qualitative study. PLoS One. 2018;13(2):1–19.
74. Maccarthy S, Saya U, Samba C, Birungi J, Okoboi S, Linnemayr S. " How am I going to live ? " : exploring barriers to ART adherence among adolescents and young adults living with HIV in Uganda. BMC Public Health. 2018;1–11.

75. Cram A, Breitkreutz J, Desset-Brèthes S, Nunn T, Tuleu C. Challenges of developing palatable oral paediatric formulations. Int J Pharm. 2009;365(1–2):1–3.
76. Ivanovska V, Rademaker CMA, van Dijk L, Mantel-Teeuwisse AK. Pediatric Drug Formulations: A Review of Challenges and Progress. Pediatrics. 2014;134(2):361–72.
77. Reporter. Four-month-old baby "dies of overdose after mother was given wrong prescription" [Internet]. Mail Online. 2010. Available from: http://www.dailymail.co.uk/news/article-1246986
78. Nunn AJ. Making Medicines that Children can take. Arch Dis Child. 2003;88(5):369–71.
79. Danziger-Isakov L, Frazier TW, Worley S, Williams N, Shellmer D, Dharnidharka VR, et al. Perceived barriers to medication adherence in pediatric and adolescent solid organ transplantation. Pediatr Transplant. 2016;20(2):307–15.
80. Cea-Calvo L, Marín-Jiménez I, de Toro J, Fuster-RuizdeApodaca MJ, Fernández G, Sánchez-Vega N, et al. Association between non-adherence behaviors, patients' experience with healthcare and beliefs in medications: a survey of patients with different chronic conditions. Curr Med Res Opin. 2020;36(2):293–300.
81. Emilsson M, Gustafsson PA, Öhnström G, Marteinsdottir I. Beliefs regarding medication and side effects influence treatment adherence in adolescents with attention deficit hyperactivity disorder. Eur Child

Adolesc Psychiatry. 2017;26(5):559–71.

82. Conn KM, Halterman JS, Fisher SG, Yoos HL, Chin NP, Szilagyi PG. Parental beliefs about medications and medication adherence among urban children with asthma. Ambul Pediatr. 5(5):306–10.

83. Hanghøj S, Boisen KA. Self-reported barriers to medication adherence among chronically ill adolescents: A systematic review. J Adolesc Heal. 2014;54(2):121–38.

84. Mäkelä MJ, Backer V, Hedegaard M, Larsson K. Adherence to inhaled therapies, health outcomes and costs in patients with asthma and COPD. Respir Med. 2013;107(10):1481–90.

85. Elliott RA, Watmough DE, Gray NJ, Conroy S, Lakhanpaul M, Pandya H, et al. Talking about medicines (TABS): a multi-method study to understand reasons for medicines non- adherence in children and young people with chronic illness , and to improve their contribution to managing their medicines. Natl Inst Heal Res. 2013;1–423.

86. Ankrah DNA, Agyepong IA, Lartey M. Facilitators and barriers to antiretroviral therapy adherence among adolescents in Ghana. Patient Prefer Adherence. 2016;10:329–37.

87. Holley S, Walker D, Knibb R. Barriers and facilitators to self-management of asthma in adolescents : An interview study to inform development of a novel intervention. Clin Exp Allergy. 2018;48:944–56.

88. Pelaez S, Lamontagne AJ, Collin J, Gauthier A, Grad RM, Blais L, et

al. Patients ’ perspective of barriers and facilitators to taking long-term controller medication for asthma : a novel taxonomy. BMC Pulm Med. 2015;15(42):1–11.

89. Coletti DJ, Pappadopulos E, Katsiotas NJ, Berest A, Jensen PS, Kafantaris V. Parent Perspectives on the Decision to Initiate Medication Treatment of Attention-Deficit/Hyperactivity Disorder. J Child Adolesc Psychopharmacol. 2012;22(3):226–37.
90. Wamboldt FS, Bender BG, Rankin AE. Adolescent decision-making about use of inhaled asthma controller medication: Results from focus groups with participants from a prior longitudinal study. Asthma. 2011;48(7):741–50.
91. Mehta P, Steinberg EA, Kelly SL, Buchanan C, Resmini A. Medication adherence among adolescent solid- -organ transplant recipients : A survey of healthcare providers. Pediatr Transplant. 2017;21:1–8.
92. Venables R, Batchelor H, Hodson J, Stirling H, Marriott J. Determination of formulation factors that affect oral medicines acceptability in a domiciliary paediatric population. Int J Pharm. 2015;480(1–2):55–62.
93. Fetzer BC, Mupenda B, Lusiama J. Barriers to and Facilitators of Adherence to Pediatric Antiretroviral Therapy in a Sub-Saharan Setting : Insights from a Qualitative Study. AIDS Patient Care STDS. 2011;25(10):611–21.
94. Bruzzese J, Carcone AI, Lam P, Ellis DA. Adherence to Asthma

Medication Regimens in Urban African American Adolescents : Application of. Heal Psychol. 2013;1–4.

95. Venditti EM, Tan K, Chang N, Laffel L, Mcginley G, Miranda N, et al. Barriers and strategies for oral medication adherence among children and adolescents with Type 2 diabetes. Diabetes Res Clin Pract. 2018;139:24–31.
96. Ratanawongsa N, Karter AJ, Parker MM, Lyles CR, Heisler M, Moffet HH, et al. Communication and medication adherence: the diabetes study of Northern California. JAMA Intern Med. 2013;173(3):210–8.
97. Dean AJ, Walters J, Hall A. A systematic review of interventions to enhance medication adherence in children and adolescents with chronic illness. Arch Dis Child. 2010;95(9):717–23.
98. Alsous M. Medication Adherence in Children. J Healthc Commun. 2017;02(01):10–2.
99. Lam WY, Fresco P, Lam WY, Fresco P. Medication Adherence Measures: An Overview. BioMed Res Int. 2015;2015:e217047.
100. Garfield S, Clifford S, Eliasson L, Barber N, Willson A. Suitability of measures of self-reported medication adherence for routine clinical use: A systematic review. BMC Med Res Methodol. 2011;11(1):149.
101. Lima-Dellamora E da C, Osorio-de-Castro CGS, Madruga LG dos SL, Azeredo TB. Use of pharmacy records to measure treatment adherence: a critical review of the literature. Cad Saude Publica. 2017;33(3):1–16.

102. Monnette A, Zhang Y, Shao H, Shi L. Concordance of Adherence Measurement Using Self-Reported Adherence Questionnaires and Medication Monitoring Devices: An Updated Review. Pharmacoeconomics. 2017;1–11.
103. Greenlaw SM, Yentzer BA, O'Neill JL, Balkrishnan R, Feldman SR. Assessing adherence to dermatology treatments: A review of self-report and electronic measures. Ski Res Technol. 2010;16(2):253–8.
104. Ruppar TM, Dobbels F, Lewek P, Matyjaszczyk M, Siebens K, De Geest SM. Systematic Review of Clinical Practice Guidelines for the Improvement of Medication Adherence. Int J Behav Med. 2015;22(6):699–708.
105. Bryant J, McDonald VM, Boyes A, Sanson-Fisher R, Paul C, Melville J. Improving medication adherence in chronic obstructive pulmonary disease: a systematic review. Respir Res. 2013;14:109.
106. Zaugg V, Korb-Savoldelli V, Durieux P, Sabatier B. Providing physicians with feedback on medication adherence for people with chronic diseases taking long-term medication. Cochrane database Syst Rev. 2018;(1).
107. Kastner M, Wilczynski NL, Walker-Dilks C, McKibbon KA, Haynes B. Age-specific search strategies for medline. J Med Internet Res. 2006;8(4):1–10.
108. von Elm E, Altman D, Egger M, Pocock SJ, Gotzsche P, Vandenbroucke JP. Annals of Internal Medicine Academia and Clinic

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement : Guidelines for Reporting. Ann Intern Med. 2007;147(8):573–8.

109. Aljebab F, Choonara I, Conroy S. Systematic review of the toxicity of short-course oral corticosteroids in children. Arch Dis Child. 2016;101(4):365–70.
110. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343(7829):1–9.
111. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. BMJ. 2009;339(7716):332–6.
112. Duncan CL, Hogan MB, Tien KJ, Chorney JM, Zettler MD, Koven L, et al. Efficacy of a parent – youth teamwork intervention to promote adherence in pediatric asthma. J Pediatr Psychol. 2013;38(6):617–28.
113. Biressaw S, Abegaz WE, Abebe M, Taye WA, Belay M. Adherence to Antiretroviral Therapy and associated factors among HIV infected children in Ethiopia: Unannounced home-based pill count versus caregivers' report. BMC Pediatr. 2013;13(1):1.
114. Farley JJ, Montepiedra G, Storm D, Sirois PA, Malee K, Garvie P, et al. Assessment of adherence to antiretroviral therapy in perinatally HIV-infected children and youth using self-report measures and pill

count. J Dev Behav Pediatr. 2008;29(5):377–84.

115. Desmond AC, Moodley D, Conolly CA, Castel SA, Coovadia HM. Evaluation of adherence measures of antiretroviral prophylaxis in HIV exposed infants in the first 6 weeks of life. BMC Pediatr. 2015;15(1):1–8.
116. Vreeman RC, Ilagan JO, Liang Y, Daubner GM, Stanley C, Ramakrishnan A, et al. Comprehensive Evaluation of Caregiver-Reported Antiretroviral Therapy Adherence for HIV-Infected Children. AIDS Behav. 2016;27(5):626–34.
117. Müller AD, Bode S, Myer L, Roux P, von Steinbüchel N. Electronic measurement of adherence to pediatric antiretroviral therapy in South Africa. Pediatr Infect Dis J. 2008 Mar;27(3):257–62.
118. Vreeman RC, Nyandiko WM, Liu H, Tu W, Scanlon ML, Slaven JE, et al. Measuring adherence to antiretroviral therapy in children and adolescents in western Kenya. J Int AIDS Soc. 2014;17:1–10.
119. Khan M, Song X, Williams K, Bright K, Sill A, Rakhmanina N. Evaluating adherence to medication in children and adolescents with HIV. Arch Dis Child. 2009;94(12):970–3.
120. Müller AD, Jaspan HB, Myer L, Lewis Hunter A, Harling G, Bekker LG, et al. Standard measures are inadequate to monitor pediatric adherence in a resource-limited setting. AIDS Behav. 2011;15(2):422–31.
121. Burack Gail G, Gaur S, Marone R, Petrova A. Adherence to

antiretroviral therapy in pediatric patients with human immunodeficiency virus (HIV-1). J Pediatr Nurs. 2010;25(6):500–4.

122. Burgess SW, Sly PD, Morawska A, Devadason SG. Assessing adherence and factors associated with adherence in young children with asthma. Respirology. 2008;13(4):559–63.
123. Garcia-Marcos PW, Brand PLP, Kaptein AA, Klok T. Is the MARS questionnaire a reliable measure of medication adherence in childhood asthma? J Asthma. 2016 Dec;53(10):1085–9.
124. Kevin A. Hommel, Christine M. Davis and RN. Objective versus Subjective Assessment of Oral Medication Adherence in Pediatric Inflammatory Bowel Disease. 2009;14(4):384–99.
125. Modi AC, Monahan S, Daniels D, Glauser TA. Development and validation of the Pediatric Epilepsy Medication Self-Management Questionnaire. Epilepsy Behav. 2010;18(1–2):94–9.
126. Shah NM, Hawwa AF, Millership JS, Collier PS, Ho P, Tan ML, et al. Adherence to antiepileptic medicines in children: A multiple-methods assessment involving dried blood spot sampling. Epilepsia. 2013;54(6):1020–7.
127. Markowitz JT, Laffel LMB, Volkening LK, Anderson BJ, Nansel TR, Weissberg-Benchell J, et al. Validation of an abbreviated adherence measure for young people with Type1 diabetes. Diabet Med. 2011;28(9):1113–7.
128. Ashley M. Kroon Van Diest, Rachelle Ramsey, Brandon Aylward, John

W. Kroner, Stephanie M. Sullivan, Katie Nause, Janelle R. Allen, Leigh A. Chamberlin, Shalonda Slater, Kevin Hommel, Susan L. LeCates, Marielle A. Kabbouche, Hope L. O'Brien, Joanne Kacpers and SWP. Adherence to Biobehavioral Recommendations in Pediatric Migraine as Measured by Electronic Monitoring: The Adherence in Migraine (AIM) Study. 2016;44(2):319–35.

129. Al-Kloub MI, A Bed MA, Al Khawaldeh OA, Al Tawarah YM, Froelicher ES. Predictors of non-adherence to follow-up visits and deferasirox chelation therapy among jordanian adolescents with thalassemia major. Pediatr Hematol Oncol. 2014;31(7):624–37.
130. Chappuy H, Treluyer JM, Faesch S, Giraud C, Ch??ron G. Length of the treatment and number of doses per day as major determinants of child adherence to acute treatment. Acta Paediatr Int J Paediatr. 2010;99(3):433–7.
131. Souares A, Moulin P, Sarrassat S, Carlotti MP, Lalou R, Le Hesran JY. Self-reported data: A major tool to assess compliance with anti-malarial combination therapy among children in Senegal. Malar J. 2009;8(1):1–7.
132. Nakonezny PA, Hughes CW, Mayes TL, Sternweis-Yang KH, Kennard BD, Byerly MJ, et al. A Comparison of Various Methods of Measuring Antidepressant Medication Adherence Among Children and Adolescents with Major Depressive Disorder in a 12-Week Open Trial of Fluoxetine. J Child Adolesc Psychopharmacol. 2010;20(5):431–9.

133. Almardini R, Taybeh EO, Alsous MM, Hawwa AF, McKeever K, Horne R, et al. A multiple methods approach to determine adherence with prescribed mycophenolate in children with kidney transplant. Br J Clin Pharmacol. 2019;85(7):1434–42.
134. Alsous MM, Hawwa AF, Imrie C, Szabo A, Alefishat E, Farha RA, et al. Adherence to Azathioprine/6-Mercaptopurine in Children and Adolescents with Inflammatory Bowel Diseases: A Multimethod Study. Can J Gastroenterol Hepatol. 2020;2020.
135. Tu W, Nyandiko WM, Liu H, Slaven JE, Scanlon ML, Ayaya SO, et al. Pharmacokinetics-based adherence measures for antiretroviral therapy in HIV-infected Kenyan children: J Int AIDS Soc. 2017;20(1):1–6.
136. Chanelle Smith1, Tanuja N. Gengiah1, Nonhlanhla Yende-Zuma1, Michele Upfold1 A, Naidoo K. Assessing adherence to antiretroviral therapy in a rural paediatric cohort in KwaZulu-Natal, South Africa. 2016;137(32):10160–3.
137. Patel NG, Lindsey T, Strunk RC, DeBaun MR. Prevalence of daily medication adherence among children with sickle cell disease: a 1-year retrospective cohort analysis. Pediatr Blood Cancer. 2010;55(3):554–6.
138. Mulvaney SA, Ho YX, Cala CM, Chen Q, Nian H, Patterson BL, et al. Assessing adolescent asthma symptoms and adherence using mobile phones. J Med Internet Res. 2013;15(7):1–10.

139. Shelagh A. Mulvaney, Russell L. Rothman, Mary S. Dietrich, Kenneth A. Wallston, Elena Grove, Tom A. Elasy and KBJ. Using Mobile Phones to Measure Adolescent Diabetes Adherence. 2012;7(4):221–9.

140. Onzenoort HAW Van, Verberk WJ, Kessels AGH, Kroon AA, Neef C, Kuy PM Van Der, et al. Assessing Medication Adherence Simultaneously by Electronic Monitoring and Pill Count in Patients With Mild-to-Moderate Hypertension. Am J Hypertens. 2009;23(2):149–54.

141. Ac G, Sl F, Am N, Ba F. Assessing associations between medication adherence and potentially modifiable psychosocial variables in pediatric kidney transplant recipients and their families. 2004;543–50.

142. JB1 N, M H, DW D, M L, SB O, L R, et al. Adherence to highly active antiretroviral therapy assessed by pharmacy claims predicts survival in HIV-infected South African adults. J Acquir Immune Defic Syndr. 2006;43:78–84.

143. Hess LM, Raebel MA, Conner DA, Malone DC. Measurement of Adherence in Pharmacy Administrative Databases: A Proposal for Standard Definitions and Preferred Measures. 2006;40:1280–8.

144. Liu H, Carol E. Golin, Miller LG, Hays RD, Beck K, Sanandaji S, et al. A Comparison Study of Multiple Measures of Adherence to. Acad Clin. 2001;1004–6.

145. Shubber Z, Mills EJ, Nachega JB, Vreeman R, Freitas M, Bock P, et al. Patient-Reported Barriers to Adherence to Antiretroviral Therapy : A Systematic Review and Meta-Analysis. PLoS Med. 2016;1–14.
146. Gellad WF, Jerry L. Grenard, Marcum ZA. A Systematic Review of Barriers to Medication Adherence in the Elderly: Looking Beyond Cost and Regimen Complexity. NIH Public Access. 2012;9(1):11–23.
147. Mills EJ, Nachega JB, Bangsberg DR, Singh S, Rachlis B, Wu P, et al. Adherence to HAART : A Systematic Review of Developed and Developing Nation Patient-Reported Barriers and Facilitators. PLoS Med. 2006;3(11).
148. Jaam M, Izham M, Ibrahim M, Kheir N, Awaisu A. Factors associated with medication adherence among patients with diabetes in the Middle East and North Africa region : A systematic mixed studies review. Diabetes Res Clin Pract. 2017;129:1–15.
149. Banerjee A, Khandelwal S, Nambiar L, Saxena M, Peck V, Moniruzzaman M, et al. Health system barriers and facilitators to medication adherence for the secondary prevention of cardiovascular disease : a systematic review. Openheart. 2016;3:e000438.
150. Yap AF, Thirumoorthy T, Kwan YH. Systematic review of the barriers affecting medication adherence in older adults. Geriatr Gerontol Int. 2016;16:1093–101.
151. Yeam CT, Chia S, Tan HCC, Kwan YH, Fong W, Seng JJB. A systematic review of factors affecting medication adherence among

patients with osteoporosis. Osteoporos Int. 2018;1–15.

152. Dharmapuri S, Best D, Kind T, Silber TJ, Simpson P, Angelo LD. Health Literacy and Medication Adherence in Adolescents. J Pediatr. 2015;166(2):378–82.

153. Susannah M. Allison, Koenig LJ, Marhefka SL, Carter RJ, John J. Farley. Assessing Medication Adherence of Perinatally HIV-Infected Children Using Caregiver Interviews. J Acquir Immune Defic Syndr. 2011;21(6):478–88.

154. Fawzi MCS, Ng L, Kanyanganzi F, Kirk C, Bizimana J, Cyamatare F, et al. Mental Health and Antiretroviral Adherence Among Youth Living With HIV in Rwanda. Pediatrics. 2016;138(4):1–9.

155. Human Development Indices and Indicators. United Nations Dev Program. 2018;22–5.

156. Nabukeera-barungi N, Elyanu P, Asire B, Katureebe C, Lukabwe I, Namusoke E, et al. Adherence to antiretroviral therapy and retention in care for adolescents living with HIV from 10 districts in Uganda. BMC Infect Dis. 2015;1–10.

157. Vreeman RC, Ayaya SO, Musick BS, Yiannoutsos T, Cohen CR, Nash D, et al. Adherence to antiretroviral therapy in a clinical cohort of HIV-infected children in East Africa. PLoS Med. 2018;1–15.

158. Shemesh E, Duncan S, Anand R, Shneider BL, Estella M. Trajectory of adherence behavior in pediatric and adolescent liver transplant recipients – the MALT cohort. Liver Transpl. 2018;24(1):80–8.

159. Blydt-Hansen TD, Pierce CB, Cai Y, Samsonov D, Massengill S, Moxey-Mims M, et al. Medication treatment complexity and adherence in children with CKD. Clin J Am Soc Nephrol. 2014;9(2):247–54.
160. Fontanella CA, Bridge JA, Marcus SC, Campo J V. Factors Associated with Antidepressant Adherence for Medicaid-Enrolled Children and Adolescents. Ann Pharmacother. 2011;45(7–8):898–909.
161. Logan SL, Carpenter L, Leslie RS, Hunt KS, Garrett-Mayer E, Charles J, et al. Rates and predictors of adherence to psychotropic medications in children with autism spectrum disorders. J Autism Dev Disord. 2014;44(11):2931–48.
162. Fischer MA, Stedman MR, Lii J, Vogeli C, Shrank WH, Brookhart MA, et al. Primary medication non-adherence: Analysis of 195,930 electronic prescriptions. J Gen Intern Med. 2010;25(4):284–90.
163. Joyce N, Eaton CB, Wellenius GA, Trivedi AN, Zachariah JP. Patterns and Predictors of Medication Adherence to Lipid Lowering Therapy in Children ages 8 to 20 Nina. J Clin Lipidol. 2016;10(4):824–32.
164. Ingerski LM, Baldassano RN, Denson LA, Hommel KA. Barriers to Oral Medication Adherence for Adolescents with Inflammatory Bowel Disease. J Pediatr Psychol. 2009;35(6):683–91.
165. Hommel KA, Baldassano RN. Brief Report : Barriers to Treatment Adherence in Pediatric Inflammatory Bowel Disease. J Pediatr Psychol. 2009;35(9):1005–10.

166. Hommel KA, Denson LA, Baldassano RN. Oral Medication Adherence and Disease Severity in Pediatric Inflammatory Bowel Disease Kevin. Eur J Gastroenterol Hepatol. 2011;23(3):250–4.
167. Gray WN, Denson LA, Baldassano RN, Hommel KA. Treatment Adherence in Adolescents With Inflammatory Bowel Disease : The Collective Impact of Barriers to Adherence and Anxiety / Depressive Symptoms. J Pediatr Psychol. 2012;37(3):282–91.
168. Reed-knight B, Lewis JD, Blount RL. Association of Disease , Adolescent , and Family Factors with Medication Adherence in Pediatric Inflammatory Bowel Disease. J Pediatr Psychol. 2011;36(3):308–17.
169. Simons L, McCormick ML, Mee LL, Blount RL. Parent and patient perspectives on barriers to medication adherence in adolescent transplant recipients. Pediatr Transplant. 2008;13(3):338–47.
170. Zelikovsky N, Ap S, Ja P, Kec M, Zelikovsky N, Aileen P, et al. Perceived barriers to adherence among adolescent renal transplant candidates. Pediatr Transplant. 2008;12:300–8.
171. Simons LE, McCormick ML, Devine K, Blount RL. Medication barriers predict adolescent transplant recipients' adherence and clinical outcomes at 18-month follow-up. J Pediatr Psychol. 2010;35(9):1038–48.
172. Lee JL, Eaton CK, Rich KL, Reed-Knight B, Liverman RS, Mee LL, et al. The interactive effect of parent personality and medication

knowledge on adherence in children awaiting solid organ transplantation. Heal Psychol. 2017;36(5):445–8.

173. Klok T, Kaptein AA, Duiverman EJ, Brand PL. High inhaled corticosteroids adherence in childhood asthma: The role of medication beliefs. Eur Respir J. 2012;40(5):1149–55.
174. Sonney J, Insel KC, Segrin C, Gerald LB, Ki Moore IM. Association of Asthma Illness Representations and Reported Controller Medication Adherence Among School-Aged Children and Their Parents. J Pediatr Heal Care. 2017;31(6):703–12.
175. Koster ES, Raaijmakers JAM, Vijverberg SJH, Zee A-HM der. Inhaled corticosteroid adherence in paediatric patients: the PACMAN cohort study Ellen. Pharmacoepidemiol Drug Saf. 2011;20:1064–72.
176. Jeganathan J, Lee CH, Rahme A, Tiao DK, Weston C, Dutt S, et al. Pediatric-to-adult Transition and Medication Adherence in Patients with Inflammatory Bowel Disease. Inflamm Bowel Dis. 2017;23(7):1065–70.
177. Gabr WM, Shams M. Adherence to medication among outpatient adolescents with epilepsy. Saudi Pharm J. 2015;23(1):33–40.
178. Goodfellow NA, Hawwa AF, Reid AJ, Horne R, Shields MD, McElnay JC. Adherence to treatment in children and adolescents with cystic fibrosis: a cross-sectional, multi-method study investigating the influence of beliefs about treatment and parental depressive symptoms. BMC Pulm Med. 2015;15(43):1–10.

179. Dean AJ, Wragg J, Draper J, McDermott BM. Predictors of medication adherence in children receiving psychotropic medication. J Paediatr Child Health. 2011;47(6):350–5.
180. Badawy SM, Thompson AA, Penedo FJ, Lai J, Rychlik K, Liem RI. Barriers to hydroxyurea adherence and health-related quality of life in adolescents and young adults with sickle cell disease. Eur J Haematol. 2017;98:608–14.
181. Naar-king S, Montepiedra G, Nichols S, Farley J, Garvie PA, Kammerer B, et al. Allocation of Family Responsibility for Illness Management in Pediatric HIV. J Pediatr Psychol. 2009;34(2):187–94.
182. Lancaster BM, Gadaire DM, Holman K, Leblanc LA. Association Between Diabetes Treatment Adherence and Parent – Child Agreement Regarding Treatment Responsibilities. Fam Syst Heal. 2015;33(2):120–5.
183. Park J, Nachman S. The link between religion and HAART adherence in pediatric HIV patients. AIDS Care. 2010;22(5).
184. Malee K, Williams P, Montepiedra G, McCabe M, Nichols S, Sirois PA, et al. Medication Adherence in Children and Adolescents with HIV Infection: Associations with Behavioral Impairment. AIDS Patient Care STDS. 2011;25(3):191–200.
185. Navarra A-M, Neu N, Toussi S, Nelson J, Elaine L. Larson. Health Literacy and Adherence to Antiretroviral Therapy Among HIV-Infected Youth Ann-Margaret. J Assoc Nurses AIDS Care.

2014;25(3):203–13.

186. Kuti BP, Omole KO, Kuti DK. Factors associated with childhood asthma control in a resource - poor center. Fam Med Prim Care. 2017;6(2):222–8.

187. Rhee H, Wicks MN, Dolgoff JS, Love TM. Cognitive factors predict medication adherence and asthma control in urban adolescents with asthma. Patient Prefer Adherence. 2018;12:929–37.

188. Silverstein DM, Fletcher A. Barriers to medication adherence and its relationship with outcomes in pediatric dialysis patients. Pediatr Nephrol. 2014;29:1425–30.

189. Vasylyeva T, Singh R, Sheehan C, Chennasamudram SP, Hernandez AP. Self-Reported Adherence to Medications in a Pediatric Renal Clinic: Psychological Aspects. PLoS One. 2013;8(7):1–5.

190. Smith AW, Mara CA, Modi AC. Epilepsy & Behavior Adherence to antiepileptic drugs in adolescents with epilepsy. Epilepsy Behav. 2018;80:307–11.

191. Modi AC, Crosby LE, Guilfoyle SM, Lemanek KL, Witherspoon D, Mitchell MJ. Barriers to Treatment Adherence for Pediatric Patients With Sickle Cell Disease and Their Families. Child Heal Care. 2009;38:107–22.

192. White YRG, Pierre RB, Palmer P, Moore J, Rodriguez B, Christie CDC, et al. Adherence to Antiretroviral Drug Therapy in Children with HIV / AIDS in Jamaica. West indian Med J. 2008;57(3):231–7.

193. Biadgilign S, Deribew A, Amberbir A, Deribe K. Barriers and facilitators to antiretroviral medication adherence among HIV-infected paediatric patients in Ethiopia: A qualitative study. J Soc Asp HIV/AIDS. 2009;6(4):148–54.
194. Castro M, González I, Pérez J. Factors Related to Antiretroviral Therapy Adherence in Children and Adolescents with HIV / AIDS in Cuba. MEDICC Rev. 2010;17(1):35–40.
195. Kunapareddy CJ, Nyandiko W, Inui T, Ayaya S, Marrero DG. A qualitative assessment of barriers to antiretroviral therapy adherence among adolescents in western Kenya. J HIV AIDS Soc Serv. 2014;13(4):1–16.
196. Arage G, Tessema GA, Kassa H. Adherence to antiretroviral therapy and its associated factors among children at South Wollo Zone Hospitals , Northeast Ethiopia : a cross-sectional study. BMC Public Health. 2014;14(1):1–7.
197. Gultie T, Amlak TG, Sebsibie G. Factors Affecting Adherence to Pediatrics Antiretroviral Therapy in Mekelle Hospital , Tigray Ethiopia. Int J Public Heal Sci. 2015;(2252–8806):1–6.
198. Coetzee B, Kagee A, Bland R. Barriers and facilitators to paediatric adherence to antiretroviral therapy in rural South Africa : a multi-stakeholder perspective. AIDS Care. 2015;27(3):315–21.
199. Wadunde I, Tuhebwe D, Ediau M, Okure G, Mpimbaza A, Wanyenze RK. Factors associated with adherence to antiretroviral therapy

among HIV infected children in Kabale district , Uganda : a cross sectional study. BMC Res Notes. 2018;11:1–6.

200. Polisset J, Ametonou ÆF, Arrive E, Aho ÆA, Perez ÆF. Correlates of Adherence to Antiretroviral Therapy ´ , Togo , West Africa in HIV-Infected Children in Lome. AIDS Behav. 2009;13:23–32.
201. Kourrouski MFC, Lima RAG de. Treatment adherence: the experience of adolescents with HIV/AIDS. Rev Lat Am Enfermagem [Internet]. 2009;17(6):947–52. Available from: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0104-11692009000600004&lng=en&tlng=en
202. le Roux SM, Cotton MF, Golub JE, le Roux DM, Workman L, Zar HJ. Adherence to isoniazid prophylaxis among HIV-infected children: A randomized controlled trial comparing two dosing schedules. BMC Med. 2009;7(67):1–13.
203. Vreeman RC, Nyandiko WM, Ayaya SO, Walumbe EG, Marrero DG, Inui TS. Factors sustaining pediatric adherence to antiretroviral therapy in Western Kenya. Qual Health Res. 2009;19(12):1716–29.
204. Mahloko JM, Madiba S. Disclosing HIV diagnosis to children in Odi district , South Africa : Reasons for disclosure and non-disclosure. Afr J Prm Heal Care Fam Med. 2012;4(1):1–7.
205. Haberer JE, Kiwanuka J, Nansera D, Ragland K, Mellins C, Bangsberg DR. Multiple measures reveal antiretroviral adherence successes and challenges in HIV-infected Ugandan children. PLoS One.

2012;7(5):1–9.

206. Martinez J, Harper G, Carleton RA, Hosek S, Bojan K, Clum G, et al. The Impact of Stigma on Medication Adherence Among HIV-Positive Adolescent and Young Adult Females and the Moderating Effects of Coping and Satisfaction with Health Care. AIDS Patient Care STDS. 2012;26(2):108–15.

207. Rudy BJ, Murphy DA, Harris DR, Muenz L, Ellen J. Prevalence and Interactions of Patient-Related Risks for Nonadherence to Antiretroviral Therapy Among Perinatally Infected Youth in the United States. AIDS Patient Care STDS. 2010;24(2):97–104.

208. Lin D, Seabrook JA, Matsui DM, King SM, Rieder MJ. Palatability , adherence and prescribing patterns of antiretroviral drugs for children with human immunodeficiency virus infection in Canada †. pharmacolepidemiology drug Saf. 2011;20:1246–52.

209. Skovdal M, Campbell C, Madanhire C, Nyamukapa C, Gregson S. Challenges faced by elderly guardians in sustaining the adherence to antiretroviral therapy in HIV-infected children in Zimbabwe. AIDS Care. 2011;23(8):957–64.

210. Nichols SL, Montepiedra G, Farley JJ, Sirois PA, Malee K, Kammerer B, et al. Cognitive, Academic and Behavioral Correlates of Medication Adherence in Children and Adolescents with Perinatally Acquired HIV Infection Sharon. J Dev Behav Pediatr. 2012;33(4):298–308.

211. Bn M, Kabunga E, Masiira B, Lubega R, Kaleebu P, Seeley J. Personal

barriers to antiretroviral therapy adherence : case studies from a rural Uganda prospective clinical cohort. Afr Health Sci. 2013;13(2):311–9.

212. Chimhuya S, Nathoo KJ, Rusakaniko S. Non-adherence to highly active antiretroviral therapy in children attending HIV treatment clinic at Harare Children ' s Hospital , Zimbabwe. Cent Afr J Med. 2013;59:63–70.
213. MacDonell K, Naar-King S, Huszti H, Belzer M. Barriers to Medication Adherence in Behaviorally and Perinatally Infected Youth Living with HIV Karen. AIDS Behav. 2013;17(1):86–93.
214. Ugwu R, Eneh A. Factors influencing adherence to paediatric antiretroviral therapy in Portharcourt, South- South Nigeria. PanAfrican Med J. 2013;(1937–8688):1–8.
215. Barennes H, Tat S, Reinharz D, Vibol U. Perceived stigma by children on antiretroviral treatment in Cambodia. BMC Pediatr. 2014;14:1–9.
216. Eticha T, Berhane L. Caregiver-reported adherence to antiretroviral therapy among HIV infected children in Mekelle ,. Eticha Berhane BMC Pediatr. 2014;14(1):1–8.
217. Mburu G, Hodgson I, Kalibala S, Haamujompa C, Cataldo F, Lowenthal ED, et al. Adolescent HIV disclosure in Zambia : barriers , facilitators and outcomes. J Int AIDS Soc. 2014;17:1–9.
218. Dachew BA, Tesfahunegn TB, Birhanu AM. Adherence to highly active antiretroviral therapy and associated factors among children at the

University of Gondar Hospital and Gondar Poly Clinic, Northwest Ethiopia: A cross-sectional institutional based study. BMC Public Health. 2014;14(1):1–6.

219. Kim S, Mcdonald S, Kim S. Importance of Self-Motivation and Social Support in Medication Adherence in HIV-Infected Adolescents in the United Kingdom and Ireland: A Multicentre HYPNet Study. AIDS Patient Care STDS. 2015;29(6):354–65.
220. Olds PK, Ware NC, Haberer JE. Explaining Antiretroviral Therapy Adherence Success Among HIV-Infected Children in Rural Uganda: A Qualitative Study. AIDS Behav. 2015;19(4):584–93.
221. Nyogea D, Mtenga S, Henning L, Franzeck FC, Glass TR, Letang E, et al. Determinants of antiretroviral adherence among HIV positive children and teenagers in rural Tanzania : a mixed methods study. BMC Infect Dis. 2015;15:1–13.
222. Bermudez LG, Jennings L, Ssewamala FM, Mellins C, Mckay M, Gauer L, et al. Equity in adherence to antiretroviral therapy among economically vulnerable adolescents living with HIV in Uganda. AIDS Care. 2016;28:83–91.
223. Madiba S, Mokgatle M. Perceptions and Experiences about Self-Disclosure of HIV Status among Adolescents with Perinatal Acquired HIV in Poor-Resourced Communities in South Africa. AIDS Res Treat. 2016;2016:1–10.
224. Inzaule SC, Hamers RL, Kityo C, Wit TFR De, Roura M. Long-Term

Antiretroviral Treatment Adherence in HIV-Infected Adolescents and Adults in Uganda : A Qualitative Study. PLoS One. 2016;1–15.

225. Ricci G, Martins E, Luz E, Rodamilans C, Brites C. Adherence to antiretroviral therapy of Brazilian HIV-infected children and their caregivers. Brazilian J Infect Dis. 2016;20(5):429–36.
226. Mehta K, Heylen E, Shet A. Adherence to antiretroviral therapy among children living with HIV in South India. AIDS Behav. 2016;20(5):1076–83.
227. Côté J, Delmas P, de Menezes Succi RC, Galano E, Auger P, Sylvain H, et al. Predictors and Evolution of Antiretroviral Therapy Adherence Among Perinatally HIV-Infected Adolescents in Brazil. J Adolesc Heal. 2016;59(3):305–10.
228. Hawkins A, Evangeli M, Sturgeon K, Le Prevost M, Judd A. Episodic medication adherence in adolescents and young adults with perinatally acquired HIV: A within-participants approach. AIDS Care - Psychol Socio-Medical Asp AIDS/HIV. 2016;28(0):68–75.
229. Kolmodin Macdonell K, Jacques-Tiura AJ, Naar S, Isabella Fernandez M. Predictors of Self-Reported Adherence to Antiretroviral Medication in a Multisite Study of Ethnic and Racial Minority HIV-Positive Youth. J Pediatr Psychol. 2016;41(4):419–28.
230. Xu L, Munir K, Kanabkaew C, Coeur S Le. Factors influencing antiretroviral treatment suboptimal adherence among perinatally HIV- infected adolescents in Thailand. PLoS Med. 2017;1–18.

231. Mafune R V., Lebese RT, Nemathaga LH. Challenges faced by caregivers of children on antiretroviral therapy at Mutale Municipality selected healthcare facilities , Vhembe District , Limpopo Province. Curations. 2017;1–9.
232. Tran CT, Pham TH, Tran KT, Nguyen TKC, Larsson M. Caretakers ' barriers to pediatric antiretroviral therapy adherence in Vietnam – A qualitative and quantitative study. Appl Nurs Res. 2017;35:1–5.
233. Garvie PA, Brummel SS, Allison SM, Malee K, Mellins CA, Wilkins ML, et al. Roles of Medication Responsibility, Executive and Adaptive Functioning in Adherence for Children and Adolescents with Perinatally Acquired HIV. Pediatr Inect Dis. 2017;36(8):751–7.
234. Chhim K, Mburu G, Tuot S, Sopha R, Khol V, Chhoun P, et al. Factors associated with viral non - suppression among adolescents living with HIV in Cambodia : a cross - sectional study. AIDS Res Ther. 2018;1–10.
235. Bulali RE, Kibusi SM, Mpondo BCT. Factors Associated with HIV Status Disclosure and Its Effect on Treatment Adherence and Quality of Life among Children 6 – 17 Years on Antiretroviral Therapy in Southern Highlands Zone , Tanzania : Unmatched Case Control Study. Int J Pediatr. 2018;1–10.
236. Lasmar L, Camargos P, Bousquet J, Goulart E, Sakurai E, Carvalhais M. Factors related to lower adherence rates to inhaled corticosteroids in children and adolescents: A prospective randomized cohort study.

J Trop Pediatr. 2008;55(1):20–5.

237. Orrell-Valente JK, Jarlsberg LG, Hill LG, Cabana MD. At What Age Do Children Start Taking Daily Asthma Medicines on Their Own? Pediatrics. 2008;122(6):e1186–92.

238. Bracken M, Fleming L, Hall P, Van Stiphout N, Bossley C, Biggart E, et al. The importance of nurse-led home visits in the assessment of children with problematic asthma. Arch Dis Child. 2009;94(10):780–4.

239. Dellen QM van, Stronksb K, Bindelsc PJE, Ry FGO, Aalderen WMC van. Adherence to inhaled corticosteroids in children with asthma and their parents. Respir Med. 2008;102:755–63.

240. Mirsadraee R, Gharagozlou M, Movahedi M, Behniafard N, Nasiri R. Evaluation of Factors Contributed in Nonadherence to Medication Therapy in Children Asthma. Iran J Allergy Asthma Immunol. 2012;11(1):23–7.

241. Chan AHY, Stewart AW, Foster JM, Mitchell EA, Jr CAC, Harrison J. Factors associated with medication adherence in school-aged children with asthma. ERJ. 2015;2:1–9.

242. Bin Aref A, Shatila A, Lababidi H. Parental perceptions and beliefs about childhood asthma : a cross-sectional study. Croat Med J. 2011;52:637–43.

243. KOSTER ES, PHILBERT D, VRIES TW, DIJK L VAN, BOUVY ML. " I just forget to take it ": asthma self-management needs and preferences

in adolescents. Asthma. 2015;52(8):831–7.

244. Riekert K a, Borrelli B, Bilderback A, Cynthia S. The Development of a Motivational Interviewing Intervention to Promote Medication Adherence among Inner-City, African- American Adolescents with Asthma Rand,. Patient Educ Couns. 2011;82(1):117–22.

245. Schultz A, Sly PD, Zhang G, Venter A, Devadason SG, Le Souëf PN. Usefulness of parental response to questions about adherence to prescribed inhaled corticosteroids in young children. Arch Dis Child. 2012;97(12):1092–6.

246. Mosnaim G, Li H, Martin M, Richardson D, Powell L. Factors Associated with Levels of Adherence to Inhaled Corticosteroids in Minority Adolescents with Asthma Giselle. Ann Allergy Asthma Immunol. 2015;112(2):116–20.

247. Pappalardo AA, Karavolos K, Martin MA. What Really Happens in the Home: the Medication Environment of Urban, Minority Youth. J Allergy Clin Immunol Pract. 2017;5(3):764–70.

248. Butz A, Morphew T, Lewis-land C, Kub J, Bellin M, Ogborn J, et al. Factors associated with poor controller medication use in children with high asthma emergency department use. Ann Allergy, Asthma Immunol. 2017;118(4):419–26.

249. RK S, RK T, RK G, YV A. Factors Affecting Drug Compliance in Paediatric Asthma. Nepal Paediatr. 2017;37(1):31–5.

250. Van Herzeele C, Alova I, Evans J, Eggert P, Lottmann H, Nørgaard

JP, et al. Poor compliance with primary nocturnal enuresis therapy may contribute to insufficient desmopressin response. J Urol. 2009;182(4):2045–9.

251. Wu YP, Aylward BS, Steele RG. Associations between internalizing symptoms and trajectories of medication adherence among pediatric renal and liver transplant recipients. J Pediatr Psychol. 2010;35(9):1016–27.

252. Fredericks EM, Dore-Stites D, Well A, Magee JC, Freed GL, Shieck V, et al. ASSESSMENT OF TRANSITION READINESS SKILLS AND ADHERENCE IN PEDIATRIC LIVER TRANSPLANT RECIPIENTS. Pediatr Transplant. 2010;14(8):944–53.

253. Javalkar K, Fenton N, Cohen S, Ferris M. Socioecologic Factors as Predictors of Readiness for Self-Management and Transition, Medication Adherence, and Health Care Utilization Among Adolescents and Young Adults With Chronic Kidney Disease. Prev Chronic Dis. 2014;11(1):1–9.

254. Claes A, Decorte A, Levtchenko E, Knops N, Dobbels F. Facilitators and barriers of medication adherence in pediatric liver and kidney transplant recipients : a mixed-methods study. Prog Transplant. 2014;24(4):311–21.

255. Ramay BM, CeroÂn A, Luis Pablo MeÂndez-Alburez RL-M. Factors associated to acceptable treatment adherence among children with chronic kidney disease in Guatemala. PLoS One. 2017;12(10):1–12.

256. Varnell CD, Rich KL, Nichols M, Dahale D, Jens W, Pai ALH, et al. Assessing barriers to adherence in routine clinical care for pediatric kidney transplant patients. Pediatr Transplant. 2017;21(7):1–15.
257. Killian MO. Psychosocial predictors of medication adherence in pediatric heart and lung organ transplantation. Pediatr Transplant. 2017;21(4).
258. Munson MR, Floersch JE. Are Health Beliefs Related to Adherence Among Adolescents with Mood Disorders ? Adm Policy Ment Heal. 2010;37:408–16.
259. Hebert J, Cand AP, Joober R. Adherence to Psychostimulant Medication in Children with Attention-Deficit/Hyperactivity Disorder: The Role of Attitudes. J Can Acad Child Adolesc Psychiatry. 2013;22(4):317–23.
260. Nagae M, Nakane H, Honda S, Hanada H. Factors Affecting Medication Adherence in Children Receiving Outpatient Pharmacotherapy and Parental Adherence. J Child Adolesc Psychoiatric Nurs. 2015;28:109–17.
261. Ramdour S, Duxbury JA, Becket G, Wilson S. A cross-sectional observational study of healthcare professional views of factors affecting teenage adherence with antipsychotic medication. J Psychiatr Ment Health Nurs. 2015;22(7):491–501.
262. Goldstein T, Krantz M, Merranko J, Garcia M. Medication Adherence Among Adolescents with Bipolar Disorder. CHILD Adolesc

PSYCHPHARMACOLOGY. 2016;26(10):864–72.

263. Ahmed R, Borst J, Wei YC, Aslani P. Parents ' Perspectives About Factors Influencing Adherence to Pharmacotherapy for ADHD. Atten Disord. 2017;21(2):91–9.

264. Zehgeer A, Ginsburg GS, Lee P, Birmaher B, Walkup J, Kendall PC, et al. Pharmacotherapy Adherence for Pediatric Anxiety Disorders : Predictors and Relation to Child Outcomes. Child Youth Care Forum. 2018;47(5):633–44.

265. Safavi P, Saberzadeh M, Tehrani AM. Factors Associated with Treatment Adherence in Children with Attention Deficit Hyperactivity Disorder. Indian J Psychol Med. 2019;41(2):138–43.

266. Kitney L, Turner JM, Spady D, Malik B, El-Matary W, Persad R, et al. Predictors of medication adherence in pediatric inflammatory bowel disease patients at the Stollery Children's Hospital. Can J Gastroenterol. 2009;23(12):811–5.

267. Greenley RN, Stephens M, Doughty A, Raboin T, Kugathasan S. Barriers to Adherence Among Adolescents with Inflammatory Bowel Disease. Inflamm Bowel Dis. 2010;16(1):36–41.

268. Hommel KA, Odell S, Sander E, Robert N, Barg FK. Treatment Adherence in Paediatric Inflammatory Bowel Disease: Perceptions from Adolescent Patients and Their Families. Heal Soc Care Community. 2011;19(1):80–8.

269. Modi AC, Morita DA, Glauser TA. One-Month Adherence in Children

With New-Onset Epilepsy: White-Coat Compliance Does Not Occur. Pediatrics. 2008;121(4):e961–6.

270. Nazziwa R, Angelina Kakooza Mwesige CO, Ssenkusu JM, Mworozi E. Adherence to antiepileptic drugs among children attending a tertiary health unit in a low resource setting. PanAfrican Med J. 2014;(8688):1–8.

271. Malik M, Shabbir N, Saeed M, Hospitals AF, Region S. Medication Nonadherence in Children with Epilepsy Attending Outpatient Clinics in Under-Resourced Community. J Pediatr Epilepsy. 2015;4:72–9.

272. Paschal AM, Mitchell QP, Wilroy JD, Hawley SR, Mitchell JB. Parent health literacy and adherence-related outcomes in children with epilepsy. Epilepsy Behav. 2016;56:73–82.

273. Ramsey RR, Zhang N, Modi AC. The Stability and Influence of Barriers to Medication Adherence on Seizure Outcomes and Adherence in Children With Epilepsy Over 2 Years. J Pediatr Psychol. 2017;43(2):122–32.

274. Gutierrez-colina AM, Smith AW, Mara CA, Modi AC. Epilepsy & Behavior Adherence barriers in pediatric epilepsy : From toddlers to young adults. Epilepsy Behav. 2018;80:229–34.

275. Alsous M, Hamdan I, Saleh M, McElnay J, Horne R, Masri A. Predictors of nonadherence in children and adolescents with epilepsy: A multimethod assessment approach. Epilepsy Behav. 2018;85(2018):205–11.

276. Bryson SP. Patient-centred, administration friendly medicines for children - An evaluation of children's preferences and how they impact medication adherence. Int J Pharm. 2014;469(2):257–9.
277. Venables R, Batchelor H, Stirling H, Marriott J. Barriers to administering non-oral formulations in a paediatric population: A semi-structured interview study. Int J Pharm. 2016;497(1–2):12–7.
278. Venables R, Stirling H, Batchelor H, Marriott J. Problems with oral formulations prescribed to children: a focus group study of healthcare professionals. Int J Clin Pharm. 2015;37(6):1057–67.
279. Inoue S, Kodjebacheva G, Scherrer T, Rice G, Grigorian M, Blankenship J, et al. Adherence to hydroxyurea medication by children with sickle cell disease (SCD) using an electronic device : a feasibility study. Int J Hematol. 2016;104(2):200–7.
280. Badawy S., Thompson AA, Liem RI. Technology Access and Smartphone App Preferences for Medication Adherence in Adolescents and Young Adults With Sickle Cell Disease. Pediatr Blood Cancer. 2016;63:848–52.
281. Klitzman PH, Carmody JK, Belkin MH, Janicke DM. Behavioral and Pharmacological Adherence in Pediatric Sickle Cell Disease : Parent – Child Agreement and Family Factors Associated With Adherence. J Pediatr Psychol. 2018;43(1):31–9.
282. Bregnballe V, Schiøtz PO, Boisen KA, Pressler T, Thastum M. Barriers to adherence in adolescents and young adults with cystic fibrosis : a

questionnaire study in young patients and their parents. Patient Prefer Adherence. 2011;5:507–15.

283. Hilliard ME, Eakin MN, Borrelli B, Green A, Riekert KA. Medication Beliefs Mediate Between Depressive Symptoms and Medication Adherence in Cystic Fibrosis Marisa. Heal Psychol. 2015;34(5):496–504.

284. Sawicki GS, Heller KS, Demars N, Robinson WM. Motivating Adherence Among Adolescents With Cystic Fibrosis : Youth and Parent Perspectives. Pediatr Pulmonol. 2015;50:127–36.

285. Saletsky RD, Trief PM, Anderson BJ, Rosenbaum P, Weinstock RS. Parenting Style, Parent-Youth Conflict, and Medication Adherence in Youth with Type 2 Diabetes Participating in an Intensive Lifestyle Change Intervention Ronald. Fam Syst Heal. 2014;32(2):176–85.

286. Katz LL, Anderson BJ, McKay S V., Izquierdo R, Casey TL, Higgins LA, et al. Correlates of medication adherence in the TODAY cohort of youth with type 2 diabetes. Diabetes Care. 2016;39(11):1956–62.

287. Chang S, Eitzman SR, Nahid P, Lourdes M, Finelli U. Factors associated with failure to complete isoniazid therapy for latent tuberculosis infection in children and adolescents. J Infect Public Health. 2014;7(2):145–52.

288. Yusuf KO, Seifu MF, Gelaw BK, Esayas Tadesse Gebremariam MA. Non Adherence and its Contributing Factors to Anti-TB Drug in Children’s at Adama Referral Hospital, Oromia, Ethiopia. Glob J Med

Res. 2015;15(2):1–8.

289. Lopez-varela E, Sequera VG, Garc AL, Augusto OJ, Munguambe K, Sacarlal J, et al. Adherence to Childhood Tuberculosis Treatment in Mozambique. J Trop Pediatr. 2016;63:87–97.

290. Chiang SS, Roche S, Contreras C, Castillo H, Canales P, Jimenez J, et al. Barriers to the treatment of childhood tuberculous infection and tuberculosis disease : a qualitative study. Int J Tuberc Lung Dis. 2017;21(2):154–60.

291. Erica F, Aimee O, Mark A, Lawson EF, Hersh AO, Applebaum MA, et al. Self-management skills in adolescents with chronic rheumatic disease : A cross-sectional survey. Pediatr Rheumatol. 2011;9(1):35.

292. Pelajo CF, Sgarlat CM, Lopez-Benitez JM, Oliveira SKF, Rodrigues MCF, Sztajnbok FR, et al. Adherence to methotrexate in juvenile idiopathic arthritis. Rheumatol Int. 2012;32(2):497–500.

293. Keppeke LDF, Molina J, Bugni V, Teresa M, Sande D, Ramos L, et al. Psychological characteristics of caregivers of pediatric patients with chronic rheumatic disease in relation to treatment adherence. Pediatr Rheumatol. 2018;1–11.

294. Thannhauser JE, Mah JK, Metz LM. Adherence of Adolescents to Multiple Sclerosis Disease-Modifying Therapy. Pediatr Neurol. 2009;41(2):119–23.

295. Lulua S, Juliana L, Shapirob E, Hudsonb K, Waubanta E. Treatment Adherence and Transitioning Youth in Pediatric Multiple Sclerosis.

Mult Scler Relat Disord. 2014;3(6):689–95.

296. Yeh EA, Chiang N, Darshan B, Nejati N, Grover SA, Schwartz CE, et al. Adherence in Youth With Multiple Sclerosis : A Qualitative Assessment of Habit Formation , Barriers , and Facilitators. Qual Health Res. 2018;1–13.

297. Lehrnbecher T, Laws HJ, Boehm A, Dworzak M, Janssen G, Simon A, et al. Compliance with anti-infective preventive measures: A multicentre survey among paediatric oncology patients. Eur J Cancer. 2008;44(13):1861–5.

298. Hullmann S, Brumley L, Schwartz LA. Medical and Psychosocial Associates of Nonadherence in Adolescents With Cancer. pediatr Oncol Nurs. 2015;32(2):103–13.

299. De Pedro S, Murillo M, Salinas I, Granada ML, Martinez M, Puig-Domingo M, et al. Variability in adherence to rhGH treatment: Socioeconomic causes and effect on children's growth. Growth Horm IGF Res. 2016;26:32–5.

300. Mohseni S, Heydari Z, Qorbani M, Radfar M. Adherence to growth hormone therapy in children and its potential barriers. J Pediatr Endocrinol Metab. 2017;31(1):13–20.

301. Al-Kloub MI, Salameh TN, Froelicher ES. Impact of psychosocial status and disease knowledge on deferoxamine adherence among thalassaemia major adolescents. Int J Nurs Pract. 2014;20:265–74.

302. Salazar ML, English TM, Eiland LS. Caregivers' baseline

understanding and expectations of antibiotic use for their children. Clin Pediatr (Phila). 2012;51(7):632–7.

303. Ariceta G, Lara E, Camacho JA, Oppenheimer F, Vara J, Santos F, et al. Cysteamine (Cystagon®) adherence in patients with cystinosis in Spain: Successful in children and a challenge in adolescents and adults. Nephrol Dial Transplant. 2015;30(3):475–80.
304. Leischow SJ, Muramoto ML, Matthews E, Floden LL, Grana RA. Adolescent Smoking Cessation With Bupropion: The Role of Adherence. Nicotine Tob Res. 2016;18(5):1202–5.
305. Tsianou K, Giannakeas N, Tsipouras M, Tzallas AT, Christodoulou D. Accessing Patient Views about Medication in Chronic Conditions using the Beliefs about Medicine Questionnaire (BMQ): A Review Study. J drug Res Dev. 2017;3.1:1–9.
306. Alsous M, Alhalaiqa F, Farha RA, Jalil MA, Mcelnay J, Horne R. Reliability and validity of Arabic translation of Medication Adherence Report Scale (MARS) and Beliefs about Medication Questionnaire (BMQ)– specific for use in children and their parents. PLoS Med. 2017;12(2):1–14.
307. Verhagen AP. Beliefs about Medicine Questionnaire. J Physiother. 2018;64(1):60.
308. Braun V, Clarke V. Thematic Analysis. Am Psychol Assoc. 2012;2:57–71.
309. Vaismoradi M, Jones J, Turunen H, Snelgrove S. Theme development

in qualitative content analysis and thematic analysis. Nurs Educ Pract. 2016;6(5):100–10.

310. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol. 2006;3:77–101.
311. Kottner J, Audige L, Brorson S, Donner A, Gajewski BJ, Hróbjartsson A, et al. Guidelines for Reporting Reliability and Agreement Studies (GRRAS) were proposed. Int J Nurs Stud. 2011;48(6):661–71.
312. Sim J, Wright CC. The Kappa Statistic in Reliability Studies: Use, Interpretation, and Sample Size Requirements. Phys Ther. 2005;85(3):257–68.
313. Rolstad S, Adler J, Rydén A. Response burden and questionnaire length: Is shorter better? A review and meta-analysis. Value Heal. 2011;14(8):1101–8.
314. Teeple E, Collins J, Shrestha S, Dennerlein J et al. Factors associated with false-positive self-reported adherence to antihypertensive drugs. Physiol Behav. 2018;176(1):139–48.
315. Alamri M. Higher Education in Saudi Arabia. J High Educ Theory Pract. 2011;11(4):88–91.
316. Arabia TE of the K of S in W. About Saudi Arabia Education [Internet]. 2020. Available from: http://www.saudiembassy.net/education
317. Batchelor HK, Marriott JF. Formulations for children: Problems and solutions. Br J Clin Pharmacol. 2015;79(3):405–18.

318. Bush PJ, Ozias JM, Walson PD, Ward RM. Ten guiding principles for teaching children and adolescents about medicines. Clin Ther. 1999;21(7):1280–4.
319. Foundation DHN. Annual Report & Accounts for the year ended 31st March 2011 [Internet]. 2011. Available from: http://www.derbyhospitals.nhs.uk/EasysiteWeb/getresource.axd?AssetID=%0A8792&type=Full&servicetype=Attachment
320. ONS. UK labour market: December 2017. Ons [Internet]. 2017;(September):1–50. Available from: https://www.ons.gov.uk/employmentandlabourmarket/peopleinwork/employmentandemployeetypes/bulletins/uklabourmarket/december2017#actual-hours-worked
321. Liu F, Ranmal S, Batchelor HK, Orlu-Gul M, Ernest TB, Thomas IW, et al. Patient-centred pharmaceutical design to improve acceptability of medicines: Similarities and differences in paediatric and geriatric populations. Drugs. 2014;74(16):1871–89.
322. Thong MY, Manrique YJ, Steadman KJ. Drug loss while crushing tablets: Comparison of 24 tablet crushing devices. PLoS One. 2018;13(3):5–7.
323. Stawarz K, Rodríguez MD, Cox AL, Blandford A. Understanding the use of contextual cues: design implications for medication adherence technologies that support remembering. Digit Heal. 2016;2:205520761667870.

324. Spomer N, Klingmann V, Stoltenberg I, Lerch C, Meissner T, Breitkreutz J. Acceptance of uncoated mini-tablets in young children: Results from a prospective exploratory cross-over study. Arch Dis Child. 2012;97(3):283–6.

Appendices

9.1 Ethical approval in Saudi Arabia

Kingdom of Saudi Arabia
Ministry of Health
King Fahad Medical City
Research Center

وزارة الصحة
مدينة الملك فهد الطبية
King Fahad Medical City

المملكة العربية السعودية
وزارة الصحة
مدينة الملك فهد الطبية
مركز الأبحاث

Ref.: **11007/321/40**
Date: 24/07/2019
21/11/1440

Dr. Meshal AlRayys

Dear **Dr. AlRayys**

Greetings!

The Institutional Review Board (IRB) has reviewed and approved the submission of **Dr. Mohammed AlDossari** relating to the research protocol titled "**Barries and Facilitators of Medicines Adherence in Childern"** IRB Log number **19-399E.** The IRB approval is from the research ethics point of view only. The authorization to undertake research in KFMC lies in your hands. The research proposal is being sent for your review and decision on the feasibility of carrying out the research in your section and your readiness to provide the necessary assistance. You can inform the researcher of your decision with a copy to us.

Best regards,

P.P.

DR. DAYEL ALSHAHRANI
Director of Satellite Research Administration
Executive Administration of Research Center
daalshahrani@kfmc.med.sa

APPROVAL BY THE HEAD OF DEPARTMENT WHERE THE RESEARCH WILL BE CARRIED OUT

☑ APPROVED
☐ NOT APPROVED

Name meshal Alrayys
Signature
Date 24-7-2019

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9.2 Participant information sheets and consent forms

University of Nottingham
UK | CHINA | MALAYSIA

Barriers and facilitators of medicines adherence in children
Parent / Legal Guardian Participant Information Sheet
(Final version 2.0 Date: 25/07/2019)

IRAS Project ID: 247581

Title of Study: Barriers and facilitators of medication adherence in children

Name of Chief Investigator: Dr Sharon Conroy
Local Researcher(s): Mohammed Aldosari

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you. One of our team will go through the information sheet with you and answer any questions you have. Talk to others about the study if you wish. Ask us if there is anything that is not clear.

What is the purpose of the study?

People have different experiences of trying to take their medicines as prescribed by the doctor. We understand that sometimes things can get in the way of following your doctor's instructions about taking medicines. We are hoping that the answers given by people like you in this questionnaire will help us to understand more about any difficulties that children and their families may have with taking medicines and also tell us what might help make it easier.

Why have I been invited?

You are being invited to take part because your child is prescribed medicines and we would like to hear your thoughts about this. We are hoping to get about 60 participants including children and parents like you to take part.

Do I have to take part?

It is up to you to decide whether or not to take part. If you don't wish to take part your and your child's medical care will not be affected in any way. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This would not affect your or your child's medical care or legal rights.

What will happen to me if I take part?

Your child; you on their behalf if they are too young to read and write down their answers; or you yourself if your child is too young to take part will be asked to complete two short questionnaires. You can do this in the hospital if possible or at home if you would prefer (we will give you an envelope to post it back to us if you choose to do this). One questionnaire is about your/your child's thoughts on medicines taking and one is about what makes it easier or harder for your child to take their medicines as prescribed. The questionnaires take about 10-20 minutes to complete depending on how much you want to tell us.

Expenses and payments

Participants will not be paid to participate in the study.

What are the possible disadvantages and risks of taking part?

The only disadvantages of this study are the inconvenience of answering our questions about your child's medicines.

What are the possible benefits of taking part?

We cannot promise the study will help you and your family but the information we get from this study may help in future to develop ways to help children with their medicines taking in future.

What happens when the research study stops?

Your and your child's care will continue as normal.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. The researchers' contact details are given at the end of this information sheet. If you remain unhappy and wish to complain formally, you can do this by contacting the Patient Advice and Liaison Service (PALS) at the Royal Derby Hospital (telephone: 01332 785156 or email: dhft.contactpals@nhs.net).

It is very unlikely that anything will go wrong as a result of taking part in this study as your and your child's treatment will not be affected in any way. If something does go wrong however and you or your child are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against the University of Nottingham but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

Will my taking part in the study be kept confidential?

We will follow ethical and legal practice and all information about you will be handled in confidence.

If you join the study, we will use information collected from you during the course of the research. This information (consent form and questionnaires) will be kept strictly confidential; stored in a secure and locked office; and the questionnaire answers on a password protected database in the University of Nottingham Medical School at the Royal Derby Hospital. Under UK Data Protection laws the University is the Data Controller (legally responsible for the data security) and the Chief Investigator of this study (named above) is the Data Custodian (manages access to the data). This means we are responsible for looking after your information and using it properly. Your rights to access, change or move your information are limited as we need to manage your information in specific ways to comply with certain laws and for the research to be reliable and accurate. To safeguard your rights we will use the minimum personally – identifiable information possible.

You can find out more about how we use your information and to read our privacy notice at:

https://www.nottingham.ac.uk/utilities/privacy.aspx.

The data collected for the study will be looked at and stored by authorised persons from the University of Nottingham who are organising the research. They may also be looked at by authorised people from regulatory organisations to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and we will do our best to meet this duty.

Where possible information about you which leaves the hospital will have your name and address removed and a unique code will be used so that you cannot be recognised from it, however we need to ensure that we can recognise your child to link the research data with their medical records so in these instances we will need to know their name and date of birth. We will also need this information if we need to follow up their medical records as part of the research, where we may need to ask the Government services that hold medical information about you (such as your child's GP surgery) to provide this information to us. By signing the consent form you agree to the above.

Your contact information will be destroyed securely by the University of Nottingham when we have the information we need from your GP about your medicines. Until then this information will be kept separately from the research data collected and only those who need to will have access to it. All other data (research data) will be kept securely for 7 years. After this time your data will be disposed of securely. During this time all precautions will be taken by all those involved to maintain your confidentiality, only members of the research team given permission by the data custodian will have access to your personal data.

In accordance with the University of Nottingham's, the Government's and our funders' policies we may share our research data with researchers in other Universities and organisations, including those

in other countries, for research in health and social care. Sharing research data is important to allow peer scrutiny, re-use (and therefore avoiding duplication of research) and to understand the bigger picture in particular areas of research. Data sharing in this way is usually anonymised (so that you could not be identified) but if we need to share identifiable information we will seek your consent for this and ensure it is secure. You will be made aware then if the data is to be shared with countries whose data protection laws differ to those of the UK and how we will protect your confidentiality.

Although what you say to us is confidential, should you disclose anything to us which we feel puts you or anyone else at any risk, we may feel it necessary to report this to the appropriate persons.

What will happen if I don't want to carry on with the study?

Your participation is voluntary and you are free to withdraw at any time, without giving any reason, and without your legal rights being affected. If you withdraw we will no longer collect any information about you or from you. However, if you withdraw then the information collected so far cannot be erased as we are not allowed to tamper with study records and this information may have already been used in some analyses and may still be used in the final study analyses.

Involvement of the General Practitioner/Family doctor (GP)

We will not tell your GP about your participation in this study.

What will happen to the results of the research study?

At the end of this study, the results of the research will be made available in reports and academic papers read by children's doctors, nurses and pharmacists. A report of the study will be written up as part of the researcher's PhD studies. Direct quotes from you/your child may be used but these will be anonymous.

Who is organising and funding the research?

This study is organised by the University of Nottingham as part of Mr. Mohammed Al dosari PhD studies.

Who has reviewed the study?

All research in healthcare is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the London-Stanmore Research Ethics Committee.

Further information and contact details

Chief investigator: Dr Sharon Conroy, Associate Professor,
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University of Nottingham
UK | CHINA | MALAYSIA

IRAS Project ID: 247581

Title of Study: Barriers and facilitators of medicines adherence in children (Patient aged 2-5 years Participant Information Sheet)

Name of Chief Investigator: Dr Sharon Conroy
Local Researcher(s): Mohammed Al dosari

How nice are your medicines?

Children sometimes have to take medicines to make them better if they are poorly.

If you are happy to talk to us we would like to ask you how your medicine tastes and do you always take it.

We would like you with your parent to help us. We would like to find out what you think about your medicines.

If you don't want to take part or at any time you don't want to do this anymore, just tell one of us. No one will be cross with you and the way the hospital looks after you won't change.

University of Nottingham
UK | CHINA | MALAYSIA

IRAS Project ID: 247581
Title of Study: Barriers and facilitators of medicines adherence in children

Name of Chief Investigator: Dr Sharon Conroy
Local Researcher(s): Mohammed Al dosari

How nice is your medicine?

Sometimes children need to take medicines to make them better. We want to know what it's like to take some of these medicines.

We would like you to help us. We would like to find out what you think about your medicines. If you agree we will ask you a few questions about them such as how it tastes and do you sometimes forget to take it.

You don't have to talk to us if you don't want to. If you say no your doctor will look after you in the same way as other children.

We cannot promise our project will help you now but it might help make things better for you or other children in the future.

If you don't want to take part that's fine or if you decide to take part you can change your mind at any time. No one will be cross with you and your care won't be affected at all.

Thanks for reading this!

Remember to ask us if you have any questions!

Barriers and facilitators of medicines adherence in children
Young Person 11-15 years Participant Information Sheet
(Final version 2.0 Date: 25/07/2019)

IRAS Project ID: 247581

Title of Study: Barriers and facilitators of medicines adherence in children

Name of Chief Investigator: Dr Sharon Conroy
Local Researcher(s): Mohammed Al dosari

We would like to invite you to take part in our project. Before you decide about joining in, we'd like to tell you why we're doing it and what it will involve for you. This leaflet tells you most things that you need to know but please talk to your family, friends, doctor, nurse or the researcher if you want to find out more.

What is the purpose of the study?

People have different experiences of trying to take their medicines as prescribed by the doctor. We understand that sometimes things can get in the way of following your doctor's instructions about taking medicines. We are hoping that the answers given by people like you in this project will help us to understand more about any difficulties that children and their families may have with taking medicines and also tell us what might help make it easier.

Why have I been invited?

You are being invited to take part because you are taking some medicine and we would like to hear your thoughts about this. We are hoping to get about 60 people like you to take part.

Do I have to take part?

No. It is up to you. We will ask you and your parent's agreement and your parents will sign a form if you are all happy to take part. We will give you a copy of this information sheet and a signed form to keep. If you don't want to take part that's fine and if you do take part you are free to change your mind at any time without telling us why. If you decide not to take part or if you do change your mind, this will not affect any of the care that you will be given.

What will happen to me if I take part?

You and your parent will be asked to complete two short questionnaires while in the hospital if possible or at home if you would prefer (we will give you an envelope to post it back to us if you choose to do this). One questionnaire is about your thoughts on taking your medicines and one is

about what makes it easier or harder for you to take your medicines. The questionnaires will take about 10-20 minutes to complete depending on how much you want to tell us.

Expenses and payments

Sorry but we cannot pay you to take part in the study.

What are the possible disadvantages and risks of taking part?

Just the few minutes it takes for you to answer our questions about your medicine.

What are the possible benefits of taking part?

We cannot promise the study will help you but the information we get from this study may help in future to treat children better.

What happens when the research study stops?

Your care will continue as normal.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. Their contact details are at the end of this information sheet. If you remain unhappy and wish to complain, you can do this by contacting the Patient Advice and Liaison Service (PALS) at the Royal Derby Hospital (telephone: 01332 785156 or email: dhft.contactpals@nhs.net).

Will my taking part in the study be kept secret?

If you join the study, we will look at your GP prescriptions and keep the forms that you fill in for us. Only the form that your parents sign to agree to the study will have your name or address on it, everything else will just have a special code. The form with your name and address will be kept separate to everything else and everything will be kept under lock and key in our University offices at the Royal Derby Hospital and your questionnaire answers on a password protected University computer.

We will only keep your personal information (name, address etc) for three months in case we have any questions to ask you or your parents. The questionnaires will be kept safely for 7 years.

What will happen if I don't want to carry on with the study?

You can stop taking part at any time, without giving any reasons. It won't affect anything.

What will happen to the results of the research study?

At the end of this study, we will share the results in reports and papers read by children's doctors, nurses and pharmacists and the researcher will write about it in his University project.

Who is organising and funding the research?

This study is organised by the University of Nottingham as part of Mr. Mohammed Al dosari PhD studies.

Who has reviewed the study?

A group of people, called an Ethics Committee have looked at the project to make sure that everything is ok with it.

Further information and contact details:

Chief investigator: Dr Sharon Conroy, Associate Professor,
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Uttoxeter Road, Derby DE22 3DT
Phone: 01332 724692
Email Sharon.Conroy@nottingham.ac.uk

Co-investigators: Dr Ana Oliveira, Assistant Professor,
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Barriers and facilitators of medicines adherence in children
Young Person 16-18 Participant Information Sheet
(Final version 2.0 Date: 25/07/2019)

IRAS Project ID: 247581

Title of Study: Barriers and facilitators of medicines adherence in children

Name of Chief Investigator: Dr Sharon Conroy
Local Researcher(s): Mohammed Al dosari

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you. One of our team will go through the information sheet with you and answer any questions you have. Talk to others about the study if you wish. Ask us if there is anything that is not clear.

What is the purpose of the study?

People have different experiences of trying to take their medicines as prescribed by the doctor. We understand that sometimes things can get in the way of following your doctor's instructions about taking medicines. We are hoping that the answers given by people like you in this questionnaire will help us to understand more about any difficulties that children and their families may have with taking medicines also tell us what might help make it easier.

Why have I been invited?

You are being invited to take part because you are taking medicines and we would like to hear your thoughts about this. We are hoping to get 60 people like you to take part.

Do I have to take part?

It is up to you to decide whether or not to take part. If you don't want to take part that's fine. If you decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. Not taking part at all or changing your mind after starting will not affect your medical care and legal rights.

What will happen to me if I take part?

You will be asked to complete two short questionnaires while in the hospital if possible or at home if you would prefer (we will give you an envelope to post it back to us if you choose to do this). One questionnaire is about your thoughts on medicines taking and one is about what makes it easier or

harder for you to take your medicines as prescribed. The questionnaires take about 10-20 minutes to complete depending on how much you want to tell us.

Expenses and payments

It is not possible to pay anyone to take part in the study.

What are the possible disadvantages and risks of taking part?

The only disadvantages of this study are the slight inconvenience of answering our questions about your medicine.

What are the possible benefits of taking part?

We cannot promise the study will help you but the information we get from this study may help in future to improve medicines adherence in children.

What happens when the research study stops?

Your care will continue as normal.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. The researchers' contact details are given at the end of this information sheet. If you remain unhappy and wish to complain formally, you can do this by contacting the Patient Advice and Liaison Service (PALS) at the Royal Derby Hospital (telephone: 01332 785156 or email: dhft.contactpals@nhs.net).

It is very unlikely that anything will go wrong as a result of taking part in this study as your treatment will not be affected in any way. If something does go wrong however and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against the University of Nottingham but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

Will my taking part in the study be kept confidential?

We will follow ethical and legal practice and all information about you will be handled in confidence.

If you join the study, we will use information collected from you during the course of the research. This information (questionnaires and consent form) will be kept **strictly confidential**, stored in a secure and locked office, and your questionnaire answers on a password protected database at the University of Nottingham Medical School at the Royal Derby Hospital. Under UK Data Protection laws the University is the Data Controller (legally responsible for the data security) and the Chief Investigator of this study (named above) is the Data Custodian (manages access to the data). This means we are responsible for looking after your information and using it properly. Your rights to

access, change or move your information are limited as we need to manage your information in specific ways to comply with certain laws and for the research to be reliable and accurate. To safeguard your rights we will use the minimum personally – identifiable information possible.

You can find out more about how we use your information and to read our privacy notice at:

https://www.nottingham.ac.uk/utilities/privacy.aspx.

The data collected for the study will be looked at and stored by authorised persons from the University of Nottingham who are organising the research. They may also be looked at by authorised people from regulatory organisations to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and we will do our best to meet this duty.

Where possible information about you which leaves the hospital will have your name and address removed and a unique code will be used so that you cannot be recognised from it, however we need to ensure that we can recognise you to link the research data with your medical records so in these instances we will need to know your name and date of birth. We will also need this information if we need to follow up your medical records as part of the research, where we may need to ask the Government services that hold medical information about you (such as your GP surgery) to provide this information to us. By signing the consent form you agree to the above.

Your contact information will be destroyed securely by the University of Nottingham when we have the information we need from your GP about your medicines. Until then this information will be kept separately from the research data collected and only those who need to will have access to it. All other data (research data) will be kept securely for 7 years. After this time your data will be disposed of securely. During this time all precautions will be taken by all those involved to maintain your confidentiality, only members of the research team given permission by the data custodian will have access to your personal data.

In accordance with the University of Nottingham's, the Government's and our funders' policies we may share our research data with researchers in other Universities and organisations, including those in other countries, for research in health and social care. Sharing research data is important to allow peer scrutiny, re-use (and therefore avoiding duplication of research) and to understand the bigger picture in particular areas of research. Data sharing in this way is usually anonymised (so that you could not be identified) but if we need to share identifiable information we will seek your consent for this and ensure it is secure. You will be made aware then if the data is to be shared with countries whose data protection laws differ to those of the UK and how we will protect your confidentiality.

Although what you say to us is confidential, should you disclose anything to us which we feel puts you or anyone else at any risk, we may feel it necessary to report this to the appropriate persons.

What will happen if I don't want to carry on with the study?

Your participation is voluntary and you are free to withdraw at any time, without giving any reason, and without your medical care and legal rights being affected. If you withdraw we will no longer collect any information about you or from you. However, if you withdraw then the information collected so far cannot be erased as we are not allowed to tamper with study records and this information may have already been used in some analyses and may still be used in the final study analyses.

What will happen to the results of the research study?

At the end of this study, the results of the research will be made available in reports and academic papers. A report of the study will be written up as part of the researcher's PhD studies. Direct quotes from you may be used but these will be anonymous.

Who is organising and funding the research?

This study is organised and funded by the University of Nottingham as part of Mr. Mohammed Al dosari PhD studies. Mohammed Aldosari is a PhD student sponsored by the Saudi Arabia Cultural Bureau.

Who has reviewed the study?

All research in healthcare is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the London-Stanmore Research Ethics Committee.

Further information and contact details

Chief investigator: Dr Sharon Conroy, Associate Professor,
University of Nottingham, Royal Derby Hospital Centre
Uttoxeter Road, Derby DE22 3DT
Phone: 01332 724692
Email Sharon.Conroy@nottingham.ac.uk

Co-investigators: Dr Ana Oliveira, Assistant Professor,
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Phone: 01332 724621
E-mail: Ana.Oliveira@nottingham.ac.uk

Mr. Mohammed Al Dosari, Postgraduate student
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Children 16 years and over Consent Form
(Final version 1.0 Date: 24/06/2019)

Title of Study: Barriers and facilitators of medicines adherence in children

IRAS Project ID: 247581
Name of Researcher: Mohammed Al dosari

Name of Participant: **Please initial box**

1. I confirm that I have read and understand the information sheet version number 1.0 dated 24.6.19 for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected. I understand that should I withdraw then the information collected so far cannot be erased and that this information may still be used in the project analysis. ☐

3. I understand that relevant sections of my medical notes and data collected in the study may be looked at by authorised individuals from the University of Nottingham, the research group and regulatory authorities where it is relevant to my taking part in this study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential. ☐

4. I understand that anonymous direct quotes from the questionnaires may be used in the study reports. ☐

5. I agree to take part in the above study. ☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

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CONSENT FORM FOR PARTICIPATING PARENTS
(Final version 1.0 Date: 24/06/2019)

Title of Study: Barriers and facilitators of medicines adherence in children

IRAS Project ID: 247581

Name of Researcher: Mohammed Al dosari

Name of Parent:

Name of Child:

Please initial box

1. I confirm that I have read and understand the information sheet version number 1.0 dated 24/06/2019 for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my or my child's medical care or legal rights being affected. I understand that should I withdraw then the information collected so far cannot be erased and that this information may still be used in the project analysis. ☐

3. I understand that relevant sections of my child's medical notes and data collected in the study may be looked at by authorised individuals from the University of Nottingham, the research group and regulatory authorities where it is relevant to our taking part in this study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from my child's participation in this study. I understand that my and my child's personal details will be kept confidential. ☐

4. I understand that anonymous direct quotes from the questionnaires may be used in the study reports. ☐

5. I agree to take part in the above study. ☐

Name of Parent	Date	Signature
Name of Person taking consent	Date	Signature

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CONSENT FORM FOR PARENTS
(Final version 1.0 Date: 24/06/2019)

Title of Study: Barriers and facilitators of medicines adherence in children

IRAS Project ID: 247581

Name of Researcher: Mohammed Al dosari

Name of Parent:

Name of Child:

Please initial box

1. I confirm that I have read and understand the information sheet version number 1.0 dated 24/06/2019 for the above study and have had the opportunity to ask questions. ☐
2. I understand that my child's participation is voluntary and that they are free to withdraw at any time, without giving any reason, and without their medical care or legal rights being affected. I understand that should they withdraw then the information collected so far cannot be erased and that this information may still be used in the project analysis. ☐
3. I understand that relevant sections of my child's medical notes and data collected in the study may be looked at by authorised individuals from the University of Nottingham, the research group and regulatory authorities where it is relevant to our taking part in this study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from my child's participation in this study. I understand that my child's personal details will be kept confidential. ☐
4. I understand that anonymous direct quotes from the questionnaires may be used in the study reports. ☐
5. I agree for my child (named above) to take part in the above study. ☐

Name of Parent	Date	Signature

Name of Person taking consent	Date	Signature

(OPTIONAL) Section for children to give assent

I agree to take part in this study

Name of Child (for assent)	Date	Signature

9.3 BMQ questionnaire Arabic and English forms

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وجهات النظر حول استطلاع رأي عن الأدوية (إصدار هورني وينمان وهانكينس 1999).

أولاً وجهة نظرك حول الأدوية الموصوفة لك.

- **أود أن أسألك عن وجهة نظرك الشخصية حول الأدوية الموصوفة لك.**
- **هذه عبارة أدلى بها أشخاص أخرون حول أدويتهم.**
- **يرجى الإشارة إلى مدى موافقتك أو عدم موافقتك عليها بوضع علامة في المربع المناسب.**
- **لا توجد إجابات صحيحة أو خاطئة، فنحن مهتمون بآرائك الشخصية فقط.**
- **يرجى فقط وضع علامة في مربع واحد لكل سؤال.**

1- تعتمد صحتي في الوقت الحالي على الأدوية الخاصة بي

موافق بشدة	موافق	غير متأكد	غير موافق	غير موافق بشدة
☐	☐	☐	☐	☐

2- الاضطرار إلى تناول الأدوية يقلقني.

موافق بشدة	موافق	غير متأكد	غير موافق	غير موافق بشدة
☐	☐	☐	☐	☐

3- حياتي ستكون مستحيلة بدون دوائي.

موافق بشدة	موافق	غير متأكد	غير موافق	غير موافق بشدة
☐	☐	☐	☐	☐

4- بدون دوائي, سأكون مريضاً جداً

موافق بشدة	موافق	غير متأكد	غير موافق	غير موافق بشدة

5- أشعر بالقلق أحيانًا بشأن الآثار الطويلة الأجل لأدويتي.

موافق بشدة	موافق	غير متأكد	غير موافق	غير موافق بشدة

6- دوائي غامض بالنسبة لي.

موافق بشدة	موافق	غير متأكد	غير موافق	غير موافق بشدة

7- ستعتمد صحتي في المستقبل على دوائي.

موافق بشدة	موافق	غير متأكد	غير موافق	غير موافق بشدة

8- دوائي يقلق حياتي

موافق بشدة	موافق	غير متأكد	غير موافق	غير موافق بشدة

9- أشعر بالقلق أحيانًا من اعتمادي على دوائي بشكل كبير جداً.

موافق بشدة	موافق	غير متأكد	غير موافق	غير موافق بشدة

10- الدواء يحميني من أن أصبح أسوأ.

غير موافق بشدة	غير موافق	غير متأكد	موافق	موافق بشدة
☐	☐	☐	☐	☐

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Beliefs about medicines questionnaire (BMQ) Horne, Weinman, Hankins, (1999)

BMQ-Specific

Code

Your views about medicines prescribed to you.

- I would like to ask you about your personal views about medicines prescribed for you.
- These are statements other people have made about their medication.
- Please indicate the extent to which you agree or disagree with them by placing a cross in the appropriate box.
- There are no right or wrong answers. I am interested in your personal views.
- Please only cross one box per question.

1) My health at present depends on my medicines

Strongly agree	agree	uncertain	disagree	strongly disagree
☐	☐	☐	☐	☐

2) Having to take medication worries me

Strongly agree	agree	uncertain	disagree	strongly disagree
☐	☐	☐	☐	☐

3) My life would be impossible without my medication

Strongly agree	agree	uncertain	disagree	strongly disagree
☐	☐	☐	☐	☐

4) Without my medication I would be very ill

Strongly agree ☐ agree ☐ uncertain ☐ disagree ☐ strongly disagree ☐

5) I sometimes worry about the long-term effects of my medication

Strongly agree ☐ agree ☐ uncertain ☐ disagree ☐ strongly disagree ☐

6) My medication is mystery to me

Strongly agree ☐ agree ☐ uncertain ☐ disagree ☐ strongly disagree ☐

7) My health in the future will depend on my medication

Strongly agree ☐ agree ☐ uncertain ☐ disagree ☐ strongly disagree ☐

8) My medication disrupts my life

Strongly agree ☐ agree ☐ uncertain ☐ disagree ☐ strongly disagree ☐

9) I sometimes worry about becoming too dependent on my medication

Strongly agree	agree	uncertain	disagree	strongly disagree
☐	☐	☐	☐	☐

10) My medication protects me from becoming worse.

Strongly agree	agree	uncertain	disagree	strongly disagree
☐	☐	☐	☐	☐

9.4 Designed questionnaire Arabic and English forms

لكل عبارة، يرجى وضع علامة في مربع واحد لتعكس مشاعرك حول الأشياء التي قد تجعل تناول الأدوية أكثر صعوبة.

الرقم	العبارة	موافق	غير موافق	لست متأكدا
1	الدواء الخاص بي نسيت أن أتناول			
2	طعم دوائي سيئاً			
3	أنني قلق بشأن الآثار الجانبية المحتملة			
4	ليس لدي ما يكفي من الدعم الأسري			
5	لا أعرف ما يكفي من المعلومات عن مرضي وعلاجه			
6	الدواء يجعلني أشعر بالمرض			
7	لم أحصل على معلومات كافية حول المرض والعلاج			
8	يجب أن أتناول الكثير من الدواء أو العديد من الجرعات يومياً			
9	أنا قلق بشأن ما قد يفكر به الآخرون عني إذا علموا أنني أتناول الأدوية.			
10	لا أحتاج إلى تناول الأدوية الخاصة بي لأن الأعراض قد زالت.			

لكل عبارة ، يرجى وضع علامة في مربع واحد لتعكس مشاعرك حول الأشياء التي قد تجعل تناول الأدوية أكثر سهولة.

1	أستخدم تذكير لإخباري بموعد دوائي أو روتين عن أدويتي (مثل تناول الأدوية قبل المدرسة).			
2	تلقيت معلومات كافية عن مرضي وأهمية العلاج.			
3	لدي دعم عائلي جيد.			
4	لدي معرفة جيدة بمرضي وعلاجي.			
5	وصف لي الطبيب الأدوية التي يمكن أن تؤخذ مرة أو مرتين في اليوم.			
6	جدول أدويتي بسيط للغاية.			
7	طبيبي يعطيني الأدوية ذات المذاق الطيب			

يرجى الإجابة على الأسئلة التالية:

1- يرجى التوضيح على الفراغات أدناه عدد الجرعات الموصوفة من الأدوية التي تمكنت من تناولها في الأسابيع الأربعة الماضية. إذا كنت تتناول عدة أدوية ، فيرجى ذكر كل دواء على خط منفصل.

اسم الدواء رقم (1):..... 0% (لا شيء)----------100%

اسم الدواء رقم (2):..... 0% (لا شيء)----------100%

اسم الدواء رقم (3):..... 0% (لا شيء)----------100%

اسم الدواء رقم (4):..... 0% (لا شيء)----------100%

ثانياً :

العبارة	نعم	لا
2-هل نسيت أن تأخذ الأدوية الخاصة بك؟ أ-إذا كانت الإجابة بنعم، فما هي الأشياء التي تجعل ذلك يحدث من وجهة نظرك؟ ..... ب-هل يمكنك التفكير في أي شيء يساعدك على التذكر؟		
3-هل أنت قلق بشأن الآثار الجانبية لأي من الأدوية الخاصة بك؟		
هل هذا يمنعك من تناول الأدوية؟ إذا كانت الإجابة بنعم، فيرجى إخبارنا بالأدوية وأعطينا مثالاً على الآثار الجانبية التي تقلقك.		
4-هل واجهت آثار جانبية بشأن أي من أدويتك؟		
هل أدى هذا إلى تأجيل تناول الأدوية؟		
إذا كانت الإجابة بنعم، فيرجى كتابة اسم الأدوية التي تسبب آثاراً جانبية وما هي الآثار الجانبية التي واجهتها.		
5-هل تعاير وتتناول أدويتك بنفسك؟ إذا لم يكن كذلك، فمن يساعدك على تناول الأدوية؟		
6-هل هناك شيء يجعل من الصعب عليك تناول ادويتك؟		
7-هل شعرت يوماً بالقلق من تناول أدويتك عندما يكون الأشخاص الآخرون حولك؟		

هل هذا جعلك تتوقف عن تناول الأدوية؟		
8-هل لديك أي مخاوف بشأن عدد جرعات الدواء التي تحتاج إلى تناولها أو وقت الجرعات؟		
هل هذا يمنعك من أخذ الأدوية.		
9-هل لديك أي مخاوف بشأن حجم الأقراص التي تحتاج إلى تناولها أو طعم الأدوية؟		
هل هذا يمنعك من أخذ الدواء ؟		
إذا كانت الإجابة بنعم، يرجى إعطائنا مثالاً		
10-هل جربت أو هل تستخدم أي طرق لمساعدتك في تناول الأدوية؟ إذا كانت الإجابة بنعم ، فيرجى وصفها ومدى فعاليتها؟		

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What makes taking medicines easier or harder?

Date		Sex of child M/F			
Child's date of birth		Child's illness		Parent's age when left full-time education	
Medicines prescribed					

There are no right/wrong answers to our questions, we're just interested in your honest views.

For each statement please tick the box best reflecting your feelings about things that may make taking medicines more difficult.

		Agree	Disagree	Uncertain
1	I forget to take my medicine.			
2	My medicine tastes bad.			
3	I worry about possible side effects.			
4	I don't have enough family support.			
5	I don't know enough about the illness and treatment.			
6	The medicine makes me feel sick.			
7	We weren't given enough information about the illness and treatment.			
8	I have to take lots of medicines or many doses per day.			
9	I worry about what other people would think of me if they knew I took medicines.			

10	I don't need to take my medicines as my symptoms have gone.			

For each statement below please tick the box which best reflects your feelings about what may make taking your medicines easier.

		Agree	**Disagree**	**Uncertain**
1	I use a medicine reminder or routine about my medicines (e.g. taking medicines before school).			
2	We were given enough information about my illness and the importance of treatment.			
3	I have good family support.			
4	I have good knowledge about my disease and treatment.			
5	The doctor has prescribed medicines which can be taken once or twice a day.			
6	My medicines schedule is quite simple.			
7	My doctor gives me medicines which taste ok.			

Please answer the following questions:

1. Please plot on the line below how many of the prescribed doses of medicines you think you managed to take in the last four weeks. If you take several medicines please plot each medicine on a separate line.

(Name of drug1……..……) 0% (none) _____100% (all)
(Name of drug 2……...…….) 0% (none) _____100% (all)
(Name of drug 3……...…….) 0% (none) _____100% (all)

(Name of drug 4……...…….) 0% (none) _____100% (all)

2. Do you ever forget to take your medicines? **Yes/ No**

a. If so can you think of anything that makes this happen?

b. Can you think of anything that could help you to remember?

3. Do you **worry** about side effects of any of your medicines? **Yes**/ **No**

   Does this ever put you off taking your medicines? **Yes**/ **No**

   If yes please tell us which medicines and give us an example of side effects that worry you.

4. Have you **experienced** side effects of any medicines? **Yes**/ **No**

   Did this ever put you off taking the medicines? **Yes**/ **No**

   If yes please write the name of the medicines causing side effects and what side effects they were.

5. Do you measure and take your medicines by yourself? If not, who helps you to take your medicine?

6. Is there anything that makes it harder for you to take your medicines?

7. Do you ever feel concerned about taking your medicines when other people are around? **Yes**/ **No**

   Does this ever put you off taking them? **Yes**/ **No**

8. Do you have any worries about the number of medicine doses that you need to take or the time of the doses?

   Yes/ **No**

   Does this ever put you off taking your medicines? **Yes**/ **No**

9. Do you have any worries about the size of tablets that you need to take or the taste of your medicines?

   Yes/ No

   Does this ever put you off taking your medicine? **Yes/ No**

   If yes can you please give us an example?

10. Have you tried or do you use any methods to help you with medicines taking? If yes, please describe them and how well they work.

9.5 Summary table for Chapter 4

No	Gender	Age	Disease	Medicines	Adherence rate (self-report) (P=Parents, C=Child)	Adherence rate (MPR)	BMQ Necessity score	BMQ Concerns score	BMQ Differential scores
1	F	8	Epilepsy	Fluticasone, Levetiracetam	100 (C)	100	20	14	6
2	M	7	Epilepsy	Levetiracetam, Topiramate, Clobazam, Phenobarbital	95 (C)	95	20	18	2
3	F	12	Heart Disease	Captopril, Digoxin, Furosemide	98 (C)	94	14	10	5
4	F	4	Epilepsy	Levetiracetam, Clobazam, Baclofen, Topiramate	100 (P)	100	22	21	1
5	M	3	Epilepsy	Levetiracetam, phenobarbital	100 (P)	100	17	16	1
6	F	9	Epilepsy	Valproate, Levetiracetam	90 (C)	100	15	12	3
7	M	6	Epilepsy	Rufinamide, Lamotrigine	90 (P)	88	17	20	-3
8	F	12	Diabetes	Insulin, Levothyroxine, Growth Hormone	100 (C)	100	18	14	4
9	F	5	Epilepsy	Levetiracetam, Baclofen	98 (P)	91	17	16	1
10	M	1	Heart Disease	Furosemide, Captopril, Salbutamol, Propranolol	100 (P)	96	20	13	7
11	M	16	haemophilia B	Factor 9	100 (C)	100	22	10	12
12	M	7	Hyperactivity	Methylphenidate	70 (C)	56	18	14	4
13	F	8	Asthma	Fluticasone, Salbutamol	100 (C)	83	21	12	9
14	F	10	Lupus Erythematous	Nitrofurantoin, Omeprazole, Metoclopramide	90 (C)	91	25	21	4
15	M	3	Anaemia	Ferric Hydroxide	98 (P)	95	18	15	3
16	F	13	Asthma	Salbutamol	80 (C)	66	14	15	-1
17	F	16	Epilepsy	Levetiracetam, Baclofen	90 (C)	100	20	18	2
18	F	14	Anaemia	Ferric Hydroxide, Multivitamins	90 (C)	100	14	17	-3
19	M	11	Epilepsy	Levetiracetam	75 (C)	67	11	17	-6
20	F	13	Epilepsy	Levetiracetam, Rufinamide, Clobazam	100 (C)	100	18	17	1
21	M	16	End-stage renal disease	Solifenacin	90 (C)	81	18	14	4
22	F	6	Epilepsy	Valproate	99 (P)	98	18	14	4
23	M	4	Epilepsy	Levetiracetam	90 (P)	100	16	18	-2
24	M	5	Asthma	Fluticasone, Salbutamol	100 (P)	91	8	10	-2

No	Gender	Age	Disease	Medicines	Adherence rate (self-report) (P=Parents, C=Child)	Adherence rate (MPR)	BMQ Necessity score	BMQ Concerns score	BMQ Differential scores
25	F	3	Heart Disease	Captopril, Digoxin	100 (P)	100	20	14	6
26	F	12	Growth hormone deficiency	Growth Hormone	99 (C)	85	10	14	-4
27	M	5	Asthma	Fluticasone, Salbutamol	100 (P)	92	15	12	3
28	M	5	Diabetes	Insulin degludec, Insulin aspart	90 (P)	80	24	13	11
29	M	5	Growth hormone deficiency	Growth Hormone	100 (P)	96	13	15	-2
30	F	11	Asthma	Fluticasone, Salbutamol	100 (C)	87	19	14	5
31	F	13	Diabetes	Insulin aspart, Insulin glargine	100 (C)	100	18	14	4
32	M	9	Asthma	Fluticasone, Salbutamol	100 (C)	70	14	16	-2
33	M	4	Anaemia	Ferric Hydroxide, Ranitidine	80 (P)	62	20	16	4
34	M	4	Epilepsy	Levetiracetam	100 (P)	100	14	16	-2
35	M	8	Sickle cell anaemia	Penicillin, Hydroxyurea	79 (C)	78	19	16	3
36	M	10	Asthma	Salbutamol, Fluticasone	100 (C)	100	14	17	-3
37	M	12	Asthma	Fluticasone, Salbutamol	70 (C)	55	16	17	-1
38	M	13	Diabetes	Insulin aspart, Metformin	99 (C)	99	15	16	-1
39	F	7	Epilepsy	Levetiracetam	100 (C)	100	16	11	4
40	F	5	Anaemia	Ferric Hydroxide, Levothyroxine	100 (P)	100	14	16	-2
41	M	6	End-stage renal disease	Prednisolone, Vitamin D	100 (C)	100	10	13	-3
42	M	1	Cancer	Methotrexate, Prednisolone, Mercaptopurine	100 (P)	100	22	13	9
43	M	11	Epilepsy	Valproate, Rufinamide, Clobazam	100 (C)	100	17	15	2
44	M	7	Asthma	Salbutamol, Fluticasone	100 (C)	88	14	11	3
45	F	8	Epilepsy	Levetiracetam, Vitamin D	75 (C)	68	14	20	-6
46	M	7	Diabetes	Multivitamins, Insulin aspart	100 (C)	100	18	17	1
47	M	10	Epilepsy	Rufinamide, Clobazam, Lacosamide	100 (C)	100	22	20	2
48	M	3	End-stage renal disease	Mycophenolate, Prednisolone	100 (P)	100	12	16	-4

No	Gender	Age	Disease	Medicines	Adherence rate (self-report) (P=Parents, C=Child)	Adherence rate (MPR)	BMQ Necessity score	BMQ Concerns score	BMQ Differential scores
49	F	17	Asthma	Salbutamol, Fluticasone	70 (C)	50	12	17	-5
50	M	8	Diabetes	Multivitamins, Insulin aspart	100 (C)	99	17	12	5
51	F	2	Gastrointestinal Disorder	Omeprazole	100 (P)	100	19	19	0
52	F	10	Cancer	Methotrexate, Dexamethasone, Mercaptopurine	100 (C)	100	21	15	6
53	M	16	Asthma	Fluticasone/Salmeterol, Salbutamol	70 (C)	53	14	18	-4
54	F	13	Gastrointestinal Disorder	Sodium bicarbonate	100 (C)	100	17	19	-1
55	M	18	Diabetes	Insulin aspart, Metformin	100 (C)	95	18	14	4
56	M	3	Epilepsy	Valproate, Levetiracetam	100 (P)	89	23	20	3
57	F	7	Growth hormone deficiency	Growth Hormone	100 (C)	100	22	13	9
58	M	12	Diabetes	Insulin aspart, Metformin	100 (C)	100	19	17	2
59	M	16	Asthma	Fluticasone, Salbutamol	75 (C)	69	19	15	4
60	F	11	Cystic fibrosis	Prednisolone, Levofloxacin	100 (C)	100	19	16	3
61	F	12	Growth hormone deficiency	Growth Hormone	100 (C)	100	11	13	-2
62	M	15	Diabetes	Insulin aspart, Metformin	100 (C)	96	12	16	-4
63	F	12	Hypothyroidism	Levothyroxine	100 (C)	100	22	14	8
64	M	1	Gastrointestinal Disorder	Omeprazole	100 (P)	100	24	22	2
65	M	13	Asthma	Fluticasone, Salbutamol	75 (C)	60	19	17	2
66	M	15	Growth hormone deficiency	Growth Hormone	100 (C)	99	25	19	6
67	M	14	Heart Disease	Digoxin, Enalapril maleate, Furosemide	100 (C)	100	22	15	7
68	M	1	Hypertension	Ranitidine, Captopril, Furosemide	100 (P)	100	21	18	3
69	M	12	Epilepsy	Levetiracetam	100 (C)	99	24	21	3
70	F	15	Anaemia	Ferric Hydroxide, Multivitamins	75 (C)	75	19	19	0
71	M	16	Diabetes	Insulin aspart, Metformin	95 (C)	78	19	20	-1

No	Gender	Age	Disease	Medicines	Adherence rate (self-report) (P=Parents, C=Child)	Adherence rate (MPR)	BMQ Necessity score	BMQ Concerns score	BMQ Differential scores
72	M	14	psychiatric disorder	Escitalopram, Diazepam	100 (C)	100	16	20	-4
73	M	15	psychiatric disorder	Escitalopram, Fluoxetine	100 (C)	100	20	17	3
74	F	2	Cystic fibrosis	Salbutamol, Levofloxacin	90 (P)	90	21	19	2
75	M	9	Asthma	Fluticasone, Salbutamol	90 (C)	88	18	15	3
76	F	12	Growth hormone deficiency	Growth Hormone	95 (C)	89	13	13	0
77	M	14	Diabetes	Insulin aspart, Metformin	100 (C)	94	24	16	8
78	M	1	Hypothyroidism	Levothyroxine	100 (P)	100	20	17	3
79	F	12	Diabetes	Insulin aspart, Metformin	100 (C)	100	19	17	2
80	M	11	Cystic fibrosis	Salbutamol, Tobramycin	100 (C)	100	20	18	2
81	F	13	Hypothyroidism	Levothyroxine	100 (C)	100	18	13	5
82	F	6	End-stage renal disease	Prednisolone, Furosemide	100 (C)	100	22	16	6
83	F	11	Sickle cell anaemia	Hydroxyurea, Folic acid	100 (C)	100	20	16	4
84	M	7	Sickle cell anaemia	Hydroxyurea, Folic acid, Ferric Hydroxide	100 (C)	92	20	16	4
85	F	12	Asthma	Fluticasone/Salmeterol, Salbutamol	100 (C)	100	19	16	3
86	F	4	Heart Disease	Digoxin, Captopril	100 (P)	100	23	15	0
87	M	13	Diabetes	Insulin aspart, Metformin	100 (C)	100	21	19	2
88	M	11	Hypertension	Captopril	100 (C)	94	19	17	2
89	F	12	End-stage renal disease	Prednisolone, Furosemide	80 (C)	72	15	19	-4
90	M	16	Asthma	Prednisolone, Salbutamol	100 (C)	96	20	15	5
91	M	9	Cancer	Prednisolone, Methotrexate	100 (C)	100	23	18	5
92	F	7	Psychiatric disorder	Escitalopram	100 (C)	100	19	18	1
93	F	14	Growth hormone deficiency	Growth Hormone	100 (C)	100	20	19	1
94	F	12	Heart Disease	Valsartan, Furosemide, Multivitamins	100 (C)	100	23	19	4
95	M	6	Cancer	Prednisolone, Methotrexate	100 (C)	100	17	20	-3
96	M	8	Diabetes	Insulin aspart, Multivitamins	100 (C)	100	16	16	0

No	Gender	Age	Disease	Medicines	Adherence rate (self-report) (P=Parents, C=Child)	Adherence rate (MPR)	BMQ Necessity score	BMQ Concerns score	BMQ Differential scores
97	F	13	Growth hormone deficiency	Growth Hormone	100 (C)	100	16	16	0
98	F	9	Heart Disease	Digoxin, Captopril, Furosemide	100 (C)	100	24	19	5
99	M	5	End-stage renal disease	Furosemide, Prednisolone	100 (P)	100	21	19	2
100	F	15	Asthma	Fluticasone, Salbutamol	90 (C)	85	19	17	2

9.6 Ethical approval in the UK (Chapter 5)

Dr Sharon Conroy

Medical School

Email: hra.approval@nhs.net
HCRW.approvals@wales.nhs.uk

Royal Derby Hospital Centre

Uttoxeter Road, Derby

DE22 3DT

30 July 2019

Dear Dr Conroy

HRA and Health and Care

Study title:	**Exploratory study on the barriers and facilitators of medicines adherence in a UK children's hospital and in a Saudi Arabia children's hospital.**
IRAS project ID:	**247581**
Protocol number:	**19038**
REC reference:	**19/LO/1250**
Sponsor	**University of Nottingham**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?

HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?

HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?

Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **247581**. Please quote this on all correspondence.

Yours sincerely,

Thomas Fairman

HRA Approvals Manager

Email: hra.approval@nhs.net

Copy to: *Ms Angela Shone, (Sponsor Contact)*

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
Covering letter on headed paper [covering letter]	1.0	25 June 2019
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Evidence of sponsor insurance]	1.0	31 July 2018
IRAS Application Form [IRAS_Form_25072019]		25 July 2019
Letter from sponsor [Sponsor letter]	3.0	27 June 2019
Non-validated questionnaire [Study questionnaire]	1.0	24 June 2019
Organisation Information Document [Organisation information document]	2.0	25 July 2019
Other [Delegation log]	1.0	24 June 2019
Other [Sponsor letter re insurance renewal]	1.0	19 July 2019
Participant consent form [Consent form parent]	1.0	24 June 2019
Participant consent form [Consent form parent participant]	1.0	24 June 2019
Participant consent form [Consent form 16yrs +]	1.0	24 June 2019
Participant information sheet (PIS) [PIS 2-5yrs]	2.0	25 July 2019
Participant information sheet (PIS) [PIS 11-15yrs]	2.0	25 July 2019
Participant information sheet (PIS) [PIS 16-18yrs]	2.0	25 July 2019
Participant information sheet (PIS) [PIS 6-10yrs]	2.0	25 July 2019
Participant information sheet (PIS) [Parent PIS]	2.0	25 July 2019
Research protocol or project proposal [Protocol]	1.0	24 June 2019
Schedule of Events or SoECAT [Schedule of events]	1.0	24 June 2019
Summary CV for Chief Investigator (CI) [Chief investigator CV]	1.0	25 June 2019
Summary CV for student [CV PhD student]	1.0	25 June 2019
Summary CV for supervisor (student research) [PhD supervisor CV]	1.0	26 June 2019
Validated questionnaire [BMQ specific]	1.0	24 June 2019

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
All sites will perform the same research activities therefore there is only one site type.	Organisations will not be required to formally confirm capacity and capability, and research procedures may begin 35 days after provision of the local information pack, provided the following conditions are met. • You have contacted participating NHS organisations (see below for details) • HRA and HCRW Approval has been issued • The NHS organisation has not provided a reason as to why they cannot participate • The NHS organisation has not requested additional time to confirm. You may start the research prior to the above deadline if HRA and HCRW Approval has been issued and the site positively confirms that the research may proceed. You should now provide the local information pack for your study to your participating NHS organisations. A current list of R&D contacts is accessible at the NHS RD Forum website and these contacts MUST be used for	An Organisational Information Document has been submitted and the sponsor is not requesting and does not expect any other site agreement to be used.	No study funding will be provided to sites as per the Organisational Information Document.	A Local Collaborator should be appointed at study sites of this type	Where arrangements are not already in place, researchers undertaking any of the research activities listed in A18 of the IRAS form would be expected to obtain a Letter of Access. This would be on the basis of a Research Passport (if university employed) or an NHS to NHS confirmation of pre-engagement checks letter (if NHS employed). These should confirm DBS checks and occupational health clearance.

	this purpose. The password to access the R&D contact list is Redhouse1.				

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.

9.7 Certificate for Research Integrity course

Certificate produced on: 6 April 2020

University of Nottingham
UK | CHINA | MALAYSIA

Certificate of Attendance

Mohammed Khurayzan S Al Dosari
has completed the following training course
Research Integrity: Comprehensive (Standalone on line learning course)
. on the 01/10/2019
and receives 2.00 training unit(s)

L Donaldson

Professor Lucy Donaldson
Associate Pro-Vice-Chancellor for the Graduate School and Researcher Career Development

D. A. Burns

Mr David Burns
Director of Professional Development

This Certificate of Attendance is issued by the University of Nottingham, for attendance at short courses.
One training point is equivalent to half a day of tutor contact time or independent study.

9.8 Summary table for Chapter 5

No	Gender	Age	Disease	Medicines	Adherence rate (self-report) (P=Parents, C=Child)	BMQ necessity scores	BMQ Concerns scores	BMQ differential scores
1	M	8	Asthma	Salbutamol, Seretide, Montelukast	100 (C)	25	8	17
2	M	1	Extreme Prematurity	Abidec, Sodium feredetate, Omeprazole	100 (P)	14	10	4
3	M	6	Epilepsy	Sodium Valproate, Clobazam	100, 80 (P)	17	13	4
4	M	12	Cystic Fibrosis	Cortisone, Antibiotic	100 (C)	23	12	11
5	M	13	Autism	Melatonin	100 (C)	16	11	5
6	M	10	Epilepsy	Circadin, Lamotrigine	70 (C)	16	17	-1
7	F	18	Diabetes	Insulin	75 (C)	16	19	-3
8	F	7	Asthma	Salbutamol, Desloratadine	80,90 (C)	20	17	3
9	M	3	Asthma	Salbutamol, Seretide, Montelukast	100 (P)	19	5	14
10	M	12	Nocturnal enuresis	Desmopressin	90 (C)	12	6	6
11	F	13	Migraine	Amitriptyline	98 (C)	18	5	13
12	F	3	Anaemia	Iron	90 (P)	19	17	2
13	M	15	Acne	Antibiotic	100 (C)	14	11	3
14	M	11	Autism	Circadin	55 (P)	18	16	2
15	M	5	Hyperactivity	Sleeping medicine	100 (P)	17	9	8
16	F	6	Asthma	Salbutamol, Montelukast,	100 (P)	25	5	20
17	F	11	Asthma	Salbutamol, Seretide	95 (C)	17	14	3
18	M	14	Asthma	Salbutamol, Montelukast	100 (C)	24	12	12
19	F	16	Asthma	Salbutamol	100 (C)	15	11	4
20	F	8	Asthma	Salbutamol, Seretide, Montelukast	85,100,90 (C)	25	18	7
21	M	11	Epilepsy	Baclofen, Mebeverine	100 (C)	21	19	2
22	M	12	Asthma	Salbutamol, Seretide, Montelukast	70 (C)	20	16	4
23	F	1	Epilepsy	Levetiracetam	100 (P)	21	14	7
24	F	1	Heart disease	Furosemide, Spironolactone, Omeprazole	90 (P)	25	8	17

No	Gender	Age	Disease	Medicines	Adherence rate (self-report) (P=Parents, C=Child)	BMQ necessity scores	BMQ Concerns scores	BMQ differential scores
25	M	4	Asthma	Salbutamol, Seretide, Montelukast	80,100,90 (P)	17	22	-5
26	M	7	Constipation	Movicol, Rifampicin	80 (P)	21	19	2
27	M	15	Acne	Isotretinoin	90 (C)	25	15	10
28	F	13	Acne	Doxycycline	80 (C)	19	10	9
29	F	14	Asthma	Salbutamol, Montelukast	90,85 (C)	20	10	10
30	M	14	Constipation	Movicol, Lactulose	100 (C)	17	16	1
31	F	9	GORD	Omeprazole, Laxido	100 (C)	17	13	4
32	M	5	Autism	Melatonin	100 (C)	17	18	-1
33	M	11	Asthma	Salbutamol, Chlorphenamine, Fluticasone propionate	85 (C)	20	13	7
34	M	9	Attention Deficit hyperactivity disorder	Medikinet, Bisacodyl	100 (C)	20	10	10
35	F	14	Attention Deficit hyperactivity disorder	Atomoxetine, Sertraline	90, 80 (C)	16	10	6
36	M	4	Asthma	Salbutamol, Budesonide	90 (P)	18	12	6
37	M	10	Pseudohypoaldosteronism	Sodium chloride, Sodium bicarbonate	100 (C)	22	22	0
38	F	14	Kidney disease	Prednisolone	100 (C)	25	9	16
39	F	17	Kidney disease	Lisinopril, Prednisolone, Azathioprine	90,80,100 (C)	23	15	8
40	M	9	Inflammatory bowel disease	Folic acid, Ursolic acid	100 (C)	13	14	-1
41	F	5	Chronic urticaria	Loratadine, Montelukast	85 (P)	16	12	4
42	F	15	Psoriasis	Imraldi	80 (C)	18	10	8
43	F	13	Kidney disease	Calcium carbonate, Darbepoetin, Vit D	90 (C)	25	10	15
44	F	3	Constipation	Lactulose	95 (P)	12	9	3
45	F	16	Acne	Isotretinoin	97 (C)	8	6	2
46	M	8	Eczema	Cetraben, Epaderm	80 (C)	19	18	1

No	Gender	Age	Disease	Medicines	Adherence rate (self-report) (P=Parents, C=Child)	BMQ necessity scores	BMQ Concerns scores	BMQ differential scores
47	F	1	GORD	Gaviscon	70 (P)	15	16	-1
48	F	3	Asthma	Salbutamol, Seretide	80 (P)	18	19	-1
49	M	15	Epilepsy	Carbamazepine	80 (C)	16	10	6
50	F	13	Acne	Doxycycline	75 (C)	9	5	4
51	F	6	Asthma	Salbutamol, Seretide, Montelukast	100 (P)	18	13	5
52	M	18	Acne	Doxycycline, Steroid cream	40,70 (C)	13	20	-7
53	F	16	Inflammatory bowel disease	Budesonide, Omeprazole, Vit D	100 (C)	20	10	10
54	F	5	Persistent bacterial bronchitis	Azithromycin	90 (P)	17	13	4
55	M	8	Attention Deficit hyperactivity disorder	Medikinet	70 (C)	19	18	1
56	F	3	Chronic bullous disease of childhood	Dapsone	100 (P)	13	14	-1
57	F	18	Acne	Isotretinoin	60 (C)	8	11	-3
58	F	10	GORD	Gaviscon, Movicol, Omeprazole	80 (C)	17	20	-3
59	M	14	Epilepsy	Sodium valproate, Circadin	100 (C)	22	9	13
60	F	11	Thalassemia	Folic acid, Iron	100 (C)	20	23	-3
61	F	16	Acne	Doxycycline, Budesonide	90,100 (C)	15	13	2
62	M	1	Bronchitis	Montelukast	100 (P)	12	10	2
63	M	14	Asthma	Salbutamol, Seretide	100 (C)	23	7	16
64	F	8	Asthma	Salbutamol, Seretide	90,100 (C)	19	19	0
65	F	7	Constipation	Movicol, Sodium picosulfate	70 (C)	16	20	-4
66	F	15	Having period	Contraceptive	100 (C)	9	5	4
67	M	3	Asthma	Salbutamol, Seretide	100 (P)	22	16	6
68	M	14	Acne	Isotretinoin	90 (C)	18	12	6
69	M	14	Epilepsy	Lamotrigine, Levetiracetam	100 (C)	25	12	13

No	Gender	Age	Disease	Medicines	Adherence rate (self-report) (P=Parents, C=Child)	BMQ necessity scores	BMQ Concerns scores	BMQ differential scores
70	F	9	Asthma	Symbicort, Azithromycin	60,70 (C)	12	19	-7
71	M	15	Hyperthyroidism	Carbimazole	90 (C)	21	12	9
72	F	15	Hypothyroidism	Levothyroxine	85 (C)	16	11	5
73	M	12	Epilepsy	Sodium valproate, Carbamazepine	100,85 (C)	21	14	7
74	M	8	Anaemia	Iron, Folic acid, Vitamin	100 (C)	20	14	6
75	F	11	Epilepsy	Levetiracetam, Circadin, Carbamazepine	100 (C)	25	20	5
76	F	8	Constipation	Movicol	100 (C)	18	5	13
77	F	5	Epilepsy	Baclofen	80 (P)	16	15	1
78	F	18	Growth hormone deficiency	Growth hormone	80 (C)	18	12	6
79	F	10	Attention Deficit hyperactivity disorder	Medikinet	70 (C)	18	10	8
80	M	14	Constipation	Movicol, Bisacodyl	100 (C)	19	8	11
81	M	14	Epilepsy	Sodium valproate	90 (C)	25	23	2
82	F	15	Heart disease	Atenolol, furosemide	80,90 (C)	14	11	3
83	F	8	Diabetes	Insulin aspart, Insulin glargine	100 (C)	24	22	2
84	F	15	Eczema	Fexofenadine, Loratadine, Doxycycline	60 (C)	16	11	4
85	M	7	Asthma	Salbutamol, Budesonide	47 (P)	13	14	-1
86	F	12	Epilepsy	Circadin, Sodium valproate	88 (C)	17	18	-1
87	F	12	Acne	Acnecide gel	80 (C)	11	10	1
88	M	14	Attention Deficit hyperactivity disorder	Lisdexamfetamine	100 (C)	13	11	2
89	F	9	Eczema	Mometasone, Tacrolimus cream, Cetirizine, Salbutamol, Fluocinolone acetonide	70 (C)	21	15	6
90	M	10	Heart disease	Propranolol	99 (C)	17	5	12
91	M	18	Asthma	Salbutamol, Seretide, Fexofenadine	90 (C)	20	11	9
92	F	13	Diabetes	Insulin	100 (C)	25	9	16

No	Gender	Age	Disease	Medicines	Adherence rate (self-report) (P=Parents, C=Child)	BMQ necessity scores	BMQ Concerns scores	BMQ differential scores
93	M	12	Constipation	Movicol	60 (C)	15	18	-3
94	F	9	Kidney disease	Trimethoprim	96 (C)	17	16	1
95	F	15	GORD	Omeprazole, Folic acid	100 (C)	16	12	4
96	M	5	Kidney disease	Tolterodine, Movicol	100 (P)	24	11	13
97	M	3	Asthma	Salbutamol, Budesonide, Cetirizine	60,75,75 (P)	13	19	-6
98	F	4	GORD	Ranitidine	55 (P)	14	15	-1
99	M	15	Scleroderma	Mofetil	100 (C)	17	12	5
100	F	4	Juvenile dermatomyositis	Hydroxychloroquine, Methotrexate	100 (P)	20	14	6