Paediatric rational prescribing: a study of paediatric rational prescribing tools and development of a novel tool for the UK

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List of abbreviations

5-HT3	Serotonin
ACOVE-3	Assessing care of vulnerable adults
ADHD	Attention deficit with hyperactivity disorder
ADR	Adverse drug reaction
AFSSAPS	Agence Nationale de Sécurité du Médicament et des Produits de Santé
AGS	American Geriatrics Society
BNFc	British National Formulary for Children
ED	Emergency department
CINAHL	Cumulative Index of Nursing and Allied Health Literature
CRF	Case report form
DPI	Dry powder inhaler
EBM	Evidence-based medicine
EMA	European Medicines Agency
ENT	Ear, nose and throat
EU	European Union
GORD	Gastro-oesophageal reflux disease
GP	General practitioner
H_1	Histamine 1 receptor
H_2	Histamine 2 receptor
HIV	Human immunodeficiency virus
IPA	International Pharmaceutical Abstracts
IV	Intravenous
LRTI	Lower respiratory tract infection
MAI	Medication appropriateness index
MEDLINE	Medical Literature Analysis and Retrieval System Online
MeSH	Medical Subject Headings
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSAID	Non-steroidal anti-inflammatory drug
OME	Otitis media with effusion
ORS	Oral rehydration solution
PCRS	Primary care reimbursement service
PIOs	Potentially inappropriate omissions

PIMs	Potentially inappropriate medicines
pMDI	Pressurised metered dose inhaler
POPI	Pediatrics: Omissions of Prescriptions and Inappropriate Prescriptions tool (French: *pédiatrie: omissions et prescriptions inappropriées*)
POPI UK	POPI (modified for the United Kingdom)
PIPc	Indicators of potentially inappropriate prescribing in children
PPI	Proton pump inhibitor
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomised control trial
REC	Research ethics committee
RSV	Respiratory syncytial virus
SIGN	Scottish intercollegiate guideline network
SSRI	Selective serotonin reuptake inhibitor
START	Screening Tool to Alert doctors to Right Treatment
STOPP	Screening Tool of Older Persons' Prescriptions
UK	United Kingdom
USA	United States of America
WHO	World Health Organisation

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Abstract

Background

Children are vulnerable to inappropriate prescribing yet rational prescribing criteria, although widely used in adult medicine, are not well-established in paediatric research. Rational prescribing tools, criteria lists of potentially irrational prescribing, are used to study the use of medicines and can be used to detect and quantify inappropriate prescribing. This allows researchers to compare quality of prescribing across different populations, identify factors associated with irrational prescribing, and evaluate the effectiveness of interventions to improve prescribing.

Aims

The aims of this thesis were to identify and appraise all existing tools for studying irrational prescribing for children; to develop a rational prescribing tool that could be used across paediatric practice in the United Kingdom (UK); and to validate the novel tool for application in research and clinical practice in the UK.

Methods

A systematic review of paediatric rational prescribing tools was undertaken and identified two such tools. One of these, the POPI (Pediatrics: omissions of prescriptions and inappropriate prescriptions) tool, was designed for application to any paediatric practice setting but founded in French clinical practice. The second, PIPc (Indicators of potentially inappropriate prescribing in children) is a tool designed for use in primary care only, in Ireland and the UK.

In order to develop criteria applicable to any UK paediatric setting, the POPI tool was modified for use in the UK, resulting in the novel POPI UK tool. Each criterion was compared to relevant UK national guidelines, with three possible outcomes: no change; modification; or omission. Criteria concordant with UK guidelines were integrated into the new tool unchanged, criteria differing from guidelines were modified, and criteria with contradicting guidelines or no relevant UK guidelines were omitted.

Two validation studies were designed and carried out to evaluate POPI UK. Firstly, a prospective clinical validation study was designed to review the prescriptions of 600 children in a UK children's hospital, in inpatient and emergency department settings. This

study evaluated the relevance of the POPI UK criteria to the study population, assessed its ability to detect potentially inappropriate prescribing, and examined factors associated with any potentially inappropriate prescribing detected.

Secondly, the precision of the POPI UK tool was tested through an inter- and intra-rater reliability study. Cohen's Kappa was calculated for agreement between two raters applying the criteria to twenty anonymised cases.

Results

The systematic review identified five articles meeting inclusion criteria. These related to three paediatric rational prescribing tools, POPI, PIPc, and POPI UK.

The POPI tool comprises 105 criteria and was designed for use in any paediatric practice setting, based on French standards of practice. The PIPc comprises twelve criteria, designed for use in primary care in Ireland and the UK. Due to the PIPc being specifically designed for use in primary care, the POPI tool was the focus of further study.

Modification of the POPI criteria was undertaken to develop the POPI UK tool. No change was made to 49 criteria., 29 were modified, four were reduced into two through combination with closely related criteria and 23 were omitted, including the omission of a category. The resulting POPI UK tool comprises 80 criteria divided into 21 clinical categories.

In the clinical validation study, the POPI UK criteria were relevant to the majority (96%) of the study population and the tool identified potentially irrational prescribing. In addition, several limitations were identified, including the detailed level of clinical information required to apply the criteria.

The inter- and intra-rater repeatability of POPI UK were rated as good, with Kappa values of 0.44 and 0.57 respectively. This was lower than the reliability of the original POPI tool. On examination of the studies, it appeared that methodological differences rather than the modification of the tool explained the observed difference in reliability of the criteria.

Conclusions

Two existing paediatric rational prescribing tools were identified and appraised, POPI and PIPc. In order to develop a tool applicable to children across UK paediatric settings a novel tool, POPI UK, was developed by modifying the POPI criteria. Validation studies demonstrated that POPI UK was relevant to a majority of the studied population and was able to identify potentially irrational prescribing with good reliability. This tool could be used in UK paediatric practice settings to evaluate rational prescribing. However, a number of significant limitations to all three paediatric rational prescribing tools have been identified and further research avenues are suggested including refinement of the POPI UK criteria.

Dissemination of research related to thesis

Corrick F, Conroy S, Sammons H, Choonara I. Paediatric Rational Prescribing: A Systematic Review of Assessment Tools. International journal of environmental research and public health. 2020;17(5):1473. (Appendix 1)

Corrick F, Choonara I, Conroy S, Sammons H, editors. Modifying a paediatric rational prescribing tool (POPI) for use in the UK. Healthcare; 2019;7(1) (Appendix 2)

Corrick F, Smith C, Choonara I, Sammons HM. Developing paediatric rational prescribing criteria: a pilot study. Midlands Academy of Medical Sciences Research Festival; 2017 (Poster) (Appendix 3)

Corrick FJ, Conroy S, Choonara I, Sammons H. Developing paediatric rational prescribing criteria. Archives of Disease in Childhood. 2017;102 (Supplement 1):A84. (Oral presentation) (Appendix 4)

Corrick F, Smith C, Choonara I, Sammons HM. Rational Prescribing for Children: Evaluating the modified POPI criteria. RCPCH Annual QI Conference; 2016 (Poster and oral presentation) – awarded best trainee project (Appendix 5)

Corrick, F, Sammons HM. Assessment Tools of Rational Prescribing in Children. Trent Paediatric Society Meeting; 2016 (Poster) (Appendix 6)

1 Background and rationale for the thesis

1.1 Introduction

Rational prescribing describes practices aimed at minimising inappropriate prescribing at a systems level or, in other words, considering all elements at all stages of the process involved in prescribing, from the legal framework governing therapeutics to individual prescriber decisions. This includes, for example, the development of essential drug lists or the use of guidelines. This approach to improving the use of medicines is supported by the World Health Organisation (WHO) and was identified as an objective of the WHO Twelfth General Programme of Work 2014-2019 (1).

Lack of rational prescribing has both human and economic costs (2). Inappropriate prescriptions may harm individual patients by causing adverse events or in opportunity cost when more effective treatments exist for a disease. They may also incur a health cost to a wider community, for instance where injudicious antibiotic prescribing practice increases the rate of resistant infections or where appropriate vaccination programmes are not implemented at the cost of subsequently higher rates of infection. There are also economic costs in terms of inefficiency of health spending and the financial implications of any detriment to health incurred by poor prescribing practices (3).

Children pose some additional challenges to rational prescribing compared with adults (4). Dosing regimens commonly require the prescriber to make calculations based on age or weight (5), therefore increasing the risk of inappropriate prescribing; for less experienced prescribers, this may compound uncertainty about what to prescribe and contribute to omissions.

Another impediment to rational use of medicines in children is the relative paucity of high-quality research exploring the use of medicines for children compared to adults. This hinders efforts to implement high-quality evidence-based practice as inadequacy of evidence forces clinical decisions to be made based on consensus or personal clinical experience alone, as is evident in a number of National Institute for Health and Care Excellence (NICE) guidelines for children and young people (6-8). There are a number of

contributing factors to this bias, including complex ethical issues, high cost and difficulty in recruiting participants for paediatric trials (9-11). This is discussed further in section 1.5

Studying prescribing for children (on page 16).

1.2 What is rational prescribing?

1.2.1 Defining rational prescribing

Rational prescribing was named an objective of the WHO Twelfth General Programme of Work 2014-2019 (1). The WHO defined rational prescribing in 1985 as *"when patients receive the appropriate medicines, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost both to them and the community* (12) and continues to use this definition in their on-going work. Other terms sometimes used as synonymous include rational use of medicines, appropriate prescribing and optimal prescribing (3).

It is important to note that some authors limit the term "rational" prescribing to prescribing that is based on reasoned motives but that may still be inappropriate, distinguishing this from "appropriate" prescribing as their preferred term to exclude both irrational and suboptimal prescribing (13) In this thesis, "rational prescribing" is used to describe optimal prescribing in line with the above WHO definition.

As indicated in the WHO definition, rational prescribing is prescribing that results in the patient receiving medicines that are appropriate to treat them, not only in terms of drug selection but also dosage, duration and use of a lower cost drug in preference to a higher cost equivalent. This means that research into rational prescribing is a broad field that incorporates studies with varied approaches, including research into inappropriate prescribing, administration errors, prescribing trends, adherence to clinical recommendations for treatments, patient concordance, accessibility of essential drugs, and use of generic versus branded drugs(14). These studies are relevant both at the level of individual prescribers or organisations, and at national or international levels.

Irrational prescribing can take a number of different forms. In the field of rational prescribing for older adults, inappropriate prescribing has been categorised into three broad groups: misprescribing, overprescribing, and underprescribing (15). Misprescribing includes choice of incorrect medication for a disease, incorrect dosage or duration of therapy, selection of a drug that is otherwise contraindicated in a patient due to a comorbid illness or concurrent drug(s) with which it may interact. Overprescribing is prescription of an unnecessary or insufficiently beneficial medication, and underprescribing is the omission of a medication that would be beneficial.

1.2.2 Barriers to rational prescribing

There are many factors that contribute to the prevalence of irrational prescribing. These include issues around education and supervision of prescribers, the prevailing culture of the medical community in terms of reference and adherence to guidelines, and patient beliefs and preferences (16-18). Infrastructure and economic pressures may prevent prescribers and patients from having access to appropriate medicines, or cultural beliefs may act as a barrier to patient use of appropriate medicines even when they are available (19). Prescriber, infrastructure, economic and patient factors have all been described as potential barriers to rational prescribing, with some examples of each shown in Figure 1-1 adapted from Holloway, 2011 (20).

Prescriber factors	Infrastructure factors	Economic factors	Patient factors
•Lack of prescriber knowledge	•Inappropriate and biased pharmaceutical promotion	•Inadequate supplies of appropriate medicines	•Perceived and actual patient demand
•Inadequate continuing education	•Inability to provide adequate observation or follow-up of patients	•Perverse economic incentives driving prescription of more expensive medicines	•Cultural beliefs leading to patient non-adherence
•Prescriber culture (where seniors may set inappropriate examples)	•Lack of diagnostic services		•Unintentional non-adherence due to lack of education, instructions or inabilities to administer medications
•Inadequate time for consultations			

Figure 1-1: Barriers to rational prescribing

Any of the categories of prescriber, infrastructure, economic or patient factors can have an impact on children and in several aspects children may be particularly vulnerable to inappropriate prescribing. The vulnerability of children to inappropriate prescribing is in part due to the diversity of the paediatric population, ranging from neonates to adolescents, with concomitant changes in body weight and maturity of metabolic pathways. These challenges affecting rational prescribing for children are examined in Section 1.5.3.

Considering examples of patient factors in a paediatric population, adherence to treatment may be hindered by children rejecting medications due to oppositional behaviour, embarrassment in taking medications around peers, difficulty in swallowing tablets, rejection of taste of medications, and other feeding issues (21). In addition, lack of education or cultural beliefs of parents may have an impact on a child's adherence to prescribed medications (22).

Prescriber factors affecting paediatric prescribing include the limited space for training on paediatric prescribing in undergraduate curricula (23) and the fact that, while decision-making is more likely to be led by senior clinicians, junior doctors are the most likely to actually complete prescriptions, whether handwritten or electronic (24).

In addition, infrastructure and economic factors have led to underrepresentation of children in pharmacological research (25), meaning that drug selection and dosage may rely upon lower quality evidence for children than for adult populations. Electronic prescribing systems designed to reduce prescribing error in adult medicine are not immediately applicable to paediatric practice due to the more varied dosing regimens appropriate to paediatric patients (24).

1.2.3 Harms of irrational prescribing

The risks of irrational prescribing are not only to the individual patient in receipt of inappropriate medicines (or lack of access to appropriate medicines), but also to their community in terms of both health costs and economic costs.

Overuse and misuse of medicines may cause significant morbidity and mortality. Irrational prescribing may lead directly to adverse drug reactions (ADRs) where contraindicated medications are used; in a meta-analysis of hospital admissions due to ADRs, it was found that one in ten hospital admissions in older patients were due to ADRS and the majority of ADRs were considered to be preventable (26). Polypharmacy has consistently been identified as a factor associated with higher risk of ADRs (27-29).

ADRs present a significant burden in terms of of morbidity and healthcare costs. Avoidable ADRs have been estimated to contribute to additional need for hospital stays amounting to 181,626 bed-days in the UK National Health Service (NHS); the cost of the additional hospital stays alone came to £98.5 million per year (30). Other studies have estimated what proportion of admissions were related to prescribing, with a systematic review of such studies finding that 3.7% of preventable hospital admissions were drug-related, one-third of which were due to prescribing problems, one-third due to patient adherence problems, and one-fifth due to monitoring problems (31). Another review similarly found 3.5% of hospital admissions were due to ADRs, and further reported that approximately 10% of inpatients will experience an ADR during their admission(32). All of these health costs translate to high economic costs. For instance, in one study considering all ADR-related admissions to UK hospitals, the total economic impact was estimated to come to £466m annually in healthcare costs(33).

Children are also vulnerable to ADRs. One study in a tertiary children's hospital in the UK estimated that 2.9% of paediatric emergency admissions were caused by ADRs. A large proportion of these related to treatment of cancer (48%), with adverse effects that are known risks such as thrombocytopaenia and neutropaenia. However, 22% of ADRs were considered avoidable (34). Examples of avoidable ADRs included; diarrhoea and vomiting secondary to antibiotics given for viral illness, and constipation secondary to opioid analgesia occurring without any prescribed prophylaxis. This study suggested that rational prescribing could prevent a number of ADRs that are serious enough to warrant emergency admission. For illustration of the healthcare associated costs of such cases,

hospital admission for a child with gastrointestinal illness was estimated to cost £989 per patient in 2015 (35).

Any admission due to an ADR clearly represents harm to the patient in terms of morbidity and economic harm in healthcare-associated costs, but also has wider ramifications. There is also an additional burden of indirect costs, such as lost productivity of affected individuals, travel, expenses, and the wider impact on others in the household (36). Additional costs like this are equally germane to paediatric medicine, where parents may experience loss of earnings and additional childcare costs for other children in the family (37) . The overall figures are therefore likely to be much higher.

Antibiotic misuse provides a clear example of community costs of inappropriate prescribing. Antimicrobial resistance carries with it significant risks of morbidity and mortality and continues to increase worldwide (38, 39). Inappropriate use of antibiotics is considered a key contributor to the rise in antimicrobial resistance, demonstrated by the correlation between outpatient antibiotic use and penicillin-resistant pneumococci found in Europe (40). In 2018, antimicrobial resistance was estimated to cost $179,000 per 100,000 population in the UK(41). This equates to £140,000 at the conversion rate at the time of publication of those figures, or a total of £92.8 million for the whole of the UK.

1.2.4 Interventions to promote rational prescribing

The WHO identified twelve core interventions to promote rational use of medicines, shown in Figure 1-2, reproduced from Promoting rational use of medicines: core components, WHO (page 3, (42)).

Twelve core interventions to promote more rational use of medicines
1. A mandated multi-disciplinary national body to coordinate medicine use policies
2. Clinical guidelines
3. Essential medicines list based on treatments of choice
4. Drugs and therapeutics committees in districts and hospitals
5. Problem-based pharmacotherapy training in undergraduate curricula
6. Continuing in-service medical education as a licensure requirement
7. Supervision, audit and feedback
8. Independent information on medicines
9. Public education about medicines
10. Avoidance of perverse financial incentives
11. Appropriate and enforced regulation
12. Sufficient government expenditure to ensure availability of medicines and staff

Figure 1-2: WHO core interventions for rational use of medicines

Many of these interventions, such as interventions eight to twelve, require state-level changes to regulations and practice. Others, like two and four, may be at the level of international or national guidelines, or more localised institution-based guidelines.

The focus of this thesis will be around intervention seven, establishing systems of supervision, audit and feedback, and in particular, the focus will be on methods of measuring quality of prescribing that can be used to facilitate such systems. In order to improve practice through these systems, it is essential to have an objective measurement that can be used as a standard against which actual practice is compared. This gives reliability and consistency to feedback and allows prescribers, managers, and researchers to make comparisons between different prescribers, different areas, or at different times. It also, therefore, enables a quantitative assessment of the effect of interventions on the quality of prescribing.

1.3 Assessing rational prescribing

As discussed in section 1.5, in order to pursue systemic improvements towards more rational prescribing, it is necessary to develop methods of measuring the quality of prescribing to identify targets for interventions and to review the results of such interventions. There are broadly two possible extremes of approach: 1) assessment of prescribing on an individual case-by-case basis taking into account the comprehensive patient and clinical context, with no predetermined definitions for appropriate or inappropriate prescriptions, or 2) using predefined standards to define appropriate and inappropriate prescribing, which can be applied by any rater. Each of these approaches has its advantages and limitations.

1.3.1 Case-by-case expert analysis

In a case-by-case assessment of rational prescribing, there are no predetermined criteria defining specific medicines that will be considered appropriate or inappropriate for a given condition. Instead, an expert or a panel of experts reviews each prescription and determines its appropriateness in the context of that specific case. For instance, this approach has been used to assess not only prescribed medicines but also the decision not to prescribe, through evaluation of recorded consultations and patient records (43). The assessment may be structured by a number of questions about the prescriptions, for instance a classification system developed by Kunin et al, shown in Figure 1-3, provides a framework for an expert rater to assess antibiotic prescriptions (44). While the classification provides a structure for the assessment, the determination of whether or not a prescription is appropriate is determined by the rater's own judgement.

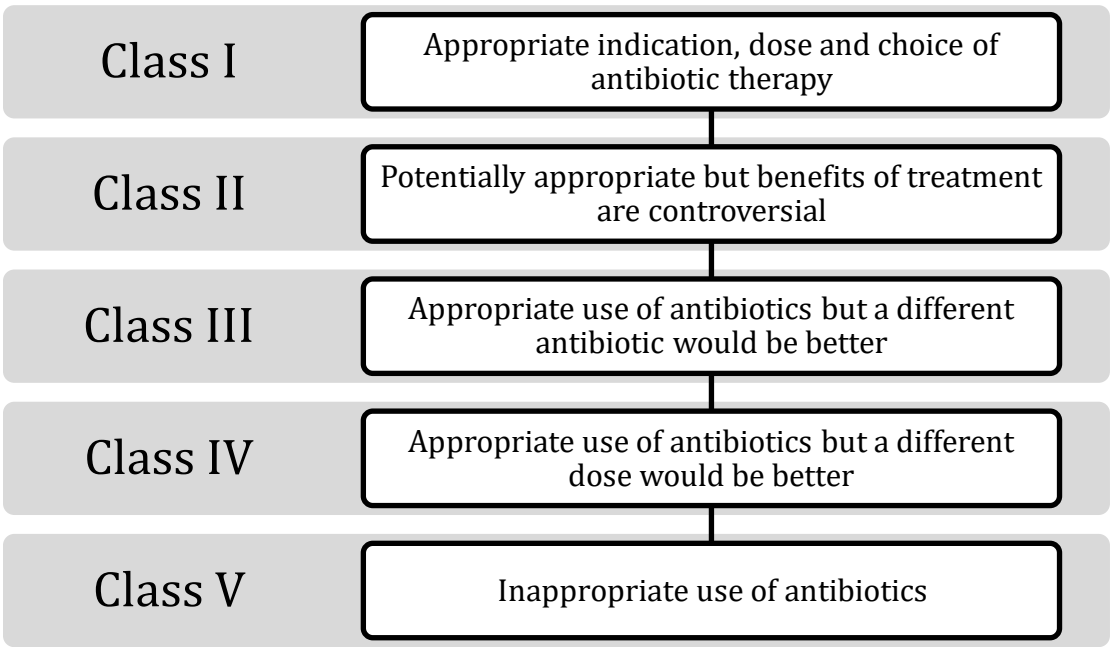

Figure 1-3: Kunin framework to evaluate antibiotic prescriptions

An advantage of this approach is that the approach can be used in any setting, accommodating differing local guidelines or formularies (45). The assessment of prescriptions by this method can also take into account the context of the individual patient, including co-morbidities, other concurrent treatments, or laboratory test results (46), which may increase the accuracy of the assessment.

However, there are also a number of drawbacks to a case-by-case approach. It may be more time-consuming than other methods and is likely to require more data about each patient (47), which may necessitate prospective data collection directly from attending clinicians or patient records. This means they cannot be applied to retrospective dispensing databases which are often used in studies into the use of medicines, as data about comorbidities or laboratory test results are unlikely to be available (48). In addition, the individuality of each assessment may increase accuracy at the cost of precision leading to inconsistent results due to subjectivity. This may reduce repeatability and therefore limit the usefulness of comparing results obtained using different experts or combining data in meta-analyses.

Methods of assessing the reliability of rational prescribing tools is discussed further in Section 4.1 Evaluating rational prescribing tools.

1.3.2 Rational prescribing assessment tools

There are a number of well-established criteria used to study rational prescribing in adult medicine. Their development and use are closely linked to the principles of quality indicators, which are explicit, measurable statements about aspects of healthcare that can be used to assess care (49, 50). Prescribing indicators have been differentiated from rational prescribing criteria by being defined as an assessment of quality of care, where rational prescribing criteria and other review criteria assess the appropriateness of specific decisions (51). It is common for indicators to contain statements that rely on measurements at a population-level, for instance the five World Health Organisation (WHO) prescribing indicators, discussed further below. As in the WHO prescribing indicators, it is common that indicators are in the form of an expected percentage or measured prevalence within the studied population (52, 53).

1.3.3 WHO prescribing indicators

The WHO has made rational prescribing and improving medicines policies one of their priorities, and began developing indicators for measuring and monitoring use of medicines at a national level in 1985 (16). The WHO core prescribing indicators were

developed through iterative studies in prescribing across a number of countries and are not intended to be comprehensive. Rather, they comprise a simple tool that is standardised, does not need adaptation for use in different nations, and can be used to reliably assess "a few critical aspects of pharmaceutical use" (54).

The five core prescribing indicators are:

1. Average number of drugs per encounter
2. Percentage of drugs prescribed by generic name
3. Percentage of encounters with an antibiotic prescribed
4. Percentage of encounters with an injection prescribed
5. Percentage of drugs prescribed from essential medicines list or formulary

The WHO core prescribing indicators have been used internationally for over twenty years, studying prescribing in a wide range of settings, including public and private institutions, in both primary and secondary healthcare (55-57). Although their use is not explicitly restricted to any particular setting, they were designed and field-tested primarily in developing countries (58)

1.3.4 Rational prescribing criteria

In contrast to indicators, rational prescribing criteria, or rational prescribing tool, would be expected to capable of assessing a specific prescription without data about the rest of a study population (51). In other words, unlike an indicator statement based upon prevalence within a population, which can never be applied to an individual prescription, criteria would be expected to enable a rater to determine whether a specific prescription was appropriate according to a predetermined standard.

Criteria lists are well-established tools in research in rational prescribing in adult medicine. A number of assessment tools have been developed to permit audit and research of rational prescribing using implicit or explicit criteria to measure prescribing practice in adults. Implicit criteria are patient-specific and take into account all medicines in the patient's current regimen (59). They rely upon the assessor's judgement of appropriateness and may accommodate patient preference, making them vulnerable to subjectivity and bias, and they are time-consuming to apply (15). Explicit criteria are

usually founded upon published reviews or consensus opinions, and often provide rigid drug-specific or disease-specific "rules" of practice (59). They are therefore unable to account for individual patient differences and require regular updating, as well as modification for different regions (15).

In a systematic review of published rational prescribing criteria, Kaufmann et al identified 46 different assessment tools (60). Of these, 61% were explicit tools, 17% were implicit, and 22% used a mixed approach. 78% of the tools targeted older people, with the remaining tools having no specified targeted group. The study did not identify any tools designed for assessment of prescribing for children. There have been no systematic reviews of published rational prescribing criteria in children.

It should be noted that rational prescribing criteria are not clinical guidelines or rulebooks for prescribers, but tools that are used to attempt to identify patterns of potentially irrational prescribing (in the very broad sense of "rational prescribing" as defined by the WHO, see Section 1.2.1) and in some cases to provide a quantifiable measurement of rational prescribing that facilitates comparative and interventional research. An individual prescription may be highlighted as potentially irrational by a criterion, but in fact be wholly appropriate and rational in the specific patient and environmental context it occurred.

1.4 Examples of rational prescribing criteria from adult medicine

1.4.1 Rational prescribing criteria for older adults

The use of rational prescribing criteria as tools to study appropriate use of medicines is particularly well-established in older adult medicine, for which at least seven sets of explicit criteria listing potentially irrational prescribing have been published, as detailed in a 2010 systematic review (61).

All seven of these criteria lists were developed through a modified Delphi consensus process. This development process is a method whereby consensus is reached by a panel of experts via an iterative activity in which members of the panel rate agreement with

statements, and the statements with levels of agreement above pre-defined cut-offs are redistributed to panellists for further consideration. Those that achieve a high level of agreement are ultimately included in the final product, in this case the list of criteria in the rational prescribing tool.

The seven rational prescribing tools for older adults identified in the 2010 systematic review are shown in Table 1-A from Chang and Chan, 2010 (61).

Table 1-A: Rational prescribing tools for older adult medicine

Rational prescribing tool	Country of development	Number of criteria
Beers	US	68
Laroche	France	34
McLeod	Canada	38
NORGEP*	Norway	36
Rancourt	Canada	111
STOPP/START**	Ireland	65
Winit-Watjana	Thailand	77

*NORGEP=Norwegian General Practice Criteria **STOPP/START=Screening Tool of Older Person's Potentially Inappropriate Prescriptions/Screening Tool to Alert doctors to Right Treatment

In order to illustrate the development, scope and application of such tools, one was selected for further discussion. The Beers Criteria are a well-known and extensively studied example of these tools, having been repeatedly modified for use in different countries and to update to current practice(62-66), and are further described below.

1.4.1.1 Beers Criteria

The Beers Criteria were originally developed by Delphi consensus in 1991 specifically for application to nursing home residents (63) and have since been modified several times, to extend application to older adults in the community (62) and to update criteria over time (64, 65). They have been utilised both in prevalence studies assessing rates of irrational prescribing and also in outcome studies examining relationships between potentially inappropriate prescribing and health outcomes. They were most recently updated into the American Geriatrics Society (AGS) 2012 Beers Criteria (64). The criteria list potentially

inappropriate medications for adults aged 65 years and older, categorised into three groups: medications to avoid in all older adults, medications considered potentially inappropriate in older adults with certain diseases or syndromes, and medications that should be used with caution.

The AGS 2012 Beers Criteria comprise fifty-three medications or medication classes. For example, fourteen fall within the category of medications considered potentially inappropriate in older adults with certain diseases or syndromes.

The Beers Criteria have been used in a diverse range of studies. One systematic review found 18 studies evaluating patient outcomes related to Beers Criteria, undertaken in community and healthcare settings (67). This review supported the clinical accuracy of the criteria in terms of a relationship between potentially inappropriate medicines and poorer patient outcomes. It showed that inappropriate prescribing (as detected by the Beers Criteria) was associated with hospitalisation of older adults who were studied in community settings, and with adverse drug reactions and increased healthcare costs in healthcare settings. The Beers Criteria have also been used to study rational prescribing in primary care settings (68) and due to their design, are applicable to retrospective datasets such as those accessible via prescribing and administrative databases (69).

The success of the Beers Criteria in achieving wide use and demonstrated usefulness has been credited to their explicit nature, simplicity for application by non-pharmacist researchers or auditors, and broad dissemination (66).

1.4.2 Validation of rational prescribing criteria

There are a number of approaches to validating rational prescribing tools. Any measurement can be considered in terms of accuracy and reliability, where accuracy represents how closely a measurement fits with a true value and reliability represents how close repeated measurements will be to one another. This is discussed further in Chapter 5.

When trying to assess the accuracy of a rational prescribing tool, the literal accuracy would be the correlation between a derived score with the true rate of irrational

prescribing. In the absence of a means to estimate the true rate, this might be calculated through comparison between different tools. Alternatively, rather than calculate the accuracy of the tool as a measure of prescribing, tools could be evaluated by assessing correlation between clinical outcomes with scores (15). Although this less closely represents the accuracy of the tool, high levels of correlation demonstrate the clinical usefulness of the tool. This validation approach is very useful for showing clinical impact of the inappropriate prescribing that has been identified but is time-consuming and technical to conduct. Only seven of the 46 adult tools discussed by Kaufmann et al had documented clinical validation studies assessing correlation between scores and clinical outcomes (60).

A common and less complex approach to validating tools is evaluating their ability to identify irrational prescriptions in practice, without then attempting to test correlation with clinical outcomes. This methodology tests whether tools are able to identify any potentially irrational prescribing, although it does not measure the sensitivity or specificity of the tool as there is no comparison to "true" values. This approach has been used widely, for instance to evaluate the START criteria (70). This can be taken further by applying two tools to the same data, such that rates of identified irrational prescribing detected can be compared between the two different tools.

In order to assess the reliability of a tool, repeatability studies should be conducted. For instance, there are two published repeatability studies assessing the STOPP/START criteria, one evaluating inter-rater reliability when scored by pharmacists (71) and one evaluating inter-rater reliability when scored by physicians (72). These studies calculated the degree of agreement between different raters when looking at the same patient data (in each case, raters scored twenty anonymised patient records according to the STOPP/START criteria) and found good levels of agreement, suggesting that studies using the STOPP/START criteria that are conducted in different institutions or regions can be validly compared.

1.5 Studying prescribing for children

1.5.1 Children are under-represented in clinical research

Children are frequently excluded from clinical trials altogether, leaving adult data to be generalised to a paediatric population(9, 73). There is a recognised bias in health research priorities towards adult research. Studies of pharmacokinetics and pharmacodynamics in children are essential and have been historically neglected; more recent work has increased understanding of pharmacokinetics in the paediatric population, but paediatric pharmacodynamics remain less well understood (76). There are a number of challenges in studying pharmacodynamics in children; for example, the development of validated outcome measures is complicated by the need to accommodate a range of developmental stages (25). An illustration of this difficulty is the well-established use of exercise tolerance in the form of a timed walking distance, which is clearly not applicable to neonates and has a normal range that changes with age. Extrapolating data from adult studies, or so-called piggy-backing of a paediatric group onto a trial designed to evaluate drug safety and efficacy in adults can result in inadequate evaluation of the dose-response relationship across the range of the paediatric population (10).

Using randomised controlled trials (RCTs) as an example, there are almost five times as many RCTs with exclusively adult participants compared with RCTs with exclusively child participants in data up to 2004 (74) and ongoing challenges despite ongoing efforts to increase the inclusion of paediatric populations (25). In studies that include both adult and child participants, data is often presented without separation by age groups and without subgroup analysis for children. This often limits conclusions for both safety and efficacy in this age group(75).

Even when children are included in research, it is often not the whole childhood population of neonates through to adolescence (10). Trials are needed in all ages due to the changing physiology during growth and development. For example, the pharmacokinetics of some therapies, such as paracetamol, vary significantly between neonates, children, and adults (76) and dose calculation needs to take into account maturation of enzymes involved in metabolism and clearance. Likewise, biological markers that may be used to measure therapeutic response vary with age, for instance urea and creatinine are high in newborns and decline with maturation, later rising again in

older age(77). Such age-related differences mean studies that incorporate only a partial range of ages or fail to report data by age may obscure clinically significant results for particular age groups.

The relative paucity of high-quality research involving children is especially acute in the field of pharmacology, as even where drugs are likely to be of significant relevance to paediatrics- such as those for treating Human Immunodeficiency Virus (HIV) and diabetes mellitus- they are often not licensed for use in children (78). Studies have shown that at least a quarter, and up to 90%, of all children treated in hospitals across Europe receive unlicensed and off-label drugs (79). Efforts to address this include the European Union (EU) regulations passed in 2006, which made it mandatory to evaluate all new medicines, or new indications for existing medicines, for potential paediatric use and sought to incentivise paediatric drug development research (80).

The 10 year report to the European Commission showed that while there had been improvement, including authorisation of over 260 new medicines between 2007-2016 and over 131 completed paediatric investigation plans by the end of 2016, there remained substantial issues with important areas, such as paediatric oncology, remaining vulnerable to continued neglect compared to adult oncology research (81, 82). This is in spite of valuable progress that has been made in paediatric oncology, which has benefitted greatly from increased research activity in recent years and is a subject of paediatric study that has high rates of success in recruitment (10). There are other areas where the relative absence of paediatric evidence has resulted in potentially significant harm and certainly controversy, for example the treatment of adolescent depression and reported increased risk of suicidality (74). In addition to child and adolescent mental health, paediatric neurology and neonatology have been highlighted as disadvantaged by neglect compared to adult medicine (73).

1.5.2 Perceived barriers to research involving children

A number of possible explanations have been proposed for the under-representation of children in research, including economic, practical, and ethical issues (9, 83).

The phenomenon may in part be attributable to funding biases driven by governments and independent funding organisations towards greater funding opportunities in adult research (9).

The disparity in funding is influenced by marketing considerations including the higher potential profitability of products and burden of disease in the adult population. Serious illness is rarer in children than adults, meaning that there are often smaller pools of potential participants available to trials targeting specific diseases in children compared with adults. Likewise, if an effective treatment is developed, there is ultimately a smaller market for the use of that treatment, which has led to children being described as "therapeutic orphans" since the phrase was coined in the 1960s (84).

There are movements to counter this bias, with some governments and international agreements providing specific financial incentives for pharmaceutical companies to include children in their research (80, 83, 85). Support is also distributed through research networks (86) and child-focussed independent groups, including charities, providing alternative funding—my own research having been supported by the Derbyshire Children's Research Fund.

In practical terms, research that involves children may be more challenging to design and undertake because of the need to accommodate the range of cognitive and emotional development of child participants, and design outcome measures that are meaningful and measureable across different ages (87).

There is also a perception that ethical issues surrounding paediatric research are more challenging than in adult research(88). Most guidelines internationally require researchers to gain both parental consent and, where children are capable of giving it, the child's assent(73). This supports the principle asserted in Article 12 of the United Nations Convention on the Rights of the Child that every child has a right for his or her views to be heard (89).

The Nuffield Council on Bioethics 2015 report on children and clinical research proposed three paradigms, or example cases, of children's capacity with respect to decision-making in research (90):

1. Some children and young people are not able (at a given time) to give their view on their participation in clinical research. This example includes all babies and very young children, and some older children at certain times, for example if very unwell or unconscious.
2. Some children and young people are not able (at a given time) to make independent decisions about their participation in clinical research but are able to form and express views, to varying degrees of sophistication.
3. Some children and young people potentially have the ability, in terms of both intellectual understanding and emotional maturity, to make their own decisions about participation in clinical research while still being considered minors in some legal capacity.

The report highlighted that many children will progress from the first through the second to the third of these paradigms with time and development, while some children may never progress past the first or second case, for instance due to developmental delay. Indeed, the progression is not necessarily always towards more capacity, as illness or injury may mean that a child moves from being more able to less able to make or express decisions. The authors emphasised that assessment of a child's abilities in relation to these paradigms should not be made on the basis of a diagnostic or age label but according to the individual child's development and maturity in the context and at the specific time of decision-making.

In order to gain informed assent, it is therefore necessary to develop information resources that are accessible to children of varying ages, literacy levels, and cognitive ability. There are a number of strategies that can be used to increase participants' engagement with written material, and it is important to consider parental literacy as well as the child's developmental stage and literacy. Strategies include improving the readability of educational materials by ensuring that they use simple language, are short, clearly organised, and illustrated. Other strategies are the provision of concurrent verbal information with the written information. These methods have been shown to improve understanding, although they do not entirely mitigate the effects of low literacy(91). Wider involvement of parents, young people and children in study design is strongly encouraged as part of a general move to increasing public engagement in research; this

has the dual aim of ensuring ethical and responsible research by empowering lay participants and improving the quality of research by optimising study design (92).

For younger children or those with developmental delay such that they do not progress past the first or second paradigms highlighted in the Nuffield Council on Bioethics report, it is not possible to gain meaningful assent, yet research in neonates and other children is still crucial to ensuring high-quality and evidence-based treatments are available for them. Neonates present unique challenges, for instance their low blood volumes mean that they are vulnerable to anaemia due to blood sampling, limiting the volume of permissible research-related blood sampling (83).

A "best interests" approach allows experimental treatments with reasonable probability of benefit to participants to proceed in the same way as any clinical therapy for the child, but in the case of neutral or non-beneficial research (for instance, where a child is included as a healthy control), there are some schools of philosophy that would deem all such research completely impermissible. This is reflected in European law, where research is only permitted when direct benefit is expected for the child (81, 82). This necessitates a close consideration of the balance between risk and benefit, as well as considering the balance between risk and benefit in the context of a child's available alternatives (83). In these areas, others argue that collective benefit, altruism, and compensation to the parents or child are morally relevant and influence the acceptability of non-beneficial (but non-harmful) research (93).

However, it should perhaps be argued that similar challenges exist in adult medicine, where a common level of education and literacy cannot be assumed across a broad field of potential participants, and clinical outcomes may need to be set in the context of patients' baseline activities of daily living. This would seem particular pertinent in older adult medicine, and it is relevant to note that adults aged over 65 are also relatively under-represented in clinical research(94-96).

In the case of literacy, the design and accessibility of information involved in consent is extremely important in adult medicine as well as paediatrics, given that more than a quarter of adults in the UK have low literacy or numeracy skills, meaning that they

"struggle with basic quantitative reasoning or have difficulty with simple written information" (97).

Equally, when considering the developmental stage of a child in terms of the paradigms presented by the Nuffield Council on Bioethics report, it must be recognised that such challenges are faced in many areas of adult research including research involving patients with cognitive impairment or dementia(98, 99), who may lack capacity to consent, and research into emergency and trauma medicine where patients may have altered levels of consciousness affecting their ability to consent(100). As in paediatric research, in these areas it is usual that consent by proxy is sought. In the case of paediatric participants this is usually from parents or guardians, but it remains important to consider the participant's views and interests throughout.

In summary, the ethical challenges present in paediatric medicine exist across the spectrum of adult research too, but are possibly more visible, in part due to the appropriate high level of attention that is paid to issues around capacity and consent. There certainly is a challenge, however, in carrying out research with meaningful application across the wide range of paediatric medicine, from neonates to adolescents.

1.5.3 Rational Prescribing for Children

Rational prescribing for children faces the challenge of a frequently limited evidence base to guide clinical decision-making and has been described as an "evidence based desert" (page 1465 (101)).

Due to the under-representation of children in research, discussed in Section 1.5.1 (page 16), it could be argued that rational prescribing for children is more challenging due to there being less available evidence to guide decision-making and the necessary use of medicines for unlicensed off-label indications in children (78). In addition, children present additional challenges to high-quality prescribing, for example the need to account for growth and maturation, affect not only bodyweight and weight to surface area ratios but also drug absorption, maturation of metabolic pathways, and drug distribution (5).

There is no published review of rational prescribing tools for children. However, there are a number of areas of prescribing for children that have been widely studied and are known to be vulnerable to inappropriate prescribing. Examples of misprescribing, overprescribing and underprescribing have been demonstrated.

Misprescribing is a broad area of irrational prescribing that includes inappropriate dosing, drug interactions, and clinical indication (15). This is an area where children may be particularly vulnerable due to the need for age- and weight-based dosing calculations, which are an added opportunity for inappropriate prescribing as compared to adult medicines with a standard dose (4). A study of antiretroviral therapy for children with HIV found that up to 62% of the time, children were prescribed inadequate doses (less than 90% of the recommended dose) (102). The study identified three key factors leading to misprescribing. The first was incorrect dose guidance at initial licensing, inconsistent dosing due to guidelines given dose by both weight and surface area, and inadequate or delayed adjustment of doses for ongoing growth. This highlights the particular challenges of chronic disease management in children, where ongoing metabolic maturation and growth necessitate regular dose adjustments (5).

A 2019 statement from the European Academy of Paediatrics identified a number of concerning areas where overtreatment is thought to be common practice across Europe, including the use of proton-pump inhibitors for gastro-oesophageal reflux (GORD) in infants (103). While these drugs are sometimes indicated to manage GORD that causes distress and may have an impact on feeding and growth, they are often prescribed with little evidence of true GORD on the basis of common feeding problems like vomiting or crying (104). This is an area where overtreatment has clear potential for harm as long-term use of acid-suppressing medications for GORD in infants is associated with a number of adverse effects, including nosocomial infections, vitamin B12 deficiency, hypomagnesaemia, and bone fragility (105).

Pain management has been an area of historical undertreatment of children, to the extent that it was previously believed neonates did not feel pain and were routinely operated on and managed in intensive care with little or no sedation (106). There continues to be evidence of undertreatment of pain in children due to a number of factors, including clinician fear of adverse effects, difficulty in assessing pain in younger age groups,

underdosing, and time constraints in emergency care exacerbated by the difficulty in securing patient compliance (107-109).

Despite the evidence of significant irrational prescribing in paediatrics, the use of rational prescribing tools to study the phenomenon is not yet widespread as it is in adult medicine. A systematic review of adult rational prescribing assessment tools was conducted in 2014 (60), this is discussed further in Chapter 2. Prior to my work there had been no such review of rational prescribing tools for children.

1.6 Summary

Rational prescribing is an area of research with the potential to have significant economic, social, and health impact. Irrational prescribing costs institutions and systems in unnecessary or needlessly expensive drugs, and in the cost of care for any subsequent morbidity that results from suboptimal treatment of patients or direct adverse reactions to superfluous medications. Patients and communities benefit from high-quality prescribing and it is essential to be able to identify good prescribing in order to recognise targets for improvement, to study interventions, and to compare systems, institutions, or regions.

The use of medicines in children has historically been under-researched and consequently paediatric pharmacology suffers from a paucity of strong evidence to support practices, with many and sometimes (such as in neonates) the majority of medications being used in an unlicensed or off-label manner. This illustrates the importance of further work examining the use of medicines in children to facilitate improvement.

1.7 Rationale for the thesis

This thesis is presented in six chapters, including this introductory chapter.

1.7.1 Aims of the thesis

The aim of the thesis was to identify any existing rational prescribing tools for studying irrational prescribing for children; to appraise existing tools; in the absence of an existing tool, to develop rational prescribing criteria that could be used across paediatric practice in the UK; and to validate the novel tool in the study of rational prescribing for children.

1.7.2 Objectives and outline

The objectives of the thesis are to:

Chapter 2

1. Conduct a systematic review of databases of medical, allied healthcare and pharmaceutical research to identify existing paediatric rational prescribing tools.
2. Analyse the characteristics of existing paediatric rational prescribing tools including the methodology of development, breadth of clinical application, and validity.

Chapter 3

1. Modify an identified paediatric rational prescribing tool designed for use outside the UK to enable its application to UK paediatric practice.

Chapter 4

1. Validate the new tool in UK paediatric practice in order to assess its usefulness to identify irrational prescribing.
2. Evaluate the patterns of irrational prescribing identified by the new tool.

Chapter 5

1. Assess the repeatability of the new tool in an inter-rater and intra-rater reliability study.

Figure 1-4 below presents an overview of how each chapter achieved the objectives of the thesis.

Chapter 2	The **systematic review** of rational prescribing tools for children identifies two extant tools for assessing rational prescribing for children. Two tools, POPI and PIPc, are discussed in detail in terms of their development, characteristics, and any existing research using the tools.
Chapter 3	The chapter on **modifying the POPI criteria** discusses the original POPI tool and describes the methods and results of identifying and applying modifications that were necessary to utilise the tool in a UK setting. The resulting POPI UK tool is presented.
Chapter 4	A study was conducted to **clinically evaluate the POPI UK criteria**, in order to assess its usefulness in a clinical setting. The methodology and results of this evaluation of the POPI UK tool are presented.
Chapter 5	A further study to **test the precision of the POPI UK criteria** was conducted. The methodology and results of inter- and intra-rater testing of the POPI UK criteria are presented and are put in context with comparison to other rational prescribing tools.
Chapter 6	The **conclusions** of the above research are summarised and discussed. The three paediatric rational prescribing tools described in the work are compared. The impact of the work is considered and future directions for further research are identified.

Figure 1-4: Overview of thesis

2 Systematic review of paediatric rational prescribing tools

2.1 Introduction

The use of criteria lists as tools to quantify rational prescribing in adult medicine has been discussed in chapter one. As described in chapter one, there are a number of potential benefits to rational prescribing tools. By enabling quantification of the quality of prescribing, assessment tools facilitate research into interventions aiming to improve prescribing by allowing before and after measurements of quality. Furthermore, explicit criteria enable objective measurement of prescribing, which allows research to reliably compare prescribing in different settings, between different institutions, nationally and internationally. This facilitates deeper research into root causes of problematic prescribing, or excellent prescribing, and fosters collaboration between different groups (64).

As discussed in Chapter 1, Kaufmann et al's 2014 systematic review of rational prescribing tools for adults identified 46 published tools (60). Of these, 22% did not have a stated targeted population, while 78% were specifically targeted to prescribing for older adults.

One possible reason for the high number of tools targeted to older adults is that some authors have identified them as being particularly vulnerable to irrational prescribing due to a variety of factors, including frequent existence of co-morbidities, polypharmacy, care taking place in a number of different settings, and the effect of ageing on the selection of appropriate medications (15, 110). Many similar challenges exist in paediatric medicine, with well-recognised developmental changes in physiology and metabolism having significant impact on pharmacokinetics in children of different ages (5) In addition, children may be prescribed medications in a number of different settings, including general practice, undifferentiated emergency departments, walk-in centres, paediatric wards in district general hospitals, and specialist paediatric hospital settings. This means

that prescribers with varied levels of paediatric experience and expertise may be responsible for prescribing.

Kaufmann et al explicitly excluded tools targeted to children in their 2014 review (60). The objective of this systematic review of paediatric rational prescribing tools was to produce a comprehensive overview of current tools available to measure rational prescribing in children. It also sought to characterise the tools in terms of methodology of development, content and scope (in terms of included drug or disease groups), and aspects of rational prescribing measured.

The systematic review reported in this chapter has been peer-reviewed and published (111), see Appendix 1. This systematic review was registered with PROSPERO, CRD42016049402.

2.2 Aims

The primary outcome of the systematic review was to identify all published paediatric rational prescribing tools. The secondary outcome was to identify the types of rational prescribing and drugs or drug groups included in these tools. The population of children was defined as aged less than or equal to 18 years.

2.3 Methods

The systematic review was designed in accordance with the PRISMA checklist (112), only excluding irrelevant items. Excluded items were those specific to reviews of interventional research (risk of bias assessment in items 12, 15, 19 and 22) and to statistical analysis in meta-analyses (13, 16 and 21). The completed PRISMA checklist with page numbers given for this thesis is shown in

Table 2-A.

Table 2-A: PRISMA checklist from Moher et al, 2009 (112).

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	26
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	xii
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	27
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	27
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	26
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	27-28
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	28
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	29
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	29
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	29-30
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	30
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	X
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	X
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	30
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	X
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	X
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	30-32

Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	33
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	X
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	34-41
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	X
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	X
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	34-41
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	42
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	52-53
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	54
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	i

2.3.1 Eligibility criteria

The search was designed to identify articles describing tools to evaluate rational prescribing for children, including updated or modified versions of established tools, adaptations of previously published tools, or the new development of tools. Eligible tools were those targeted at prescribing for children aged less than or equal to 18 years. Tools targeted at prescribing for adults or without a specified target patient group were not eligible. Indicators that did not identify individual prescriptions as rational or irrational but relied upon population datasets to suggest appropriate levels of prescribing (e.g. as percentages) were also not eligible.

An age range of 0-18 was selected as the most inclusive definition; 0-16 or 0-17 years are alternative definitions which have been used in some texts but not others, and these therefore risks inappropriately excluding some relevant tools.

Inclusion criteria were: articles describing tools targeted at evaluating the rationality or appropriateness of prescriptions for children aged less than or equal to 18 years, updated and revised versions of previously published tools, and including tools limited to specific drugs, drug groups, diseases or disease groups.

Exclusion criteria were: tools targeting adults, tools without specified target patient groups, indicators that assess rates or percentages of prescription types in a population, articles describing a validation study of a previously published tool, educational interventions aimed at improving prescribing, and guidelines describing recommended prescribing.

2.3.2 Search strategy

The search was conducted in four databases in order to attempt to capture relevant medical, allied healthcare and pharmaceutical research. These were: Medical Literature Analysis and Retrieval System Online (MEDLINE), Embase, International Pharmaceutical Abstracts (IPA) and the Cumulative Index of Nursing and Allied Health Literature (CINAHL). Databases were searched on 23rd February 2016 from their earliest records possible, i.e. until 2016 week 8. The same search strategy was subsequently used to update the review on 29th July 2019 until 2019 week 31.

2.3.2.1 Search terms

Search terms to capture studies including children were derived from the recommended search strategy described by Kastner et al 2006 (113), as these have demonstrated high sensitivity. The MeSH term "inappropriate prescribing" was introduced in 2011 and was previously incorporated in the broad term "Drug therapy". Search terms for rational prescribing were derived from the systematic review of adult rational prescribing tools by Kaufmann et al 2014 (60), as this review had very similar aims to my own search (for adult rather than paediatric tools). Therefore the combined terms were:

(inappropriate prescribing or suboptimal prescribing or inappropriate medication or inappropriate practices or drug prescriptions or Medication Appropriateness Index) and (child* or children* or p*ediatric* or infant* or adolescent*).

The terms were applied to each database, results collated and duplicates removed prior to screening.

2.3.3 Study selection

All potentially relevant publications were screened by the author by title and abstract and articles that met the exclusion criteria were excluded. The remaining articles were retrieved in full. Full-texts were examined by the author and a research nurse (JA) who performed independent full-text screening, independently assessing articles according to the inclusion and exclusion criteria. In the updated search in 2019, the full-text sceening was completed by the author and a doctor (TM). After this process, any articles without consensus were resolved by discussion and mutual agreement.

2.3.4 Data collection

The following proforma was designed to record data from included articles. Aspects of inappropriate prescribing were divided, as has previously been described, into misprescribing, underprescribing, and overprescribing, with further categories of misprescribing adapted from the results of Kaufmann et al 2014 (60). This is shown in Figure 2-1.

Rational prescribing tool	Development method	Healthcare setting	Patient group	Aspects of inappropriate prescribing								
				Misprescribing							Overprescribing	Underprescribing
				Drug choice	Dosage	Duration	Duplication	Drug-disease	Drug-drug interaction	Drug-food interaction		

Figure 2-1: Data collection proforma, adapted from Kaufmann et al (60)

2.4 Results

2.4.1 Original search results

The search performed in 2016 produced 1,462 potentially relevant publications in 2016. One hundred and seventy-two duplicated articles were removed, 1,290 articles were screened by title and abstract and 1,143 were excluded. Four full-texts were unavailable online, from University library resources, and from the British Library. Both reviewers then reviewed 143 full-texts and 140 were excluded.

In terms of reasons for exclusion of the 140 excluded full-texts, 110 did not describe rational prescribing tools, 21 did not relate to children, 8 were not related to rational prescribing, and one reported a validation study of a previously published tool.

In the case of the four full-texts that were unavailable the abstracts suggested that these articles would not meet inclusion criteria, although this could not be determined with certainty. Three articles met the inclusion criteria. Bibliography mining of the included articles did not produce any further relevant articles. This is depicted in the flowchart in Figure 2-2.

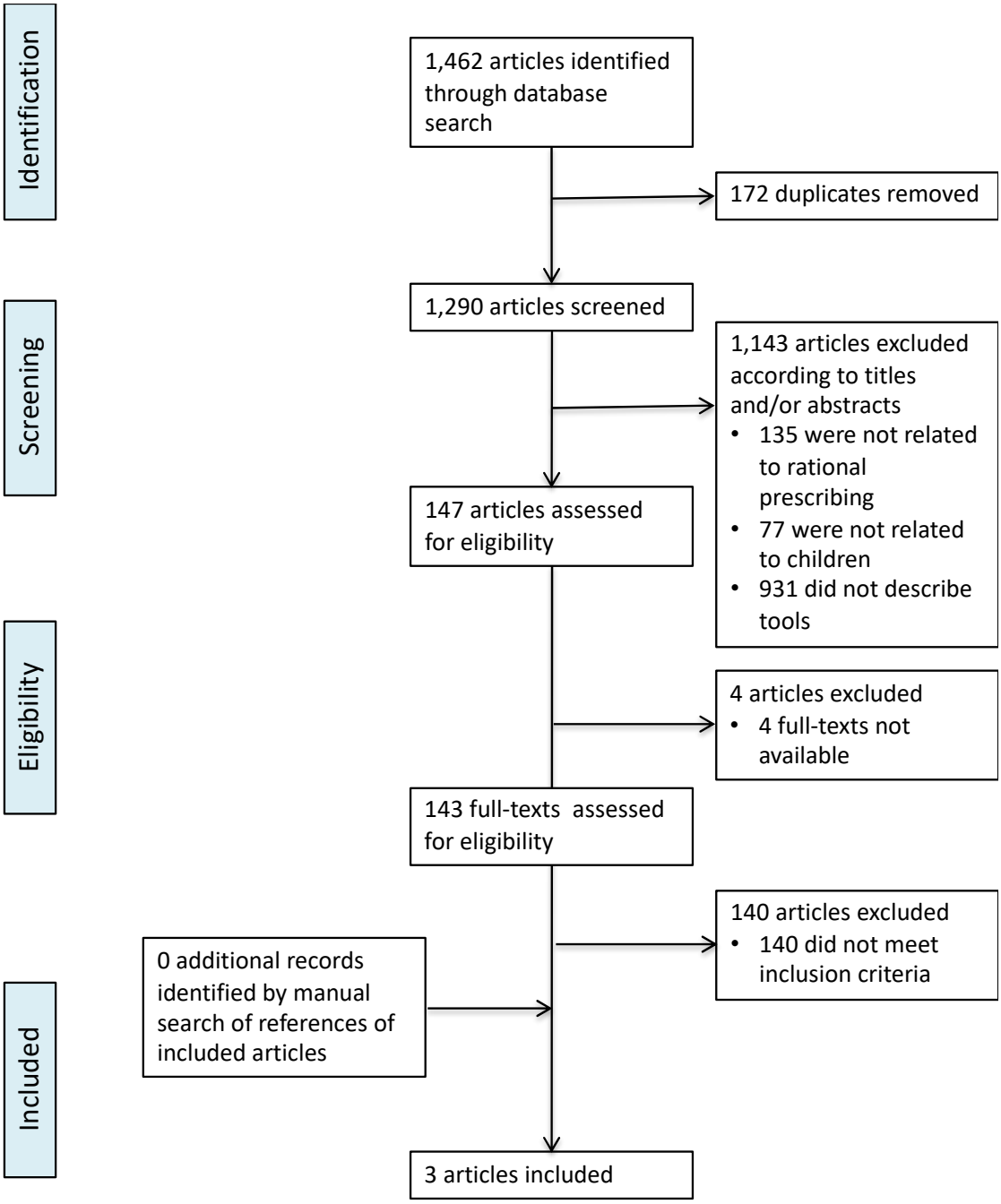

Figure 2-2: Flowchart of screening process for original search in 2016.

Figure 2-2 is adapted from*:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement.* PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

2.4.2 Updated search results

The literature search was updated in June 2019 to ensure currency of the findings. The updated search identified 680 potentially relevant new publications since the search in 2016. Sixty-two duplicated articles were removed. Of the 618 articles screened by title and abstract, 593 were excluded, 25 full-texts were reviewed by both reviewers and 23 were excluded. Two articles met the inclusion criteria. Bibliography mining of the included articles did not produce any further relevant articles. This is depicted in the flowchart in Figure 2-3.

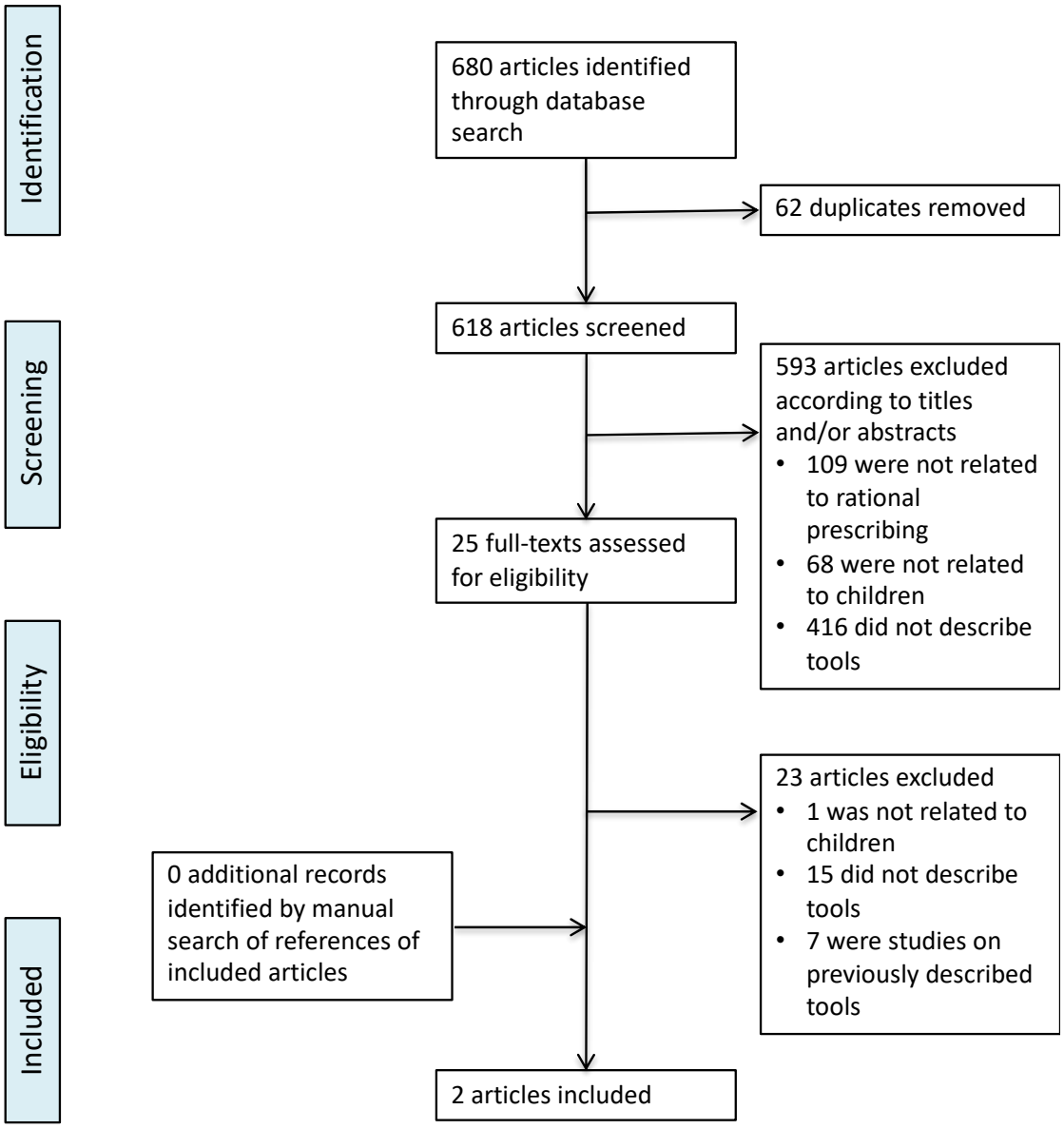

Figure 2-3: Flowchart of screening process for updated search in 2019.

Figure 2-3 is adapted from*:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement.* PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

2.4.3 Rational prescribing tools identified

In total, five relevant articles were identified, relating to three paediatric rational prescribing tools: POPI, PIPc and POPI UK. These are shown below in Table 2-B.

Table 2-B: Included articles describing paediatric rational prescribing tools.

Included article	Rational prescribing tool	Year	Language	Country
POPI; pédiatrie: omissions et prescriptions inappropriées [POPI: A tool to identify potentially inappropriate prescribing practices for children.] (114)	POPI	2011	French	France
POPI (Pediatrics: Omission of Prescriptions and Inappropriate prescriptions): development of a tool to identify inappropriate prescribing (115)	POPI	2014	English	France
Validation par consensus d'un outil d'identification de prescriptions inappropriées en pédiatrie (POPI) [Consensus validation of a tool to identify inappropriate prescribing in paediatrics (POPI)] (116)	POPI	2016	French	France
PIPc study: development of indicators of potentially inappropriate prescribing in children (PIPc) in primary care using a modified Delphi technique. (117)	PIPc	2016	English	Ireland and UK
Developing paediatric rational prescribing criteria. (118)	POPI UK	2017	English	UK

The initial systematic search identified three relevant articles, all relating to a single tool: POPI (English: Pediatrics: Omissions of Prescriptions and Inappropriate Prescriptions; French: *pédiatrie: omissions et prescriptions inappropriées*) tool (114-116). All three included articles are very similar, two in French and one in English, and describe the process of developing the POPI tool. All three articles have the same first author, S. Prot-Labarthe, with various other authors contributing to each. The earliest, from 2011, is a letter describing the tool. This does not detail all the criteria, only giving nine examples. The 2014 and 2016 articles are English and French language respectively and both report the consensus validation of the tool and give full details of the criteria.

For the purposes of clarity, from this point onwards reference to the POPI criteria is specifically to the wording and numbering in the English 2014 publication unless otherwise stated. The differences between the versions are described in Section 2.5.4 (page 55).

Two additional relevant articles were identified in the 2019 updated search, each relating to separate tools. One of these was a publication related to the novel tool developed within this thesis, describing the POPI UK tool as discussed in Chapter 3 (118). As this publication was a product of this thesis, it is not further analysed within this chapter but can be viewed in full in Appendix 2.

The other article related to the development of a rational prescribing tool for evaluation of paediatric prescribing in primary care, indicators of potentially inappropriate prescribing in children (PIPc) (117). This was developed in Ireland and the UK and was published in September 2016.

2.4.4 Characteristics of POPI

The POPI tool comprises 105 criteria (80 PIMs and 25 PIOs) categorised by the authors according to broadly grouped clinical conditions: diverse illnesses, digestive problems, ENT-pulmonary problems; dermatological problems; and neuropsychiatric disorders. The groups are further subdivided into particular symptoms or conditions. The criteria

cover a range of aspects of inappropriate prescribing, including overprescribing, underprescribing, and almost all areas of misprescribing except drug-food interactions. No specific target setting for the tool's application is identified, although the majority of guidelines and all experts in the panel were French.

The POPI tool is not specifically limited to use in any particular clinical setting. The propositions were selected from paediatric health problems in the general population and as causes for hospitalisation, suggesting the tool would be relevant to both primary and secondary care. However, no primary care specialists or general practitioners were involved in the development of the tool. The paediatric population targeted by the tool as a whole is not defined by the authors but some propositions are age-specific, for instance pharmacological treatment for attention deficit disorder is described as inappropriate "before age 6 (before school)" (page 7, (115)) and topical 0.1% tacrolimus is considered inappropriate for atopic eczema "before 16 years of age" (page 6, (115)).

The criteria of the POPI tool cover a wide range of types of irrational prescribing, including all three categories of underprescribing, overprescribing, and misprescribing. Underprescribing is specifically identified in the tool as omissions. The inappropriate prescription propositions include some examples of overprescribing and misprescribing. Further examples of types of irrational prescribing are listed in Figure 2-4.

Aspect of rational prescribing	**Example of related inappropriate prescription or inappropriate omission of prescription proposition from POPI (theme)**
Drug	Nitrofurantoin used as a curative agent in children under six years (Urinary infections)
Dosage	Oral solutions of ibuprofen administered in more than three doses per day using a graduated pipette of 10mg/kg (Pain and fever)
Duplication	The combined use of two NSAIDs (Pain and fever)
Duration	The application of benzyl benzoate… for periods longer than eight hours… (Scabies)
Drug-drug interaction	Isotretinoin in combination with a member of the tetracycline family of antibiotics (Acne Vulgaris)
Drug-disease interaction	Loperamide in the case of invasive diarrhoea (Diarrhoea)
Overprescribing	Antibiotic treatment for a sore throat, without a positive rapid diagnostic test… (ENT infections)
Underprescribing	Omission: Oral rehydration solution (Diarrhoea)

Figure 2-4: Aspects of rational prescribing included in the POPI tool

2.4.5 Characteristics of PIPc

PIPc comprises twelve criteria of PIMs and PIOs, categorised according to four physiological systems: respiratory, gastrointestinal, dermatological, and neurological.

Seven statements describe PIMs with potential overprescribing or misprescribing practices, five statements relate to PIOs. PIPc is designed specifically for use in primary care in Ireland and the UK.

By contrast to POPI, the PIPc is by design a tool that is simpler to apply and that requires minimal clinical information about a patient. The only clinical diagnosis specified in the tool is a presumed diagnosis of asthma in two criteria. In the absence of clinical information, this diagnosis is presumed on the basis of the prescriptions described, e.g., "An inhaled short-acting ß2 agonist should be prescribed to children under 5 years who are also taking a leukotriene receptor antagonist for presumed asthma" (page 8 (117)).

It should be noted that the authors of PIPc use the term "indicators" to describe and name the tool, however the statements all meet the definition of rational prescribing criteria as discussed in Section 1.4.1 (page 12). The authors use the terms interchangeably: "prescribing criteria (indicators)" (page 1, (117)). In this thesis the terms are used distinctly to facilitate greater nuance in some areas of discussion.

The PIPc is a tool that has been designed specifically for application in a primary care setting. Unlike the POPI tool, it was developed with the intention of being applicable without access to clinical information, meaning that it can be used to evaluate data from large previously collected prescribing databases where clinical information is often either omitted or concealed.

The authors of the PIPc defined their paediatric population as children less than 16 years of age. The age at which young people transition from paediatric to adult healthcare services can vary depending on health needs, social circumstances such as attendance in full-time education, and availability of specialist services (119). In addition, to the specified population for the tool, some criteria further specify particular age ranges, for example, "Loperamide should not be prescribed to children under 4 years" (page 8, (117)); this particular criterion fits with the licensing restriction of loperamide as recorded in the BNFc (120).

As shown in Figure 2-5, the PIPc criteria describe almost as broad a range of types of potentially irrational prescribing as POPI despite having far fewer criteria. An example

criterion for each aspect of irrational prescribing described in the PIPc criteria is shown below in Table 2-C.

Table 2-C: Aspects of irrational prescribing included in PIPc

Aspect of rational prescribing	Related inappropriate prescription or inappropriate omission of prescription proposition from PIPc (theme)
Drug choice	Tetracyclines should not be prescribed to children under 12 years (Dermatological)
Drug-disease interactions	An inhaled short-acting ß2 agonist should be prescribed to all children who are prescribed two or more inhaled corticosteroids for presumed asthma (Respiratory)
Drug-drug interactions	Domperidone should not be prescribed concomitantly with erythromycin (Gastrointestinal)
Overprescribing	Sedating antihistamines should not be prescribed to children under 2 years (Neurological)
Underprescribing	Children under 12 years who are prescribed a pressurised metered-dose inhaler should also be prescribed a spacer device at least every 12 months (Respiratory)

2.4.6 Development of POPI

The methodology used to develop the POPI tool was designed to closely match the development of STOPP/START criteria, according to the authors (page 7, (115). As discussed in Section 1.4.1 (page 12), the STOPP/START criteria were developed in Ireland as a rational prescribing tool for use in older adult medicine (121) comprising two lists; the "STOPP" list of medications that are inappropriate and should be stopped, and the "START" list of potentially inappropriate omissions. They were designed to update the widely used Beers Criteria (62), as it listed a number of medications not in use in Europe and at the time had a number of out-dated criteria. In the STOPP/START tool, the authors chose to structure their criteria according to physiological systems in order to mirror the usual organisation of drug formularies. The propositions of STOPP/START were finalised via an eighteen-member panel two-round Delphi consensus where agreement was determined according to the Kappa (κ) statistic for agreement and participants were able to suggest additional criteria if desired (122). The propositions of

POPI were determined by a similar sixteen-member panel two-round Delphi consensus approach.

The authors aimed to structure POPI around approximately 100 propositions classified according to biological system and divided into PIOs and PIMs. The number of propositions was chosen as "a good compromise between the number of major biological systems to explore, the number of items in the geriatric lists and the maximum number of items compatible with a tool easy use" (page 2, (115)). The authors then compiled a list of health problems that are frequently encountered in paediatric practice, according to frequency in the general population (source not specified), prevalence (derived from data from the French National Insurance Fund for Employers for long term conditions), and frequency as cause for hospitalisation (per French hospital medico-administrative records). The authors identified health problems from this list, referred to as themes, that would either require drug intervention or where pharmacological intervention would be considered inappropriate.

For each selected theme, the authors then conducted a literature search (unpublished) to identify recommendations on management. There was a requirement for recommendations to be evidence-based, but the authors did not specify the level of evidence. Only recommendations published after 2000 were accepted, and these were then weighted by date of publication. Accepted sources of recommendations were the French Health Products Safety Agency (*Agence Française de Sécurité Sanitaire des Produits de Santé)*, the French National Authority for Health (*Haute Autorité de Santé Française*), the French Society for Paediatricians (*Sociétè Française de Pédiatrie*), the American Academy of Pediatrics (National Guideline Clearing House), and the National Institute for Health and Clinical Evidence Cochrane Library. They also used the MEDLINE database to search for examples of medication error and inappropriate prescription (search strategy unpublished). The selection of French versus international guidelines was not explored further in the report describing POPI's development.

Subsequently, the propositions were then validated by a two-round Delphi consensus. Sixteen experts, including pharmacists and paediatricians, were included, of which ten responded to both rounds of the Delphi consensus. The process of recruitment of

experts is not explicitly stated, only that most pharmacists were members of the French Society of Clinical Pharmacy and most paediatricians were members of the French Society of Pediatricians. Propositions were rated by panellists on a nine-point Likert scale for agreement; additionally the panellist experts were invited to make free text comments and to suggest dosage, frequency or duration of therapies if they could provide evidence-based sources to support the suggestions. Propositions with a median score in the upper tertile (i.e. 7-9 points) with agreement above 65% were retained, modified according to comments, then sent out in the second round. Propositions with a median score in the upper tertile with agreement above 75% were then retained.

2.4.7 Development of PIPc

PIPc was also developed by a two round Delphi consensus method. Initial propositions were selected via a systematic literature search for previously developed indicators for paediatric prescribing with the criteria as shown in Table 2-D, adapted from Barry et al, 2016 (117).

Table 2-D: Inclusion and exclusion criteria of indicators selected for PIPc

Inclusion criteria	describe hazardous or ineffective prescribing
	describe prescribing outwith best practice or current guidelines
	apply to children < 16 years
Exclusion criteria	medications unavailable in the study setting
	criteria that require clinical information
	criteria containing rarely used medications

A steering group from Ireland and Northern Ireland, comprising academic and clinical general practitioners (GPs), academic and clinical pharmacists, a pharmacoepidemiologist/statistician, and a postdoctoral researcher, assessed each indicator. Indicators that were not felt to meet the above criteria were excluded. In some cases, indicators were modified to meet the need for criteria that could be applied without access to clinical information, for example when evaluating data from a dispensing database.

The panel for the Delphi consensus was recruited by email invitation, which was sent to 30 specialists identified by the project steering group as experts in their field. Of those invited, eighteen accepted the invitation, nine from the Republic of Ireland (three GPs, three paediatricians, and three pharmacists) and nine from the UK (three GPs, three paediatricians, and three pharmacists). Web-based questionnaires were sent to panel members containing proposed indicators, rationale for their inclusion, and relevant evidence such as national or international guidelines. Panellists indicated level of agreement with the inclusion of indicators on a five-point Likert scale and items with consensus among the panel were accepted. Items without consensus were reviewed and either rejected or revised and presented in the second questionnaire. After the second round, any criteria without consensus were rejected.

The literature search identified 47 potential criteria, of which 31 were removed by the steering group after assessment against the inclusion and exclusion criteria listed in Table 2-D. Sixteen indicators were presented in the first round of the Delphi process and nine items had consensus for inclusion, with seven being reviewed. Two of the seven were rejected on the basis of comments from the Delphi panel and five were amended and presented in the second round. Three of these reached consensus while two were again rejected. This resulted in twelve criteria being ultimately accepted into the final PIPc.

Reasons for rejected criteria included the need for clinical information, for example in determining the appropriateness of use of very potent corticosteroids. Other criteria were rejected due to panellists commenting that on rare occasions, the described prescribing would be appropriate, for example systemic corticosteroids in children aged 5-15 years was rejected with comments such as, "*Agree unless there is a clinical indication such as flare of juvenile rheumatoid arthritis"*.

The twelve accepted criteria came within four clinical categories: respiratory system (six criteria), gastrointestinal system (two criteria), dermatological system (two criteria), and neurological system (two criteria).

2.5 Discussion

This systematic literature review identified two paediatric rational prescribing tools, the PIPc and the POPI tool.

2.5.1 Comparison of rational prescribing tools

The PIPc is designed for use in primary care settings, while the POPI tool is developed for application in a range of settings and has already been tested in emergency department and community pharmacy paediatric practice (123). This breadth of settings where POPI can be applied is similar to the range of settings in which rational prescribing tools for older adults are used, which include residential or nursing homes (Sloane (124)), hospitals (Oborne's (125)), and primary care (NORGEP (126)).

Both paediatric tools identified cover a range of types of rational prescribing, the POPI tool covering a particularly broad range. By comparison, the majority of adult rational prescribing tools identified by Kaufmann et al (60) had a narrower focus. Kaufmann et al described twelve categories of irrational prescribing, listed below.

- Drug choice
- Dosage
- Duration of therapy
- Duplication
- Drug-drug interaction
- Drug-disease interactions
- Drug-food interactions
- Overprescribing
- Underprescribing
- Cost effectiveness
- Non-adherence
- Alternative therapies

Of the 46 adult tools identified by Kaufmann et al, the median number of categories of rational prescribing covered by each tool was 4.5, similar to the PIPc, which covers five aspects. However, four tools did cover eight or nine categories of prescribing, comparable to POPI, which covers eight.

Of the adult tools evaluated by Kaufmann et al, the majority of tools (28) were explicit, a minority (eight) were implicit, and the remaining 10 used a mixed approach. As described, PIPc was developed as an explicit tool while POPI has both implicit and explicit criteria. There are advantages to each as discussed in Chapter 1. Implicit criteria may be more accurate, as they can take into account individual patient requirements, but this may come at the cost of reliability as they are more dependent on the rater's knowledge and judgement (15). The reverse is true of explicit tools, which are less reliant on rater judgement and therefore might be expected to have greater repeatability and reliability and be less time-consuming to apply, with concomitant lower accuracy. Mixed tools therefore may stand to inherit both the advantages and disadvantages of each approach.

Defining implicit criteria as those which require information about a patient's other medications or medical history, and explicit criteria as those which only require basic demographic information and the indication for a given prescription, both POPI and PIPc are shown to be mixed implicit and explicit criteria lists.

These definitions can be illustrated from PIPc; an example of an implicit criterion is: "An inhaled short-acting B2 agonist should be prescribed to all children who are prescribed two or more corticosteroids for presumed asthma". An example of an explicit criterion is: "Loperamide should not be prescribed to children under 4 years". POPI comprises 65% implicit and 35% explicit criteria, while PIPc comprises 50% of each type, as shown in Table 2-E.

Table 2-E: Number of implicit and explicit criteria in POPI and PIPc

Tool	Implicit criteria	Explicit criteria
POPI	68 (65%)	37 (35%)
PIPc	6 (50%)	6 (50%)

In terms of structure and complexity the POPI tool comprises a relatively high number of criteria compared with many tools, although there is one published tool targeted at older adults with 392 quality indicators (not all of which relate to rational prescribing), Assessing Care of Vulnerable Adults 3 (ACOVE-3) (127). The PIPc has closer to the lowest number of criteria of the adult tools. Some of the tools detailed in the Kaufmann systematic review have as few as ten criteria, for instance the Medication Appropriateness Index (MAI) (128), also targeted at older adults. A simple count of criteria is not necessarily a useful measure of complexity, however. For example, in the case of the MAI, it is intended that all ten criteria are applied to each drug in turn, where some systems simply list medications that are contraindicated or essential.

As a result of the higher number of criteria, POPI covers a wider range of clinical conditions that are not contained within PIPc. PIPc covers four systems: respiratory, gastrointestinal, dermatological, and neurological. POPI has four category groups, each with subsidiary categories for a total of 22 categories: diverse illness (pain and fever; ; urinary infections; vitamin supplements and antibiotic prophylaxis; mosquitos); digestive problems (nausea, vomiting, or gastroesophageal reflux; diarrhoea); ear, nose and throat (ENT)-pulmonary problems (cough; bronchiolitis in infants; ENT infections; asthma); dermatological problems (acne vulgaris; scabies; lice; ringworm; impetigo; herpes simplex; atopic eczema); neuropsychiatric disorders (epilepsy; depression; nocturnal enuresis; anorexia; attention deficit hyperactivity disorder (ADHD).

The PIPc is likely to be quicker to apply and does not require the high level of clinical information required by POPI. However, it is also narrower in scope and therefore will not identify some aspects of irrational prescribing such as duplication, inappropriate drug duration, or incorrect drug dosage. As there are fewer clinical conditions included within the PIPc as compared with POPI, this may not reduce its efficacy as a screening tool in general settings but might reduce its usefulness in more specialist settings.

There are several areas of clinical practice not covered by either paediatric rational prescribing tool, for instance renal medicine, cardiology, hepatology, and endocrinology.

The characteristics of the identified tools (excluding the POPI UK tool, see Chapter 3) are summarised in Figure 2-5.

Rational prescribing tool	Healthcare setting	Patient group	Number	Aspects of inappropriate prescribing								
				Misprescribing								
				Drug choice	**Dosage**	**Duration**	**Duplication**	**Drug-disease interactions**	**Drug-drug interaction**	**Drug-food interaction**	**Overprescribing**	**Underprescribing**
POPI (114-116)	Not specified	Children	105	✓	✓	✓	✓	✓	✓		✓	✓
PIPc (117)	Primary care	Children <16 years	12	✓				✓	✓		✓	✓

Figure 2-5: Characteristics of the two identified paediatric rational prescribing tools

2.5.2 Comparison of validation of POPI and PIPc

2.5.2.1 Validation studies of POPI

One clinical validation study of POPI has been disseminated at a conference (129) and more recently published (123). This took the approach described in Section 1.4.2 (page 14) of testing whether POPI identifies any potentially inappropriate prescribing practice in clinical settings. The authors evaluated the ability of POPI to retrospectively detect PIMs and PIOs in an emergency department and community pharmacy. The reported rates of inappropriate prescriptions differ slightly between the reports. Unless stated otherwise, figures discussed will be from the more comprehensive latter publication.

A total of 23,342 prescriptions for 18,198 patients were assessed using the POPI criteria. The number of prescriptions differed significantly between settings, with 18,562 prescriptions for 15,973 patients in the emergency department group and 4,780 prescriptions for 2,225 patients in the community setting. In this report, the authors state POPI comprises 101 criteria and that only 82 applicable to patients in hospital were

applied to the emergency department setting, while only 28 that did not require an assessment of diagnosis were applied in the community pharmacy. They furthermore state that among five criteria related to analgesia and antipyrexics, only three were evaluated "due to an overwhelming number of prescriptions and their association with many diseases" (page 6, (123)). The discrepancy in the number of criteria and selective approach to using the criteria is discussed further in Section 2.5.3 (page 50).

Rates of PIMs and PIOs per prescription in the emergency department setting were 2.9% and 2.3% respectively, but 12.3% and 6.1% in the community pharmacy setting. When assessed as the proportion of patients affected, rates of PIMs and PIOs in the emergency department were 3.3% and 2.7% respectively, and 26.4% and 11.2% in the community pharmacy. The very high rate of PIMs in the community pharmacy is ascribed by the authors to the availability of medications that they report were not available in the hospital setting, such as cough suppressants.

Logistic regression was used to analyse risk factors associated with irrational prescribing as detected by POPI and in the earlier brief report the authors described that prescriptions in the community pharmacy setting and age between 2 and 6 years were both significantly associated with higher risk (129). The age range at increased risk was broadened to 0-12 years in the later report (123). The uncertain significance of the age-based risk finding is discussed in Section 2.5.4 (page 55).

As discussed in 2.3.7 Characteristics of the POPI tool, clinical information is required to rate a number of the criteria. Such criteria were excluded from the analysis of the community data. Since both datasets were evaluated used different criteria, the comparability of the identified rates of PIMs and PIOs is compromised.

The POPI tool was developed using French, American and UK guidelines but has only been validated to a limited degree, with the above study showing that it is able to detect some potentially irrational prescribing in French settings. It is not known whether it detects irrational prescribing that correlates to adverse events or patient outcomes, or whether it could be used to evaluate prescribing outside French practice.

There is also a published reliability study of the POPI tool (130). Twenty cases were selected from the dataset used for the clinical validation study and assessed by two raters familiar with the tool. Their assessment was used as a gold standard against which eleven other raters' findings were compared. The POPI tool was reported to have inter-rater reliability of 0.8 (for PIMs) and 0.71 (for PIOs). As the publication is only available abstract from conference proceedings, full details are not available. In particular, it is not made clear whether only the limited selection of POPI criteria applied in the clinical validation study were again used in the inter-rater study, which would mean the entire tool had not been tested. Accepting these limitations, the study demonstrated good repeatability despite the high complexity and mixed implicit and explicit approach of the tool. This is discussed further in Chapter 5.

2.5.2.2 Validation studies of PIPc

Although not published as a clinical validation study, the group who developed PIPc have published one study using the criteria to detect potentially irrational prescribing (131). In this study, the criteria were applied using a cross-sectional methodology to a national pharmacy claims database in Ireland, the Primary Care Reimbursement Service (PCRS). The database records pharmacy claims for medicines for eligible patients prescribed by general practitioners or transcribed from hospital prescriptions by general practitioners, with limited patient demographic data (age, gender and region). No clinical details of the patient are recorded. The study included 414,856 children aged <16 years.

The prevalence of PIMs and PIOs was reported as 3.5% and 2.5% respectively. These rates are quite comparable to those observed in the POPI study, excluding the outlying high rate of PIMs in the POPI community setting. However, the rate of PIO using all PIPc criteria was in fact 11.5% when including all criteria, as the above rates excluded one of the reported PIPc indicators.

The excluded criterion was a PIO related to a spacer device (omission of a spacer device being prescribed at least annually to children prescribed a pMDI aged <12 years). This PIO had a prevalence of 70% among eligible children. The second most prevalent PIO (failure to prescribe emollient to children who were prescribed greater than two topical

corticosteroids) will also have heavily influenced the overall rates of reported PIOs, with a prevalence of 54% among eligible children.

In their discussion of the high prevalence of PIO relating to a spacer device, the authors acknowledged that as spacer devices can be bought over-the-counter, this omission is difficult to interpret, although they did note that the devices would be much cheaper to parents if prescribed than if bought without prescription (page 5, (131)). The rate of emollient omission was not further discussed, but this criterion is equally affected by the availability of a wide variety of emollients without prescription.

Similarly, a single criterion had a large impact on PIMs and when this criterion, relating to carbocisteine, was discounted the PIM rate fell to 0.29%. The authors discussed the impact of the criterion relating to carbocisteine further. The full criterion, not listed in the clinical study but from the original publication about the development of PIPc, is "Carbocisteine should not be prescribed to children" (page 8, (117)). This was the most prevalent PIM identified in the study. The authors noted that two Cochrane reviews how found little evidence for the efficacy of mucolytics for respiratory tract infections although carbocisteine is licensed in children aged more than 2 years.

In this study, there was a significantly higher risk of PIOs in males compared to females, with no gender difference observed for PIMs (page 4, (117)). This remained the case even when the above dominating criteria (carbocisteine and spacer devices) were discounted. The specific PIOs and potential reasons for this difference are not further discussed in the study.

There is no published repeatability study of PIPc.

2.5.3 Limitations of POPI

In the reported development process of POPI, initially 108 propositions were presented to the experts. There is inconsistency between the published reports as to how many propositions were ultimately accepted into the final list. The 2014 English language report states 104 criteria were validated, whereas the 2016 French language paper states 101 criteria were validated (115, 116). Furthermore, while it is stated in the 2014 paper that

104 propositions were validated, two removed, and 102 ultimately included, in fact 105 propositions are included in the published list. In the clinical application study published in 2019, the criteria list used comprised the 101 criteria from the 2016 publication (123).

The differences between the two papers includes three cases of combining two statements into a single criterion in the 2016 (French) publication. Specifically, two propositions about desmopressin for nocturnal enuresis are combined into one and six propositions about atopic eczema are combined into four. One proposition about benzyl benzoate for scabies is omitted from the 2016 list entirely. The combined propositions are listed in Figure 2-6. Other than this, the described process and criteria are the same.

Two propositions, which related to codeine and permethrin, were removed following the consensus study due to new contraindications having been published for the use of these drugs in children, therefore it is stated that 102 propositions were ultimately validated. However, as described above, the final list of POPI criteria contained 105 propositions. In the 2016 French language publication also describing the consensus validation of the POPI tool(116), the authors state that 101 of 108 criteria were validated. For the purposes of evaluation and discussion below, the English language published list of 105 validated propositions in the 2014 report is used.

Propositions combined into a single criterion in the 2016 publication of POPI	
Desmopressin administered by a nasal spray.	Desmopressin in the case of daytime symptoms.
A strong dermocorticoid (clobetasol propionate 0.05% Dermoval, betamethasone diproprionate Diprosone) applied to the face, the armpits or groin, and the backside of babies or young children.	More than one application per day of a dermocorticoid except in cases of severe lichenification.
Topically applied 0.03% tacrolimus before 2 years of age.	Topically applied 0.1% tacrolimus before 16 years of age

Figure 2-6: Propositions combined into one criterion in 2016 publication compared to 2014 publication

Rating the POPI criteria requires access to all of a patient's prescriptions; because the tool rates omissions as well as inappropriate prescriptions, it cannot be used in whole to evaluate a single prescription for a child. Equally, it could not be used in application to anonymised retrospective prescribing data such as pharmacy reimbursement records, as such datasets do not generally show all prescriptions an individual has received, meaning that omissions could not be scored.

The authors of POPI stated that the tool comprises explicit (evidence/opinion based) criteria; however, a number of criteria contain judgement-based and patient-specific considerations. Other propositions require taking into account the patient's co-morbidities and entire medication regimen, characteristics which are usually considered components of implicit (patient-specific) criteria. For example, within the clinical category of cough a stated omission is: "Failure to propose whooping cough booster vaccine for adults who are likely to become parents in the coming months or years…" (page 5, (114)). Several propositions require the rater to make subjective judgements, including the criterion "Pharmacological treatment before age 6… except in severe cases" (page 7, (114)) in the category of attention deficit disorder and "The use of type H_2 antihistamines for long periods of treatment" (page 4, (114)) in the category of nausea, vomiting, or gastroesophageal reflux. In each case, "severe" and "long periods" are not specifically defined.

Furthermore, prescribing information alone is insufficient to rate prescribing using the POPI tool as detailed clinical information is required, beyond even the coding of an indication for a prescription. For instance, in the category ENT infections, one of the inappropriate prescription criteria is "Antibiotics to treat otitis media with effusion (OME), except in the case of hearing loss or if OME lasts for more than three months". Clearly, in order to evaluate a prescription against this criterion, clinical information about the patient would be required.

Some of the criteria require an even higher level of information about the patient's medical care. Two examples are, "Failure to give sugar solution to new-born babies and infants under four months old two minutes prior to venepuncture", in which case it would be necessary to have access to clinical notes expected to record every venepuncture the infant had received, and "Failure to propose a whooping cough booster

vaccine for adults who are likely to become parents in the coming months or years (only applicable if the previous vaccination was more than 10 years ago)…" in which case, records would need to indicate every adult present and even each adult's vaccination history during the consultation or clinical contact whose quality of prescribing is being assessed.

In addition, the criterion on whooping cough vaccination relates to perinatal healthcare for a mother rather than directly to paediatric prescribing; the decision to include this criterion in POPI, which is expressly designed as a paediatric rational prescribing too is not discussed by the author.

Several of the POPI criteria also require a high degree of clinical knowledge and a subjective judgement to be taken by the rater. For example, in the category bronchiolitis in infants, an inappropriate prescription criterion is the prescription of antibiotics "in the absence of signs indicated a bacterial infection (acute otitis media, fever, etc.)". By not providing a prescriptive list of signs of bacterial infection, the tool requires a rater to have the clinical knowledge to determine whether any unlisted signs of bacterial infection were present in the patient.

The high number of propositions and the mixed implicit and explicit approach of the POPI tool makes it quite high in complexity. There are criteria requiring a high level of clinical information to apply, for example one criterion in the atopic eczema category states that "More than one application per day of a dermocorticoid, except in cases of severe lichenification" as an inappropriate prescription. This criterion requires the rater therefore to assess the severity of lichenification of eczema, which would require detailed clinical information to determine.

On the other hand, in one criterion, the absence of subjectivity or detail reduces the accuracy of the criterion, which states that prescribing anything other than paracetamol first-line for pain (except migraine) is potentially inappropriate. This criterion would therefore rate opiates for severe pain as inappropriate if they are given before paracetamol. Although explicit criteria by definition lack the nuance to apply to all circumstances at all times, this criterion would flag a common (appropriate) practice, i.e. appropriate early analgesia for severe pain, as irrational.

Some patients may fall within multiple themes, for instance pain and fever might be expected alongside a number of other themes with infectious focuses, such as urinary infections and ENT infections, and other themes describe long-term conditions that any child might have as a co-morbidity. The theme of vitamin supplements and antibiotic prophylaxis includes a proposition describing minimum vitamin D intake, which would need to be assessed for every child. This would therefore require a high level of familiarity with the tool for accurate use and necessitates access to a high level of information about each patient.

The clinical application study of POPI highlighted a number of these issues. Only 82 of the criteria were applied to the hospital population studied, and just 28 to the community pharmacy population. While this is a pragmatic solution to the applying the criteria to limited datasets (such as the absence of clinical data about one group), this significantly impairs the ability to make meaningful comparisons between studied groups. The list of criteria used in each case were not included, therefore comparison between even the included criteria is not possible.

In addition, only three out of five criteria applying to analgesics and antipyrexics were applied, due to the "overwhelming" (page 6, (123)) frequency of this indication. Similarly, the authors stated that rating a criterion relating to amoxicillin prescribing was "not possible due to the fact that this drug is prescribed in great quantity" (page 7, (123)). For this criterion, a randomly selected 100 prescriptions were assessed from the hospital. It is not stated whether all or a selection of prescriptions for amoxicillin were analysed in the community group, but the rate of inappropriate prescribing for this criterion is reported as 97% out of 13.2% of patients.

In the clinical application study of POPI, the authors identified a higher rate of irrational prescribing in children aged between 2 and 6 years (129) or 0 to 12 years in the later report (123). However, given a number of age-specific propositions for children under 6 years of age, this may rather represent the population for whom the POPI criteria are most sensitive rather than the population most at risk of any types of irrational prescribing. By having a varying number of criteria that are applicable to age groups, this

may reduce the usefulness of POPI for accurately identifying variance in irrational prescribing between children of different ages, if such variance exists.

2.5.4 Limitations of PIPc

The authors of PIPc stated that the tool comprises explicit (evidence/opinion based) criteria; however, a number of criteria contain patient-specific considerations. Although the criteria of PIPc were designed for application without access to clinical information, two require assumption of the clinical indication, specifically for presumed asthma. The authors state in the development of the tool that prescription of "two or more inhaled corticosteroids" is used as a proxy for the diagnosis of asthma. The phrase "for presumed asthma" (page 8 (117) used in the report of the development of the PIPc tool is absent from the listed criteria in the clinical application study (131).

Using such a proxy for a diagnostic category enables the criteria to be used on anonymised prescribing data alone so long as all prescriptions are linked to patients, for instance through allocated participant numbers to facilitate reviewing prescriptions in the context of the prescribing history. However, there are other possible diagnoses such as viral-induced wheeze in children under 2 years, where there is evidence supporting the episodic use of inhaled corticosteroids (132) but not for ß2-agonists (133). Therefore, using prescription data without information about the indication for the prescription may reduce the usefulness of the criterion "An inhaled short-acting ß2 agonist should be prescribed to all children who are prescribed two or more inhaled corticosteroids for presumed asthma" (page 8 (117).

In addition, one of the criteria states that "Tetracyclines should not be prescribed to children under 12 years". However, doxycycline is the recommended first-line treatment for Lyme disease in children aged 9 to 12 years according to NICE guidance (134). This guidance recognises that use of tetracyclines in children under twelve years is contraindicated and does not have market authorisation, but that this use is accepted specialist practice. The authors of PIPc reported that indications considered appropriate under specialist use were removed from the proposed list of criteria (page 7, (117)). Lyme

disease is endemic in the UK,but with much higher prevalence in Scotland than England, Wales or Northern Ireland, as demonstrated in a 2019 cohort study (135). The study showed incidence was low in Northern Ireland with an incidence per 100,000 population of 6.3 and highest in Scotland at 37.3 per 100,000 (37). The study did not report on Ireland, but the Irish Health Protection Surveillance Centre reported in 2019 an estimated 200 cases of Lyme disease per year in Ireland (136), giving an approximate incidence of 3 per 100,000.

As all members of the PIPc steering group were affiliated with institutions in Ireland and Northern Ireland, it is possible that low incidence of Lyme disease in their clinical practice due to the low prevalence in Northern Ireland and Ireland may have led to the decision to include the tetracycline criterion. The regions of practice of the Delphi consensus experts were not listed beyond Ireland and the UK. This issue may be a limitation in the applicability of PIPc to practice across the whole of the UK, particularly in Scotland. Issues such as this are a limitation of the Delphi consensus process acknowledged by the authors of PIPc in their published report of its development; "the information gathered using a Delphi method represents the views of chosen experts about a specific practice at a given time and this may vary depending on the experts involved" (page 7, (117)).

Like POPI, PIPc has several criteria that identify a specific target age group. As already discussed, this may make it more challenging to use PIPc to evaluate whether there are differences in rational prescribing due to different age groups in studied populations.

Another significant limitation of PIPc identified in its clinical application study was that it highlighted the difficulty in applying even the intentionally simple and explicit criteria of PIPc to retrospective anonymised data (131). The age of patients in the PCRS database was recorded in age bands of 0-4 years, 5-11 years, and 12-15 years. In several cases, these bands overlapped age limits described in PIPc criteria. In order to analyse the data, the authors made calculations to estimate the number of children of a certain age. For example, to calculate the number of children under 2 years in the 0-4 years band, the total number of children in the band was divided by five and multiplied by two. This assumes a normal distribution of ages, which may not be the case.

2.6 Conclusion

There are two published rational prescribing tools for use in paediatrics, the PIPc and the POPI tool. Both rational prescribing tools comprise a number of explicit criteria defining potentially inappropriate medicines (PIMs) and potentially inappropriate omissions (PIOs). POPI also contains some criteria with implicit features.

The POPI tool was the only paediatric rational prescribing tool in publication at the date of my initial work undertaken in this thesis. As the PIPc is focused on primary care settings, the development of this tool in the UK did not fill the gap in availability of rational prescribing tools that can be applied across the broad range of paediatric practice settings. For both of these reasons, the POPI tool is the focus of the work of this thesis.

Prior to utilisation in the UK, comparison of the propositions to UK formularies and clinical guidelines was needed to establish the appropriateness of the criteria for assessing UK practice. Repeatability studies were also considered useful in order to evaluate whether subjective implicit criteria were similarly scored by independent raters. Greater repeatability would increase the usefulness of a tool for comparison between different institutions or regions, where different raters may use the tool. Therefore, modification of the POPI tool for applicability to UK practice followed by both clinical validation of the POPI tool in UK practice settings and reliability studies of the modified tool were identified as valuable avenues of further research.

3 Developing the POPI UK criteria

3.1 Introduction

3.1.1 The POPI tool in context

As described in Chapter 2, the POPI tool is one of two published paediatric rational prescribing tools. Unlike the PIPc, which is developed for application to primary care, the POPI tool is designed for use in any paediatric clinical setting. The tool comprises explicit criteria based on French, American, and UK guidelines, although the report is not explicit as to the selection process of guidelines or how incongruity between national guidelines was dealt with to reach consensus for the purposes of the tool. A specific grade of evidence was not stated, only that selected recommendations had to be "backed up by evidence and… published after 2000" (page 2, (115)). Given that all experts involved in the Delphi consensus were based in France, it may be that French practices and guidelines were given preference; in the references supporting the selected criteria, 27 are French, eight are American, and five are British. In addition, the selection of clinical indications was based upon French prevalence data. Given variation in prevalence of disease, availability of different formularies, and diversity in paediatric practice internationally, it is therefore probable that there will be some elements of a tool designed in the specific context of one country that may not be universally applicable internationally.

There are a number of rational prescribing tools for adults or undifferentiated populations that are designed for use in a specific context, for example the Laroche Criteria (137) evaluate potentially inappropriate prescribing for older adults and are designed for use in France. Some tools have also been adapted for use in other settings, with various adaptation of the (US-based) Beers Criteria including the Maio Criteria (138) for use in Italy and the Lechevallier Criteria (139) for use in France. On the other hand, some rational prescribing tools are intentionally broad enough to be applicable in a wide range of settings, with perhaps the best example being the WHO prescribing indicators (140), which were described in Section 1.3.3 (page 10).

The validity of rational prescribing criteria in clinical practice can be in a number of ways, as discussed in Section 1.4.2 (page 14). One approach is to test whether a higher level of irrational prescribing as identified by the tool correlates with adverse patient outcomes; a simpler approach is simply to evaluate the ability of the tool to identify types of irrational prescribing that occur in the target population. In a comparison of screening tools for inappropriate prescriptions in older people, Chang and Chen (61) found that all four of the tools that had been tested in their ability to reduce the prevalence of inappropriate prescribing were successful in doing so. None of the criteria they evaluated had been assessed in its ability to reduce negative clinical outcomes, an assessment that would require complex longitudinal studies.

Another limitation of rational prescribing tools is that the Delphi method by which they are most commonly developed are eminence-based, which runs counter to the principles of evidence-based medicine (EBM) (141). However, while the POPI UK criteria are derived from propositions reached using the Delphi consensus method, these criteria have been subjected to two rounds of scrutiny from the perspective of EBM: firstly, the propositions were produced with reference to American, French and British guidelines; in the modification process, they were then each individually tested against the explicitly evidence-based guidelines produced by NICE, Scottish Intercollegiate Guidelines Network (SIGN) and the BNFc. This method of producing the tool therefore draws upon an enormous body of evidence condensed into a relatively simple tool that is practical for clinical application.

The study described in this chapter was designed to develop paediatric rational prescribing criteria that could be applied in any paediatric setting in the UK.

The modification of an established tool to increase its applicability to another setting, commonly another country, has been used for a number of adult rational prescribing tools. For example, Beers criteria, developed in the USA, have been adapted for application in Germany, France, Italy and Austria (60). In other cases, entirely new rational prescribing tools have been developed anew through the Delphi consensus method, such as the development of the STOPP/START criteria in the UK (61).

The approach used in this study was to evaluate the appropriateness of the original POPI criteria to application in the UK through comparison to the British National Formulary for Children (BNFc) and national clinical guidelines. The aim was to modify the tool where necessary for application to UK paediatric practice and therefore to facilitate further evaluation of the tool using UK prescribing data. The intention was to minimise changes to the tool as far as possible, so that it remained as far as possible the product of the original Delphi consensus, while making any amendments necessary to produce criteria relevant to evaluate prescribing against accepted standards in the UK.

The development of the POPI UK criteria, reported in this chapter, has been disseminated in oral and poster presentations (118), and has also been peer-reviewed and published (142) (see Appendix 2).

3.2 Methods

The 105 propositions of the POPI criteria were compared to evidence-based UK clinical guidelines and clinical knowledge summaries from NICE, SIGN, the BNFc, and the European Medicines Agency (EMA). The national guidance from NICE, SIGN and the BNFc were preferred; EMA recommendations were referred to when no national guidelines were available. This process was based on the most recent guidelines available at the time the study was undertaken in October 2015. Where amendments were made, the specific related guideline is cited.

Following comparison with the guidelines, there were three possible outcomes:

1. Guidelines concurred with the POPI criteria. No change was made.
2. There was partial discordance. POPI criteria were amended to match UK guidance.
3. There was no guidance available or the criterion was in complete discordance with UK guidance and the criterion was omitted.

The final wording of the POPI UK criteria was reached as consensus in consultation with two paediatric clinical pharmacology consultants.

3.3 Results

The resulting POPI UK comprises 80 criteria. Having started with 105 propositions in the original POPI criteria, no change was made to 49 propositions. Twenty-nine were amended to concord more closely with UK guidelines. Four were reduced into two criteria where they could be combined with closely related propositions due to the relevant guidelines referring to them together, simplifying the tool. Twenty-three were omitted altogether, which included the omission of an entire category. One category title was amended— from "attention deficit disorder with or without hyperactivity" to "attention deficit hyperactivity disorder" (ADHD)— as the diagnosis of attention deficit disorder without hyperactivity is not in use in the UK; variants are described in the International Classification of Diseases 11th Revision (ICD-11) system describes subtypes without hyperactivity under the umbrella diagnosis of ADHD (143) . Appendix 7 shows the original POPI criteria and Appendix 8 the modified criteria comprising POPI UK.

The most substantial single change was the omission of the category of "Mosquitos[sic]". As there are not currently any areas of the UK where insect-borne diseases are endemic, this was not considered applicable to UK practice and therefore the category, comprising seven criteria, was removed.

Twelve criteria were omitted due to a lack of relevant clinical guidelines. These are all listed in

Table 3-A. In other cases, four criteria were omitted where UK clinical guidelines contradicted the proposition. These are listed in

Table 3-B.

Table 3-A: Criteria omitted due to absence of relevant UK clinical guidelines

Symptom or illness category	Omitted POPI criterion
Pain and fever (inappropriate prescriptions)	Rectal administration of paracetamol as a first-line treatment
Pain and fever (omission)	Failure to give sugar solution to new-born babies and infants under four months old two minutes prior to venepuncture
Urinary infection (inappropriate prescription)	Nitrofurantoin used as a prophylactic
Diarrhoea (inappropriate prescription)	The use of Diosmectite (Smecta) in combination with another medication
	The use of Saccharomyces boulardii (Ultralevure) in powder form, or in a capsule that has to be opened prior to ingestion, to treat patients with a central venous catheter or an immunodeficiency
	Intestinal antiseptics
Cough (inappropriate prescription)	Mucolytic drugs, mucokinetic drugs, or helicidine before 2 years of age
	Alimemazine (Theralene), oxomemazine (Toplexil), promethazine (Phenergan, and other types)
	Terpene-based suppositories
Bronchiolitis (inappropriate prescription)	0.9% NaCl to relieve nasal congestion (not applicable if nasal congestion is already being treated with 3% NaCl delivered by a nebulizer)
ENT infections (inappropriate prescription)	Ethanolamine tenoate (Rhinotrophyl) and other nasal antiseptics
Acne vulgaris (inappropriate prescription)	Androgenic progestins (levonorgestrel, norgestrel, norethisterone, lynestrenol, dienogest, contraceptive implants or vaginal rings)

In several of the criteria listed in

Table 3-A, the lack of related UK guidelines was due to named medicines in the proposition not being in use in the UK. For example, diosmectite is not approved for use, helicidine is not available, and ethanolamine tenoate is not listed in the BNFc. In other instances, there was a lack of guidelines related to the topic, for instance in the case of first-line rectal administration of paracetamol; the possible reasons for absence of guidelines are further considered in the discussion in Section 3.4 (page 78).

Table 3-B: Criteria omitted due to conflicting UK clinical guidelines

Symptom or illness category	Omitted POPI criterion *Conflicting UK guideline*
Urinary infection (inappropriate prescription)	Nitrofurantoin used as a curative agent in children under 6 years of age, or indeed any other antibiotic if avoidable *NICE guidance CG54* *http://www.nice.org.uk/guidance/CG54/chapter/1-Guidance* *(Recommends nitrofurantoin for children aged three months and over.)*
Vitamin supplements and antibiotic prophylaxis (inappropriate prescription)	Fluoride supplements prior to 6 months of age *SIGN guidance 138* *http://www.sign.ac.uk/pdf/SIGN138.pdf* *(Describes risks and benefits as balanced.)* *NICE Delivering Better Oral Health Toolkit* *http://www.nice.org.uk/guidance/ph55/chapter/context#delivering-better-oral-health-toolkit* *(Recommends fluoride toothpaste as soon as teeth erupt)*
Nausea, vomiting, or gastroesophageal reflux (inappropriate prescription)	The use of setrons (5-HT3 antagonists) for chemotherapy-associated nausea and vomiting *BNFc* *https://bnfc.nice.org.uk/drug/ondansetron.html* *(Chemotherapy-associated nausea and vomiting listed as an indication for ondansetron.)*
Acne vulgaris (inappropriate prescription)	Isotretinoin in combination with a member of the tetracycline family of antibiotics *NICE Acne Vulgaris Clinical Knowledge Summary* *http://cks.nice.org.uk/acne-vulgaris#!topicsummary* *(Recommended second-line for moderate acne.)*

The criteria listed in

Table 3-B were omitted due to national guidelines in the UK conflicting with the statements, suggesting that it would not be reasonable to consider such prescribing behaviour irrational in the UK. The case of setrons for chemotherapy-associated nausea and vomiting is considered in more depth in the discussion, as their inclusion in the original POPI criteria seems unusual given that setrons are widely used internationally for this very indication (144).

Two criteria were combined with closely related propositions where the recommendations were linked in a single UK guideline. The combined criteria are shown over page in Table 3-C.

Table 3-C: Criteria with shared UK guidelines and the simplified combined proposition

Original POPI criteria	Relevant UK guidance (NICE, SIGN or BNFc)	Combined criteria
ß2 agonists, corticosteroids to treat an infant's first case of bronchiolitis (PIM)	NICE guidance NG9 http://www.nice.org.uk/guidance/ng9/chapter/1-Recommendations Recommendation 1.4.3 *Do not use any of the following to treat bronchiolitis in children: antibiotics, hypertonic saline, adrenaline (nebulised), salbutamol, montelukast, ipratropium bromide, systemic or inhaled corticosteroids, a combination of systemic corticosteroids and nebulised adrenaline.*	Antibiotics, ß2 agonists or corticosteroids to treat bronchiolitis
Antibiotics in the absence of signs indicating a bacterial infection (acute otitis media, fever, etc.) (PIM)		
An antibiotic other than amoxicillin as a first-line treatment for acute otitis media, strep throat, or sinusitis (provided that the patient is not allergic to amoxicillin). An effective dose of amoxicillin for a pneumococcal infection is 80–90 mg/kg/day and an effective dose for a streptococcal infection is 50 mg/kg/day (PIM)	NICE guidance CG69 http://www.nice.org.uk/guidance/cg69/chapter/1-Guidance *A no antibiotic prescribing strategy or a delayed antibiotic prescribing strategy should be agreed for patients with the following conditions: acute otitis media, acute sore throat/acute pharyngitis/acute tonsillitis, common cold, acute rhinosinusitis, acute cough/acute bronchitis* *Depending on clinical assessment of severity, patients in the following subgroups can also be considered for an immediate antibiotic prescribing strategy (in addition to a no antibiotic or a delayed antibiotic prescribing strategy): bilateral acute otitis media in children younger than 2 years, acute otitis media in children with otorrhoea, acute sore throat/acute pharyngitis/acute tonsillitis when three or more Centor criteria are present.* SIGN guideline 117 *In severe cases, where the practitioner is concerned about the clinical condition of the patient, antibiotics should not be withheld. (Penicillin V 500 mg four times daily for 10 days is the dosage used in the majority of studies. A macrolide can be considered as an alternative first line treatment, in line with local guidance.)*	An antibiotic for < 4 days symptoms of acute upper respiratory tract infection except: • *bilateral acute otitis media in children younger than 2 years* • *acute otitis media in children with otorrhoea* • *acute sore throat/acute pharyngitis/acute tonsillitis when three or more Centor criteria are present.*
Antibiotics for nasopharyngitis, congestive otitis, sore throat before 3 years of age, or laryngitis; antibiotics as a first-line treatment for acute otitis media showing few symptoms, before 2 years of age (PIM)		

The combined propositions described in Table 3-C involved amendments of the wording of the original POPI criteria in order to closely match UK guidelines, while also avoiding unnecessary duplication within the POPI UK criteria.

Twenty-nine criteria were amended to more closely concord with UK guidelines. These are listed with their related guidelines in Table 3-D. In addition, the category title of "Attention deficit disorder with or without hyperactivity" was amended to "Attention deficit hyperactivity disorder".

Table 3-D: PIM criteria modified to concord with UK guidelines

Original POPI criteria	Relevant UK guidance (NICE, SIGN or BNFc) Source and title Link ***Recommendation***	Modified criteria
Prescription of a medication other than paracetamol as a first line treatment [for pain] (except in the case of migraine)	NICE Clinical Knowledge Summary: Management of mild-to-moderate pain http://cks.nice.org.uk/analgesia-mild-to-moderate-pain#!scenario *Prescribe either paracetamol or ibuprofen alone. Both are suitable first-line choices for treating mild-to-moderate pain in children.*	Prescription of a medication other than paracetamol or ibuprofen as a first-line treatment for pain (except in the case of migraine)
Oral solutions of ibuprofen administered in more than three doses per day using a graduated pipette of 10mg/kg (other than Advil)	BNFc Ibuprofen **https://bnfc.nice.org.uk/drug/ibuprofen.html** *Child 1–3 months 5 mg/kg 3–4 times daily* *Child 3–6 months 50 mg 3 times daily; max. 30 mg/kg daily in 3–4 divided doses* *Child 6 months–1 year 50 mg 3–4 times daily; max. 30 mg/kg daily in 3–4 divided doses* *Child 1–4 years 100 mg 3 times daily; max. 30 mg/kg daily in 3–4 divided doses* *Child 4–7 years 150 mg 3 times daily; max. 30 mg/kg daily in 3–4 divided doses* *Child 7–10 years 200 mg 3 times daily; max. 30 mg/kg (max. 2.4 g) daily in 3–4 divided doses* *Child 10–12 years 300 mg 3 times daily; max. 30 mg/kg (max. 2.4 g) daily in 3–4 divided doses* *Child 12–18 years initially 300–400 mg 3–4 times daily; increased if necessary to max. 600 mg 4 times daily; maintenance dose of 200–400 mg 3 times daily may be adequate*	Doses of ibuprofen administered in more than three doses per day or exceeding maximum dose of 30mg/kg given over three doses per day
Gastric antisecretory drugs to treat gastroesophageal reflux, dyspepsia,	NICE guidance NG1 http://www.nice.org.uk/guidance/NG1/chapter/1-Recommendations Recommendation 1.3.1	Acid-suppressing drugs to treat overt regurgitation in the absence of feeding

the crying of new-born babies (in the absence of any other signs or symptoms), as well as faintness in infants	*Do not offer acid-suppressing drugs, such as proton pump inhibitors (PPIs) or H_2 receptor antagonists (H_2RAs), to treat overt regurgitation in infants and children occurring as an isolated symptom.* Recommendation 1.3.2 *Consider a 4-week trial of a PPI or H_2RA for those who are unable to tell you about their symptoms (for example, infants and young children, and those with a neurodisability associated with expressive communication difficulties) who have overt regurgitation with 1 or more of the following:* • *unexplained feeding difficulties (for example, refusing feeds, gagging or choking)* • *distressed behaviour* • *faltering growth.*	difficulties, distress, or faltering growth
The use of type H_2 antihistamines for long periods of treatment	NICE guidance NG1 http://www.nice.org.uk/guidance/NG1/chapter/1-Recommendations Recommendation 1.3.4 *4 week trial then stop, assess response, refer if symptoms recur*	Amend: The use of H_2 receptor antagonists for more than 4 weeks
Erythromycin as a prokinetic agent	NICE guidance NG1 http://www.nice.org.uk/guidance/NG1/chapter/1-Recommendations *Do not offer metoclopramide, domperidone or erythromycin without seeking specialist advice*	Amend: Erythromycin
Loperamide before 3 years of age	BNFc Loperamide https://bnfc.nice.org.uk/drug/loperamide-hydrochloride.html *Licensed from 4 years*	Amend: Loperamide before 4 years of age
Antibiotic treatment for a sore throat, without a positive rapid diagnostic test result, in children less than three years old	SIGN guideline 117 http://www.sign.ac.uk/guidelines/fulltext/117/ Minimises usefulness of rapid diagnostic test results in guiding therapy *In severe cases, where the practitioner is concerned about the clinical condition of the patient, antibiotics should not be withheld. (Penicillin V 500 mg four times daily for 10 days is the dosage used in the majority of studies. A macrolide can be considered as an alternative first line treatment, in line with local guidance.)*	Amend: Antibiotic treatment for a sore throat except in severe cases (where the patient's clinical condition is documented as concerning)
Antibiotics to treat otitis media with effusion (OME), except in the case of hearing loss or if OME lasts for more than three months	NICE Clinical Knowledge Summary http://cks.nice.org.uk/otitis-media-with-effusion#!scenario Period of active observation for 6-12 weeks *During this period, do not prescribe antibiotics, steroids, antihistamines, decongestants, or mucolytics specifically for the treatment of otitis media with effusion (OME).*	Amend: Antibiotics to treat otitis media with effusion in the first 6-12 weeks
-antagonists with sedative or atropine-like effects (pheniramine, chlorpheniramine), or camphor;	BNFc https://www.evidence.nhs.uk/formulary/bnfc/current/3-respiratory-system/34-antihistamines-immunotherapy-and-allergic-emergencies/341-antihistamines#PHP11980	Amend: Sedating antihistamines (pheniramine, chlorpheniramine) before 2 years

inhalers, nasal sprays, or suppositories containing menthol (or any terpene derivatives) before 30 months of age	Sedating antihistamines not for use in neonates, phenothiazine sedating antihistamines not for use < 2 years, chlorphenamine not licensed < 1 year. https://www.evidence.nhs.uk/formulary/bnfc/current/3-respiratory-system/38-aromatic-inhalations Menthol inhalations permissible, no sprays or suppositories in BNFc nor terpene-containing medicines	(except for anaphylaxis)
Ketotifen and other H_1-antagonists, sodium cromoglycate	SIGN guidance 141 (British guideline on the management of asthma) http://www.sign.ac.uk/pdf/SIGN141.pdf *Antihistamines and ketotifen are ineffective.* *Sodium cromoglicate advocated for exercise-induced asthma*	Amend: Ketotifen and other antihistamines
The application of benzyl benzoate (Ascabiol) for periods longer than eight hours for infants and 12 hours for children or for pregnant girls	BNFc http://www.evidence.nhs.uk/formulary/bnf/current/13-skin/1310-anti-infective-skin-preparations/13104-parasiticidal-preparations/scabies and NICE Clinical Knowledge Summary http://cks.nice.org.uk/scabies#!scenario *Benzyl benzoate should be avoided in children (permethrin or malathion are less irritant and more effective and should be used instead)*	Amend: Benzyl benzoate
Treatment other than griseofulvin for Microsporum	NICE Clinical Knowledge Summary Fungal Skin infections http://cks.nice.org.uk/fungal-skin-infection-body-and-groin#!scenario Recommends topical treatment first-line. Gruseofulvin the only oral treatment appropriate for children	Amend: Oral treatment other than griseofulvin
Any antibiotic other than mupirocin as a first-line treatment (except in cases of hypersensitivity to mupirocin)	NICE Clinical Knowledge Summary Impetigo http://cks.nice.org.uk/impetigo#!scenario • *For localized* [sic] *infection, treat with topical fusidic acid… Topical mupirocin, retapamulin, and antiseptics are not recommended initially.*	Amend: Any antibiotic other than fusidic acid as a first-line treatment (except in cases of hypersensitivity to fusidic acid)
Orally administered aciclovir to treat primary herpetic gingivostomatitis	NICE Clinical Knowledge Summary Herpes Simplex (oral) http://cks.nice.org.uk/herpes-simplex-oral#!scenario:1 *Consider oral antivirals for immunocompetent individuals with severe gingivostomatitis.*	Amend: Orally administered aciclovir to treat severe herpetic gingivostomatitis
A strong dermocorticoid (clobetasol propionate 0.05% Dermoval, betamethasone dipropionate	NICE guidance CG57 https://www.nice.org.uk/guidance/CG57/chapter/1-Guidance • *use mild potency for the face and neck, except for short-term (3–5 days) use of moderate potency for severe flares*	Amend: A potent topical corticosteroid applied to the face, or for > 14 days applied to the axilla or groin

Diprosone) applied to the face, the armpits or groin, and the backside of babies or young children	• *use moderate or potent preparations for short periods only (7–14 days) for flares in vulnerable sites such as axillae and groin* • *do not use very potent preparations in children without specialist dermatological advice.* BNFc Dermoval not listed http://www.evidence.nhs.uk/formulary/bnf/current/13-skin/134-topical-corticosteroids/topical-corticosteroid-preparation-potencies	
Local or systemic antihistamine during the treatment of outbreaks	NICE guidance CG57 https://www.nice.org.uk/guidance/CG57/chapter/1-Guidance Recommendation 1.5.6 *Healthcare professionals should offer a 1-month trial of a non-sedating antihistamine to children with severe atopic eczema or children with mild or moderate atopic eczema where there is severe itching or urticaria.* *Healthcare professionals should offer a 7–14 day trial of an age-appropriate sedating antihistamine to children aged 6 months or over during an acute flare of atopic eczema if sleep disturbance has a significant impact on the child or parents or carers.*	Amend: Prescription of antihistamines except as a trial for severe itching or where sleep disturbance has a significant impact on the child or carers
Cyproheptadine (Perlactin), clonidine	NICE guidance CG9 https://www.nice.org.uk/guidance/CG9/chapter/1-Guidance Recommendation 1.2.3.1 *Medication should not be used as the sole or primary treatment for anorexia nervosa.*	Amend: Prescription of medications as a sole or primary treatment for anorexia nervosa
Antipsychotic drugs to treat attention deficit disorder without hyperactivity	NICE guidance CG72 https://www.nice.org.uk/guidance/cg72/chapter/1-Guidance Recommendation 1.5.5.7 *Antipsychotics are not recommended for the treatment of ADHD in children and young people.*	Amend: Antipsychotic drugs to treat attention deficit hyperactivity disorder
Slow release methylphenidate as two doses per day, rather than only one dose	NICE guidance CG72 https://www.nice.org.uk/guidance/cg72/chapter/1-Guidance Recommendation 1.8.2.2 *modified-release preparations should be given as a single dose in the morning*	Amend: Modified release methylphenidate as two doses per day rather than only one dose

Of the PIM criteria amended, shown in Table 3-D, several of the amendments resulted in simplification of the criterion, for instance from "The application of benzyl benzoate… for periods longer than eight hours for infants and 12 hours for children or for pregnant girls" to "Benzyl benzoate", which is considered less appropriate than permethrin or

malathion according to the cited clinical guidance. In other cases, the only amendment was the age range, which usually arose from licensing of the medication, for instance loperamide and chlorphenamine.

In some cases, the amendments introduced subjectivity to the criterion, such as changing "antibiotic treatment for sore throat, without a positive rapid diagnostic test result, in children less than three years" to "antibiotic treatment for a sore throat except in severe cases". While this may increase the complexity of the criterion, this change reflected UK national guidelines which advised against reliance upon rapid diagnostic testing, therefore the original proposition would not appropriately assess the rationale behind clinicians' decision-making in the UK context.

It should be noted that, as Table 3-D shows, ibuprofen dosing is recommended as three to four times daily in the BNFc, however the modified criterion more closely mirrored the original POPI criterion by stating it should be dosed only three times daily. This was an error as the modified criterion does not therefore accurately represent UK national guidance. The error was detected after completion of validation studies, therefore modified POPI criteria referred to in subsequent chapters include this criterion.

PIOs that were modified are shown in Table 3-E.

Table 3-E: PIO criteria modified to concord with UK guidelines

Original POPI criterion	Relevant UK guidance (NICE, SIGN or BNFc) Source and title Link *Recommendation*	Modified criterion
Insufficient intake of vitamin D. Minimum vitamin D intake: Breastfed baby = 1,000 to 1,200 IU/day; Infant,18 months of age (milk enriched in vitamin D) = 600 to 800 IU/day; Child aged between 18 months and 5 years, and adolescents aged between 10 and 18 years: two quarterly loading doses of 80,000 to 100,000 IU/day in winter (adolescents can take this dose in one go)	NICE guidance PH56 http://www.nice.org.uk/guidance/ph56/chapter/1-Recommendations *Vitamin D supplements should be available for at-risk groups, including infants and children < 5years, Healthy Start vitamins*	Healthy Start vitamins for infants and children 6 months- 5 years or having less than 500ml infant formula per day

Antibiotic prophylaxis with phenoxymethylpenicillin (Oracilline) starting from 2 months of age and lasting until 5 years of age for children with sickle-cell anemia: 100,000 IU/kg /day (in two doses) for children weighing 10kg or less and 50,000 IU/kg/day for children weighing over 10kg (also in two doses)	NICE Clinical Knowledge Summary http://cks.nice.org.uk/sickle-cell-disease#!scenario:3 • *Explain that lifelong prophylaxis is recommended, but it is particularly important that there is full adherence up to 5 years of age.* • *Prescribe phenoxymethylpenicillin (penicillin V) prophylaxis from the age of 1 month, at a dose of:* o *125 mg twice a day for infants and children up to 5 years of age.* o *250 mg twice a day for children from 6 to 12 years of age.* o *500 mg twice a day for adults and children older than 12 years of age.* • *Erythromycin is recommended for people who are allergic to penicillin, at a dose of:* o *125 mg twice a day for infants and children up to 2 years of age.* o *250 mg twice a day for adults and children older than 2 years of age.*	Antibiotic prophylaxis with phenoxyethylpenicillin (penicillin V) from age 1 month until 5 years for children with sickle-cell anaemia at a dose of: • 125 mg twice a day for infants and children up to 5 years of age. • 250 mg twice a day for children from 6 to 12 years of age. • 500 mg twice a day for adults and children older than 12 years of age. OR Erythromycin for children who are allergic to penicillin, at a dose of: • 125 mg twice a day for infants and children up to 2 years of age. 250 mg twice a day for children older than 2 years of age.
Oral rehydration solution	NICE guidance CG84 http://www.nice.org.uk/guidance/cg84/chapter/1-Guidance#fluid-management *Offer ORS solution as supplemental fluid to children at risk of dehydration or use in dehydrated children unless IV fluid is indicated*	Amend: Oral rehydration solution for dehydrated children unless IV fluid therapy is indicated (shock, red flag symptoms despite ORS, persist vomiting of ORS)
Oral rehydration solution	NICE guidance CG84 http://www.nice.org.uk/guidance/cg84/chapter/1-Guidance#fluid-management *Offer ORS solution as supplemental fluid to children at risk of dehydration or use in dehydrated children unless IV fluid is indicated*	Amend: Oral rehydration solution for dehydrated children unless IV fluid therapy is indicated (shock, red flag symptoms despite ORS, persist vomiting of ORS)
Failure to propose a whooping cough booster vaccine for adults who are likely to become	NICE Clinical Knowledge Summary: Antenatal care of uncomplicated pregnancy	Amend: Failure to propose a whooping

parents in the coming months or years (only applicable if the previous vaccination was more than 10 years ago). This booster vaccination should also be proposed to the family and entourage of expectant parents (parents, grand-parents, nannies/child minders)	http://cks.nice.org.uk/antenatal-care-uncomplicated-pregnancy#!scenario *28 weeks gestation: Offer vaccination against pertussis*	cough vaccine for pregnant women.
Palivizumab in the following cases: (1) babies born both at less than 35 weeks of gestation and less than six months prior to the onset of a seasonal RSV epidemic; (2) children less than two years old who have received treatment for bronchopulmonary dysplasia in the past six months; (3) children less than two years old suffering from congenital heart disease with hemodynamic abnormalities	SIGN guidance 91 (Bronchiolitis in children) http://www.sign.ac.uk/guidelines/fulltext/91/index.html … *recommends use of palivizumab in high risk groups, as defined by the committee (children under 2 years of age with chronic lung disease, on home oxygen or who have had prolonged use of oxygen; infants less than 6 months of age who have left to right shunt haemodynamically significant congenital heart disease and/or pulmonary hypertension; children under 2 years of age with severe congenital immuno-deficiency)*	Amend: Palivizumab in high-risk cases, defined as: 1) children < 2 years with chronic lung disease on home oxygen or who have prolonged use of oxygen 2) infants < 6 months with left-to-right shunt haemodynamically significant congenital heart disease and/or pulmonary hypertension children < 2 years with severe congenital immunodeficiency
Asthma inhaler appropriate for the child's age	NICE guidance TA10 https://www.nice.org.uk/guidance/ta10 *NICE has recommended that for children under the age of 5 years who have chronic stable asthma:* • *both corticosteroids and bronchodilator therapy should routinely delivered by Pressurised Metered Dose Inhaler (pMDI) and spacer system, with a facemask where necessary.* • *where this combination is not clinically effective for the child, and depending on the child's condition, nebulised therapy may be considered and in the case of children aged 3 to 5 years, a dry powder inhaler (DPI) may also be considered.* *the choice of which pMDI device and spacer to use should be determined by the specific needs of the child and how well it works for them. Once these factors have been taken into account the choice should be made on the basis of reducing costs.*	Amend: Asthma inhaler appropriate for the child's age (aged < 5 years, either Metered Dose Inhaler with spacer system or nebuliser; age 3-5 years Dry Powder Inhaler may be appropriate)

Contraception (provided with a logbook/diary) for menstruating girls taking isotretinoin	BNFc https://www.evidence.nhs.uk/formulary/bnf/current/13-skin/136-acne-and-rosacea/1362-oral-preparations-for-acne/oral-retinoid-for-acne/isotretinoin *Effective contraception must be used.*	Amend: Contraception for menstruating girls taking isotretinoin
A second dose of ivermectin two weeks after the first	BNFc https://bnfc.nice.org.uk/treatment-summary/skin-infections.html Ivermectin only available by special order, unlicensed for scabies. https://bnfc.nice.org.uk/drug/permethrin.html https://bnfc.nice.org.uk/drug/malathion.html *Apply once weekly for 2 doses*	Amend: A second application of permethrin or malathion one week after the first
Decontamination of household linen and clothes and treatment for other family members	NICE Clinical Knowledge Summary http://cks.nice.org.uk/scabies#!scenario *Decontamination of household linen and clothes and same day treatment of all members of the household*	Amend: Decontamination of household linen and clothes and same day treatment of all members of the household

As shown in Table 3-E, several of the modified omissions related to the provision of prophylactic treatments, such as vitamin supplementation, antibiotic prophylaxis, and vaccination, to identified at-risk groups. In these cases, the amendments reflected differences in national guidelines identifying who should be considered to fall within the at-risk group category. One subjective criterion, "Asthma inhaler appropriate for the child's age", was amended into explicit recommendations as per national UK guidelines.

The amendment relating to contraception for isotretinoin omits the inclusion of a mandatory logbook or diary. However, this does not reflect a lower degree of vigilance in adherence to careful measures against accidental pregnancy while using isotretinoin. In the UK, the Pregnancy Prevention Programme for women and girls of childbearing potential who are taking isotretinoin is supported by a number of additional measures, including new prescriber checklists, patient reminder cards, and pharmacy checklists (120).

Following the process of updating the original criteria to fit within UK clinical practice, the resulting POPI UK criteria comprise 80 propositions assessing rational prescribing

for children in accordance with up-to-date UK guidelines. The full criteria are shown in Table 3-F.

Table 3-F: The POPI UK tool

DIVERSE ILLNESSES
PAIN AND FEVER
Inappropriate prescriptions
Prescription of two alternating antipyretics as a first-line treatment
Prescription of a medication other than paracetamol or ibuprofen as a first-line treatment for pain (except in the case of migraine)
The combined use of two NSAIDs
Doses of ibuprofen administered in more than three doses per day or exceeding maximum dose of 30mg/kg over three doses per day
Opiates to treat migraine attacks
Omissions
Failure to give an osmotic laxative to patients being treated with morphine for a period of more than 48 hours
URINARY INFECTIONS
Inappropriate prescriptions
Antibiotic prophylaxis following an initial infection without complications (except in the case of uropathy)
Antibiotic prophylaxis in the case of asymptomatic bacterial infection (except in the case of uropathy)
VITAMIN SUPPLEMENTS AND ANTIBIOTIC PROPHYLAXIS
Omissions
Healthy Start vitamins for infants and children 6 months- 5 years or having less than 500mL infant formula per day
Antibiotic prophylaxis with phenoxyethylpenicillin (penicillin V) from age 1 month until 5 years for children with sickle-cell anaemia at a dose of: • 125 mg twice a day for infants and children up to 5 years of age. • 250 mg twice a day for children from 6 to 12 years of age. • 500 mg twice a day for adults and children older than 12 years of age. OR Erythromycin for children who are allergic to penicillin, at a dose of: • 125 mg twice a day for infants and children up to 2 years of age. • 250 mg twice a day for children older than 2 years of age.
DIGESTIVE PROBLEMS
NAUSEA, VOMITING, OR GASTROESOPHAGEAL REFLUX
Inappropriate prescriptions
Metoclopramide
Domperidone

Oral administration of an intravenous proton pump inhibitor (notably by nasogastric tube)
Acid-suppressing drugs to treat overt regurgitation in the absence of feeding difficulties, distress, or faltering growth
The combined use of proton pump inhibitors and NSAIDs, for a short period of time, in patients without risk factors
The use of H_2 receptor antagonists for more than 4 weeks
Erythromycin
Omissions
Oral rehydration solution (ORS) for dehydrated children unless IV fluid therapy is indicated (shock, red flag symptoms despite ORS, persist vomiting of ORS)
DIARRHOEA
Inappropriate prescriptions
Loperamide before 4 years of age
Loperamide in the case of invasive diarrhoea
Omissions
Oral rehydration solution (ORS) for dehydrated children unless IV fluid therapy is indicated (shock, red flag symptoms despite ORS, persist vomiting of ORS)
ENT-PULMONARY PROBLEMS
COUGH
Inappropriate prescriptions
Pholcodine
Omissions
Failure to propose a whooping cough vaccine for pregnant women.
BRONCHIOLITIS IN INFANTS
Inappropriate prescriptions
Antibiotics, ß2 agonists or corticosteroids to treat bronchiolitis
H_1-antagonists, cough suppressants, mucolytic drugs, or ribavirin to treat bronchiolitis
Omissions
Palivizumab in high-risk cases, defined as: 3) children < 2 years with chronic lung disease on home oxygen or who have prolonged use of oxygen 4) infants < 6 months with left-to-right shunt haemodynamically significant congenital heart disease and/or pulmonary hypertension 5) children < 2 years with severe congenital immunodeficiency
ENT INFECTIONS
Inappropriate prescriptions
An antibiotic for < 4 days symptoms of acute upper respiratory tract infection (except: • bilateral acute otitis media in children younger than 2 years • acute otitis media in children with otorrhoea

• acute sore throat/acute pharyngitis/acute tonsillitis when three or more Centor criteria are present.
Antibiotic treatment for a sore throat except in severe cases (anticipated to be no more than 20% of cases)
Antibiotics to treat otitis media with effusion in the first 6-12 weeks
Corticosteroids to treat acute suppurative otitis media, nasopharyngitis, or strep throat
Nasal or oral decongestant (oxymetazoline (Aturgyl), pseudoephedrine (Sudafed), naphazoline (Derinox), ephedrine (Rhinamide), tuaminoheptane (Rhinofluimicil), phenylephrine (Humoxal))
Sedating antihistamines (pheniramine, chlorpheniramine) before 2 years (except for anaphylaxis)
Ear drops in the case of acute otitis media
Omissions
Doses in mg for drinkable (solutions of) amoxicillin or josamycin
Paracetamol combined with antibiotic treatment for ear infections to relieve pain
ASTHMA
Inappropriate prescriptions
Ketotifen and other antihistamines
Cough suppressants
Omissions
Asthma inhaler appropriate for the child's age (aged < 5 years, either Metered Dose Inhaler with spacer system or nebuliser; age 3-5 years Dry Powder Inhaler may be appropriate)
Preventative treatment (inhaled corticosteroids) in the case of persistent asthma
DERMATOLOGICAL PROBLEMS
ACNE VULGARIS
Inappropriate prescriptions
Minocycline
The combined use of an oral and a local antibiotic
Oral or local antibiotics as a monotherapy (not in combination with another drug)
Cyproterone+ethinylestradiol (Diane 35) as a contraceptive to allow isotretinoin per os
Omissions
Contraception for menstruating girls taking isotretinoin
Topical treatment (benzoyl peroxide, retinoids, or both) in combination with antibiotic therapy
SCABIES
Inappropriate prescriptions
Benzyl benzoate
Omissions
A second application of permethrin or malathion one week after the first
Decontamination of household linen and clothes and same day treatment of all members of the household
LICE

Inappropriate prescriptions
The use of aerosols for infants, children with asthma, or children showing asthma-like symptoms such as dyspnoea
RINGWORM
Inappropriate prescriptions
Oral treatment other than griseofulvin
Omissions
Topical treatment combined with an orally-administered treatment
Griseofulvin taken during a meal containing a moderate amount of fat
IMPETIGO
Inappropriate prescriptions
The combination of locally applied and orally administered antibiotic
Fewer than two applications per day for topical antibiotics
Any antibiotic other than fusidic acid as a first-line treatment (except in cases of hypersensitivity to fusidic acid)
HERPES SIMPLEX
Inappropriate prescriptions
Topical agents containing corticosteroids
Topical agents containing aciclovir before six years of age
Omissions
Paracetamol during an outbreak of herpes
Orally administered aciclovir to treat severe herpetic gingivostomatitis
ATOPIC ECZEMA
Inappropriate prescriptions
A potent topical corticosteroid applied to the face, or for > 14 days applied to the axilla or groin
More than one application per day of a dermocorticoid, except in cases of severe lichenification
Prescription of antihistamines except as a trial for severe itching or where sleep disturbance has a significant impact on the child or carers
Topically applied 0.03% tacrolimus before 2 years of age
Topically applied 0.1% tacrolimus before 16 years of age
Oral corticosteroids to treat outbreaks
NEUROPSYCHIATRIC DISORDERS
EPILEPSY
Inappropriate prescriptions
Carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine, or vigabatrin in the case of myoclonic epilepsy
Carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabaline, tiagabine, or vigabatrin in the case of epilepsy with absence seizures (especially for childhood absence epilepsy or juvenile absence epilepsy)

Levetiracetam, oxcarbamazepine in mL or in mg without systematically writing XX mg per Y mL
DEPRESSION
Inappropriate prescriptions
An SSRI antidepressant other than fluoxetine as a first-line treatment (in the case of pharmacotherapy)
Tricyclic antidepressants to treat depression
NOCTURNAL ENURESIS
Inappropriate prescriptions
Desmopressin administered by a nasal spray
Desmopressin in the case of daytime symptoms
An anticholinergic agent used as a monotherapy in the absence of daytime symptoms
Tricyclic agents in combination with anticholinergic agents
Tricyclic agents as a first-line treatment
ANOREXIA
Inappropriate prescriptions
Prescription of medications as a sole or primary treatment for anorexia nervosa
ATTENTION DEFICIT DISORDER WITH HYPERACTIVITY
Inappropriate prescriptions
Pharmacological treatment before age 6 (before school), except in severe cases
Antipsychotic drugs to treat attention deficit hyperactivity disorder
Modified release methylphenidate as two doses per day, rather than only one dose
Omissions
Recording a growth chart (height and weight) if the patient is taking methylphenidate

3.4 Discussion

The POPI criteria were modified to develop a list of PIMs and PIOs for children in the UK. The POPI tool was the first paediatric prescribing screening tool, and the modified tool was the first paediatric rational prescribing tool for use in the UK when it was developed for use in our research in 2016. It remains the only paediatric rational prescribing tool for application to paediatric practice outside primary care and is designed to closely reflect national clinical guidelines and prescribing practice. The POPI UK criteria have a number of potential applications: the tool could be used in a research context to estimate prevalence of irrational prescribing using basic prescribing data of medications and their indication on either a local or national level; it could also be used as a tool for service evaluation and quality improvement, for instance through use in audit.

3.4.1 Criteria modified for inclusion in POPI UK

Twenty-nine of the propositions of the original POPI criteria were amended. The majority of these changes were subtle modifications to bring the wording of propositions more closely in line with the specific wording of UK clinical guidelines. For example, "Antipsychotic drugs to treat attention deficit disorder without hyperactivity" was amended to "Antipsychotic drugs to treat attention deficit hyperactivity disorder".

In other cases, the criteria contained specific differences such as age ranges or first-line drug recommendations and were amended accordingly. Examples of these include some criteria where the amendment increased the specificity of the proposition, such as changing from "The use of type H^2 antihistamines for long periods of treatment" to "The use of H^2 receptor antagonists for more than four weeks". In other cases, the amendment added complexity or subjectivity, in order to better reflect the UK guidance, for instance a criterion relating to atopic eczema was changed from "Local or systemic antihistamine during the treatment of outbreaks" to "Prescription of antihistamines except as a trial for severe itching or where sleep disturbance has a significant impact on the child or carers".

In order for this tool to be useful in appraising rational prescribing in the UK, it is important that prescribers are being measured against the specific standards they are striving for, and this would also facilitate straightforward interventions using UK guidelines for education and service improvement.

3.4.2 Criteria omitted from POPI UK

For 22 criteria, there were no relevant UK clinical guidelines or guidelines were directly contradictory to the original POPI criterion. Absence from guidelines does not necessarily invalidate the recommendations of those criteria but they were omitted as they appeared to relate to irrational use of medicines that do not appear to be prevalent in the UK. In some cases, the propositions related to medications not available in the UK, for instance in the case of diosmectite for diarrhoea there is some emerging evidence supporting its use (145) but this is not reflected in UK availability of the product.

In other cases, differences in national clinical practices may explain the absence if the type of irrational prescribing described is already rare in UK practice. This explanation likely underlies guidance about rectally administered drugs including paracetamol per rectum for pain and suppositories for cough. The cultural difference that may give rise to this variance in clinical practice was recognised in the EMA *Guideline on pharmaceutical development of medicines for paediatric use* (146) when discussing medication acceptability in different countries, giving the example that "the rectal route of administration is not generally favoured in the UK".

Two of the omitted criteria, in relation to sucrose for painful procedures in infants and nitrofurantoin as prophylaxis for urinary infection, may be absent from national UK guidelines because these are areas where there is not a national consensus of best practice. In reviewing these topics, local guidelines were found to differ. Some UK guidelines were found recommending nitrofurantoin for prophylaxis (147, 148). In guidelines relating to sucrose for painful procedures, some UK guidelines preferred breast- or bottle-feeding over sucrose, described contraindications, and qualified the guideline according to gestation and age of infant (149, 150). In the absence of a unifying national guideline on these topics, they were therefore not considered to be good candidates for screening prescribing practice nationally.

Four criteria were omitted due to the existence of UK clinical guidelines that were in direct conflict with the original proposition (see

Table 3-B).

Three of these appear to have been included as PIMs in the original French tool due to risk of interactions or side effects. One related to nitrofurantoin for treatment of urinary infections. According to the report describing the development of the original POPI tool, this criterion was derived from a statement issued by Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS, the French Agency for the Safety of Health Products) in 2011 warning of cases of severe hepatic and pulmonary complications following long-term treatment with nitrofurantoin (151).

The BNFc does recommend monitoring liver function and for pulmonary symptoms if prescribing nitrofurantoin long-term, but it is licensed and indicated in acute uncomplicated urinary tract infections for children aged 3 months and older (120) and is second-line for children aged 3 months and older in the most recent NICE guideline NG109 (152).

The second related to isotretinoin and tetracycline antibiotics. This appears to be derived from a Good Practice Recommendation from AFSSAP describing isotretinoin as contraindicated with tetracyclines due to the reported occurrence of benign intracranial hypertension with this combination (153). This risk is recorded in the BNFc as a possible interaction, rated as "Serious" with an anecdotal evidence base (120). The combination is not recorded as a contraindication and combined topical retinoids and oral tetracyclines and recommended in the NICE Clinical Knowledge Summary.

The third related to fluoride supplements before age 6 months. The related French guideline, an AFSAPPS statement in 2008, recommended that fluoride-containing supplements such as toothpaste be commenced when teeth erupt, on average at age 6 months (154). This statement, like the relevant UK guidelines, discusses the risk of dental fluorosis with excess fluoride consumption during tooth development and recommends lower dose fluoride in toothpaste for young children. Both the NICE and SIGN guidelines quoted in

Table 3-B acknowledge the risk of dental fluorosis and state that the benefit of reduced caries favours starting fluoride supplementation as soon as teeth erupt with no definitive lower age limit of benefit to the child.
These all appear to reflect differing risk tolerance between the French and UK guidelines. In order that the modified tool reflects what is considered nationally to be good practice, the criteria were therefore omitted from the modified tool.

The fourth omitted criterion listed "The use of setrons (5-HT3 antagonists) for chemotherapy-associated nausea and vomiting" as a PIP. It was not clear what evidence was used to develop this proposition as none of the references in the report describing the development of the original tool related to chemotherapy-associated nausea and vomiting. The only reference mentioning setrons in the section explaining the evidence-base for each criterion was from the American Centers for Disease Control and Prevention, which recommended ondansetron as an effective anti-emetic for children, noting it is not usually required for gastroenteritis but not making any reference to chemotherapy (155).

Chemotherapy-induced nausea and vomiting is one of the listed indications for ondansetron in the BNFc (120). It is possible that the inclusion of this criterion in the original tool constitutes a typographical error, and that it was intended to read as an inappropriate omission given the importance of treating chemotherapy-associated nausea. It was therefore felt not to accurately reflect rational prescribing and was omitted from the modified tool.

3.4.3 Impact of the modification process on the criteria list

Of the 105 criteria of the original POPI tool, the majority were amended or omitted, with 49 remaining unchanged.

One entire clinical category was removed from the list, relating to mosquitoes. Otherwise, the breadth of clinical indications covered by the criteria remains unchanged. In addition, the range of categories of irrational prescribing described in the criteria (discussed in Section 2.4.4, page 36) remains equally broad. Examples from both the original POPI and

POPI UK relating to various types of misprescribing, as well as over- and underprescribing, are shown over page in Table 3-G.

Table 3-G: Examples of criteria relating to different categories of irrational prescribing

Aspect of rational prescribing	Example of related PIM or PIO from original POPI (theme)	Example of related PIM or PIO from POPI UK (theme)
Drug	Nitrofurantoin used as a curative agent in children under six years (Urinary infections)	Loperamide in the case of invasive diarrhoea (Diarrhoea)
Dosage	Oral solutions of ibuprofen administered in more than three doses per day using a graduated pipette of 10mg/kg (Pain and fever)	Doses of ibuprofen administered in more than three doses per day or exceeding maximum dose of 30mg/kg over three doses per day (Pain and fever)
Duplication	The combined use of an oral and a local antibiotic (Acne vulgaris)	The combined use of an oral and a local antibiotic (Acne vulgaris)
Duration	The use of H^2 type antihistamines for long periods of treatment (Nausea, vomiting, or gastrooesophageal reflux)	The use of H^2 receptor antagonists for more than 4 weeks (Nausea, vomiting, or gastrooesophageal reflux)
Drug-drug interaction	Isotretinoin in combination with a member of the tetracycline family of antibiotics (Acne Vulgaris)	The combined use of two NSAIDs (Pain and fever)
Drug-disease interaction	ß2 agonists, corticosteroids to treat an infant's first case of bronchiolitis (Bronchiolitis)	Antibiotics, ß2 agonists or corticosteroids to treat bronchiolitis (Bronchiolitis)
Overprescribing	Antibiotic treatment for a sore throat, without a positive rapid diagnostic test… (ENT infections)	Antibiotic treatment for a sore throat except in severe cases (ENT infections)
Underprescribing	Omission: Oral rehydration solution (Diarrhoea)	Omission: Preventative treatment (inhaled corticosteroids) in the case of persistent asthma (Asthma)

There is also no evidence that the modification of the tool had any impact on the degree of complexity, as represented by the proportion of criteria with implicit features. All modifications shown in Table 3-D and Table 3-E either maintained implicit features (that is, reference to patient characteristics or clinical details) or in one case changed a criterion from implicit to explicit: from "The application of benzyl benzoate for periods longer

than eight hours for infants and 12 hours for children or pregnant girls" to "Benzyl benzoate" as a PIM for children.

In some cases, amendments increased the subjectivity of a criterion, such as the change to antibiotics for sore throats, shown as the example of overprescribing in Table 4-B above. However, others reduced subjectivity, such as the proposition relating to treatment of gastrooesophageal reflux with H^2 receptor antagonists, shown as the example of misprescribing duration shown in Table 4-B, or the amendment of the PIO "Asthma inhaler appropriate for the child's age" by adding specifically "aged <5 years, either Metered Dose Inhaler with spacer system or nebuliser; age 3-5 years Dry Powder Inhaler may be appropriate" shown in Table 3-E.

Therefore, the POPI UK tool, like the original POPI tool, has mixed implicit and explicit features, with some criteria requiring the rater to make subjective assessments to determine appropriateness.

3.5 Conclusion

The POPI UK criteria are the first rational prescribing tool designed to assess rational prescribing for children across any setting in the UK. The tool comprises 80 criteria describing PIMs and PIOs.

Although the POPI UK criteria are founded in evidence-based practice, their usefulness and validity and usefulness required testing. As discussed in Chapter 2, both clinical validation and inter-rater reliability studies have been published for the original POPI tool.

In order to assess the POPI UK criteria, two studies were undertaken to test, respectively, the clinical application and repeatability of the new criteria. Firstly, a clinical validation study was undertaken in which the criteria would be applied to inpatient and emergency department prescriptions in a UK children's hospital to identify the proportion of prescriptions that fall within the categories of the tool and any inappropriate prescriptions or omissions that it detects in that setting. This is described in Chapter 4. Secondly, a

repeatability study was completed in which inter- and intra-rater agreement would be assessed to study the reliability of scores produced by using the criteria is described in Chapter 5.

4 Clinically assessing the POPI UK criteria

4.1 Introduction

This chapter describes the clinical assessment of the POPI UK criteria, with an overview of how rational prescribing tools are validated followed by the methodology and results of the study designed to evaluate the usefulness of the POPI UK criteria in UK paediatric practice.

4.1.1 Evaluating rational prescribing tools

As discussed in Chapter 1, rational prescribing criteria enable research into the quality of prescribing. The reliability of any measurement can be described in terms of two paradigms: accuracy and precision. Accuracy (sometimes called validity) has been described as meaning the closeness of the measurements to some external "true" value, or else to the results of a previously established gold standard(156). In particular, accuracy should be applied specifically to the results of measurement, rather than the measurement tool itself, as it is considered a descriptor of the meaningfulness of test results in serving a specific purpose(157). Precision (sometimes called reliability), on the other hand, has been described as reflecting the agreement between repeated measurements, whether scored by a single assessor at different times or scored by different assessors. There has been criticism of conflating precision with reliability, which in fact should take into account true variance (the variability that exists in the external "true" values) whereas precision usually only accommodates error variance (the variability that appears due to measurement error) (156). Nonetheless, for the purposes of this thesis, "reliability" and "precision" are used to mean the agreement between repeated measurements, accepting that this excludes some nuance in statistical terms.

The analogy of a bull's eye target has often been used to visually represent accuracy and precision. In this analogy, the centre of the bull's eye target represents the "true" value of what is being measured, and marks on the target represent values produced by measurement. Accurate measurements are close to the centre of the target, and a precise

method of measurement will produce values that are close to one another. This is illustrated in Figure 4-1.

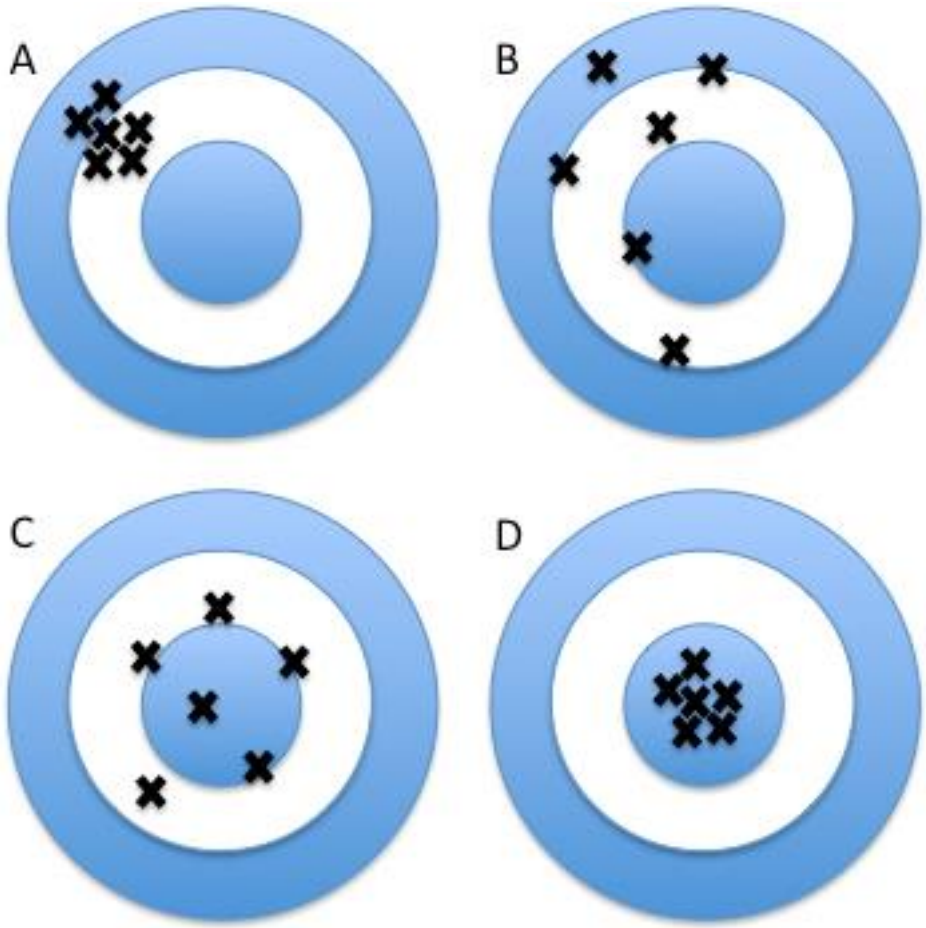

Figure 4-1: The bull's-eye analogy of accuracy and precision

A) Low accuracy, high precision; B) Low accuracy, low precision; C) High accuracy, low precision; D) High accuracy, high precision. Adapted from Streiner et al, 2006 (156).

As discussed in Section 1.4, different types of rational prescribing tools have different utilities and may vary in terms of accuracy or usefulness. For example, implicit criteria may be more accurate than explicit criteria because they are patient-specific and take into account co-prescriptions and patient factors (59). However, implicit criteria rely upon subjective judgements or understanding of clinical context by the assessor (15) meaning that they necessitate skilled or even expert assessors and may have lower precision. Correspondingly, explicit criteria may be less accurate in identifying "true" rates of rational prescribing due to inability to take into account individual patient factors or regional differences (for instance, in the case of differing patterns of antibiotic resistance

in different regions) (15), but these may have higher precision due to the objectivity of the criteria, represented by example A in Figure 4-1. Implicit criteria, which may be more accurate but less precise, are represented by example C.

Also described briefly in Section 1.4, there are several potential approaches to testing the accuracy and precision of rational prescribing tools. Their accuracy can be considered in two different ways. Firstly, the accuracy of a rational prescribing tool could reflect the degree to which it detects true rates of rational and irrational prescribing, as compared to their true incidence (which is unknowable) or to their measurement by another tool. Alternatively, bearing in mind that accuracy relates to the test results in the context of a specific purpose, the accuracy of rational prescribing tools could be considered to reflect the degree to which a tool detects rates of rational and irrational prescribing as correspond with adverse drug events or patient outcomes. In other words, the accuracy of a rational prescribing tool could be considered either its sensitivity to detecting non-gold standard prescribing, or its closeness of correlation with patient outcomes.

In order to be amenable to a clinical validation study, rational prescribing tools must either be limited to criteria that can be applied to large datasets that are already available, or authors must carry out a large, complex and costly study to collect all data required prospectively and follow-up patient outcomes. In their 2013 systematic review of rational prescribing tools for adults, Kaufmann et al found that 39 of the 46 tools they described had not had any clinical validation studies assessing correlation with patient outcomes (60). These studies had demonstrated correlation between potentially irrational prescribing as indicated by the tools and adverse patient outcomes, including probability of hospitalisation and risk of adverse drug reactions.

Many rational prescribing tools without clinical validation studies have instead been studied in their ability to detect potentially irrational prescribing in an appropriate clinical context. Without a comparator, these studies cannot be considered assessments of the accuracy of the tools, as the "true" value for potentially irrational prescriptions in those populations is not known. However, these studies do provide evidence of the potential usefulness of the tools by demonstrating their ability to highlight some inappropriate prescriptions and identifying the types of PIMs or PIOs the tool finds. They could

therefore be used to study these types of irrational prescribing futher, for instance investigating causative factors or interventions designed to improve rational prescribing.

As the POPI criteria were the first rational prescribing tool published for paediatric applications, and the only extant tool at the time of this work, it was not possible to design a protocol that compared the POPI UK criteria to an alternative measurement. Since the completion of the study reported in this chaper, a clinical validation study of the original POPI criteria has been published; this is discussed in comparison with the POPI UK study in 4.7.4.

4.2 Aims

The purpose of this study was to evaluate the applicability of the POPI UK criteria in clinical practice in a UK children's hospital.

The primary objective was to identify what proportion of children received prescriptions that can be assessed using the POPI UK criteria, and thereby to test the relevance of the tool in a UK paediatric population.

The secondary objectives were to assess rational prescribing according to the POPI UK criteria by:

- recording instances of PIMs or PIOs in screened prescriptions
- recording the setting of prescription and test whether there is any difference in rates of rational prescribing between settings, with the null hypothesis that there will be no difference between settings
- recording the age of patients and test whether there is any difference in rates of rational prescribing between age groups (infant, child and adolescent), with the null hypothesis that there will be no difference between patient groups

4.3 Methods

4.3.1 Study design

The POPI UK tool was used to prospectively assess paediatric prescriptions with a cross-sectional approach (i.e. each child's drug chart was scored against the POPI criteria at a single point in time), with reference to patient notes for information on symptoms and diagnoses, in inpatient and emergency department settings in the Royal Derby Hospital, Derby. This did not replace any usual practice of on-going review of prescriptions, for instance by clinical pharmacists.

Using retrospective pre-anonymised data was considered as an alternative to prospective data collection, however the POPI criteria require contemporaneous information about participants' symptoms and their prescriptions. As a combination of paper and electronic prescribing and paper and electronic medical record-keeping was in use in the Royal Derby Hospital at the time of data collection, prospective recruitment was felt to be a more reliable method of ensuring complete data collection. For example, some patients received handwritten outpatient prescriptions from the Children's Emergency Department; these did not automatically produce copies for filing on discharge and therefore information of how the prescription was written would not be available for retrospective analysis. This was necessary for full evaluation under the POPI criteria, for instance of the way in which liquid formulations have been prescribed (by dose and volume).

4.3.2 Recruitment

Participants were recruited from current inpatients in the paediatric inpatient wards and the Children's Emergency Department (children's ED) at the Royal Derby Hospital. All children in these departments were eligible for recruitment whether or not they presented with illnesses within the remit of the POPI criteria, and whether or not any medications were prescribed. The aim was to recruit 300 participants in each setting (sample size is discussed in 4.5.2).

Recruitment was undertaken between August 2016 and February 2017. All recruitment was undertaken during the day, including all days of the week.

4.3.3 Eligibility criteria

4.3.3.1 Inclusion criteria

- Age 0-15 years with parent/carer consent and optional assent or 16-18 with their own informed consent
- Inpatient in a paediatric ward or attendee to the Children's Emergency Department (children's ED) at the Royal Derby Hospital

4.3.3.2 Exclusion criteria

- Lack of good English language skills in the consenting parent/guardian and patient.
- Lack of informed consent given by parent/guardian in children aged 0-15 years, declining to assent aged 6-15 years or lack of consent in participants aged 16-18 years

4.3.4 Participant information literature

Parental participant information sheets and age-appropriate leaflets were developed to provide families with information about the study prior to obtaining consent. There is evidence that participant information provided in the course of research studies is often difficult for participants to read(158), which presents ethical challenges in ensuring consent is fully informed.

As discussed in Chapter 1.8.2, research that involves children may be perceived as more challenging because is likely to include children with varying developmental ages and literacy levels, all of whom must be catered for in the process of providing participants with information. However, while children's differing developmental ages are likely to be taken into account, it is often not considered that more than a quarter of adults in the UK have low literacy or numeracy skills, meaning that they "struggle with basic quantitative

reasoning or have difficulty with simple written information"(97). Readability assessments of sample educational materials intended to support informed consent have shown that texts produced in institutions with guidelines recommending language at a set reading level- the most common standard was eighth grade, the average reading level of adults in the US (159)- less than 10% meet this standard (160).

Strategies such as improving the readability of educational materials through ensuring that they use simple language, are short, clearly organised, and illustrated with images, and providing concurrent verbal information with the written information have been shown to improve understanding, although they do not entirely mitigate the effects of low literacy (91). These strategies are equally appropriate in research involving children as in adult studies, and it is important to consider parental literacy as well as the child's developmental stage and literacy.

For these reasons, in order to design information sheets that were accessible and useful to families, several steps were taken to maximise the readability and usefulness of the participant information sheets. All of the development and design of leaflets was undertaken by the author.

Firstly, parental information leaflets and information posters were designed. The drafts were then tested for accessibility and usefulness by attendance at the paediatric outpatient department and discussion of their design and content with families attending clinics, which included children of ages ranging from 1 year to 15 years. The majority of feedback was positive, such as comments of, "It explains everything" and "It is self-explanatory". Specific positive features included the detail about data storage, and a comment on the language being accessible for a family for whom English was a second language. However, one parent found that the information was "a bit worrying", as it made her concerned that her child might be being exposed to medication errors. Another parent felt that the word "tool" was misleading and commented that examples of POPI criteria would be helpful.

Taking into account participant and parent feedback, parental leaflets were redesigned, and then further designed leaflets containing the same information in simplified language

and with additional pictures for children. These were designed by age group, for participants aged 16-18 years, 13-15 years, and 6-13 years.

All leaflets were evaluated using Microsoft Word in-built readability statistics, which provide a Flesch-Kincaid reading grade level. This is a score that is used to reflect the number of years of education that might be required to understand a text, and it has been widely used to evaluate patient information material (160-162). The score takes into account length of sentences and average number of syllables in words to represent complexity of text. All leaflets were designed with the aim of a reading grade level less than 8.0, which corresponds approximately to an age of thirteen years. Work was then undertaken to amend the parent information sheets to achieve a Kincaid reading grade of 8.8 (see Appendix 9); this was partly limited by needing to include contact information for researchers including many polysyllabic words, e.g. "university" and "department".

The age-appropriate leaflets for ages 6-13 years were designed aiming for a lower age grade. Although grade 1 would approximately correspond to age six, this readability level was not targeted as it is extremely limiting given that polysyllabic words such as "medicines" and "children" needed to appear in the sheet. The draft of the age 6-13 participant information leaflet achieved a Kincaid reading grade of 4.1 (see **Error! Reference source not found.**10). The draft of the age 13-15 years leaflet and 16-18 leaflet (which used the same body text) achieved a Kincaid reading grade of 8.4, corresponding approximately to a reading age of 13 years (see Appendices 11 and 12).

However, subsequent to the design of the participant and parental information sheets, after submission to the University ethics board, required phrasing had to be introduced for many sections to meet University requirements of specific language that had to be included in any participant information sheets used in University research. These rules did not mandate changing the information sheets for children under the age of 16 years but required inclusion of mandatory phrases in all parental information sheets and those for participants aged 16-18 years who might be consenting for themselves. The leaflets were therefore redesigned using the University mandated language (see **Error! Reference source not found.** 13). As a result, the Kincaid reading grade of each was 9.5, corresponding approximately to a reading age of 15 years, above the recommended readability standard of most institutions.

4.3.5 Data collection

Families were approached by a researcher, who explained the study and sought informed consent for participation. As discussed in 4.3.4 written participant information sheets were provided to parents, with age-appropriate information leaflets for children (see Appendices 10, 11, and 13). After consent was given, there was no further active involvement with the participant.

The author fulfilled the role of researcher for the majority of recruitment (86%), with assistance from two research nurses, Janine Abramson and Coral Smith, who recruited 14% of participants.

The researcher reviewed the participants' records in the department and transcribed data from the participants' prescriptions and medical notes onto a case report form (CRF), see Figure 4-2. POPI UK criteria were recorded using codes for relevant diagnoses and PIMs or PIOs with reference to a POPI UK criteria code document (see Appendix 8).

PIN: Completed by: Date:Macintosh
HD:Users:ella:Documents:PhD:Writing:Thesis writing:Chapter 4 Clinical assessment of modified POPI:Documents for ethics approval etc:Final versions:CRF Rational prescribing in children v1.5 date 6.4.16 amended.docx

CASE REPORT FORM

A Study into the Validity and Usefulness of the modified Pediatrics: Omission of Prescriptions and Inappropriate Prescriptions (POPI) Tool to Assess Rational Prescribing in Children

Rational Prescribing in Children

Chief Investigator: Dr Helen Sammons
Sponsor Reference: RGS 15097
IRAS Project ID: 191321
Site: Derby Children's Hospital
CRF version number: v1.1

Figure 4-2: Case report form

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

PIN: Completed by: Date:Macintosh
HD:Users:ella:Documents:PhD:Writing:Thesis writing:Chapter 4 Clinical assessment of modified POPI:Documents for ethics approval etc:Final versions:CRF Rational prescribing in children v1.5 date 6.4.16 amended.docx

CRF Completion Instructions

Complete the CRF using a **black ballpoint pen** and ensure that all entries are complete and legible.

Avoid abbreviations and acronyms.

Complete the Participant Information Number reference sheet before completing the CRF.

Do not use subject identifiers anywhere on the CRF, such as name, hospital number etc., in order to maintain the confidentiality of the subject. Ensure that the PIN is completed on each page.

Each page should be signed and dated by the person completing the form.
The 'completed by' Name in the footer of each page must be legible and CRFs should only be completed by individuals delegated to complete it.

Ensure that all fields are completed on each page:

- Where information is Not Known write **NK** in relevant space
- Where information is not applicable write **NA** in the relevant space

Corrections to entries
If an error is made, draw a single line through the item, then write the correct entry on an appropriate blank space near the original data point on the CRF and initial and date the change.

Do NOT

- Obscure the original entry by scribbling it out
- Try to correct/ modify the original entry
- Use Tippex or correction fluid

Age should be recorded to the nearest whole month if under 2 years, or to the nearest whole year if over 2 years.

Storage
CRF documents should be stored in a locked, secure area when not in use where confidentiality can be maintained. Ensure that they are stored separately to any other documents that might reveal the identity of the subject.

Rational prescribing in children CRF: v1.5 date 6.4.16 Page 2 of 3

Figure 4–2: Case report form

PIN: Completed by:

UNITED KINGDOM • CHINA • MALAYS

Case Report Form

Site: (delete as appropriate) Ward / CED

Participant age: _____

Participant diagnoses/symptoms:

Diagnoses	Symptoms

Does the participant have symptoms or a diagnosis within the modified POPI tool? (delete as appropriate)

Yes / No

If yes, what? (Use modified POPI tool codes A-T): _____

Medications prescribed:

Medication	Dose	Route	Frequency	Duration if indicated	Prescriber (profession & grade)	Indication if documented

Does the participant have any errors or omissions according to the modified POPI tool? (delete as appropriate)

Yes / No

If yes, what? (Use modified POPI tool codes A#-T#): _____

Rational prescribing in children CRF: v1.5 date 6.4.16 Page 3 of 3

Figure 4–2: Case report form

4.4 Ethics approval

Ethics approval was secured from the Brighton & Sussex Research Ethics Committee (REC reference 15/LO/2191), see Appendix 14. In addition, the University of Nottingham Research & Development department approved and sponsored the study (Appendix 15). Trust approval was granted by the Derby Hospitals NHS Foundation Trust (Appendix 16).

4.5 Statistical analysis

4.5.1 Methods of statistical analysis

All data were analysed in Microsoft Excel. Analysis included calculation of mean and median number of prescriptions per child, rates of inappropriate prescribing types according to the POPI screening tool, and calculation of difference between mean rates of inappropriate prescribing in different age groups, sex, and by types of prescribers using the chi-squared test.

4.5.2 Sample size and justification

A sample size power calculation was not calculated, as there are no relevant data available about expected proportions of participants who will fall within the POPI UK criteria to inform a power calculation. The WHO have recommended a sample size of 600 clinical encounters in total in studies evaluating rational prescribing (54) Therefore, the target was to recruit 300 patients for each clinical area, with a total of 600 patients recruited.

4.6 Results

4.6.1 Population characteristics

In total, 598 participants were recruited (due to erroneous numbering of consecutive consented patients) with 299 patients recruited from the paediatric inpatient wards and

299 from the Children's Emergency Department (children's ED). A total of 1,608 prescriptions were analysed, of which 1,279 were prescribed for the inpatient population, and 329 in the ED. Patient demographics including clinical (diagnostic) codes and common medications prescribed are shown in Table 4-A.

Table 4-A: Patient demographics

	Number of participants		
	Inpatient	ED	Total
Age (years)			
<1	109	42	151
1-5	97	112	209
6-10	42	73	115
11-15	33	64	97
>15	18	8	26
Number of medications prescribed			
0	23	103	126
1-5	202	195	397
6-10	60	1	61
11-15	9	0	9
>15	5	0	5
Clinical indications (affecting five or more participants)			
Pain and fever	183	190	373
Vitamin supplements and antibiotic prophylaxis	115	127	242
Nausea, vomiting, or gastrooesophageal reflux	97	65	162
Cough	65	37	102
ENT infections	20	31	51
Diarrhoea	29	17	46
Urinary infections	17	3	20
Bronchiolitis	13	2	15
Asthma	7	4	11
Atopic eczema	4	3	7
Epilepsy	5	1	6
Medications (prescribed to 20 or more participants)			
Paracetamol	223	93	316
Ibuprofen	130	75	205
Salbutamol	54	19	73
Amoxicillin	60	5	65
Morphine	54	5	59
Co-amoxiclav	42	9	51
Cefotaxime	42	0	42
Ondansetron	38	1	39
Ipratropium	26	4	30
Prednisolone	26	3	29
Oral fluids	9	17	26
Cefuroxime	25	0	25
Cyclizine	24	1	25

Patient age ranged from 3 days to 17 years; distribution of patient age is shown in Figure 4-3 and Figure 4-4.

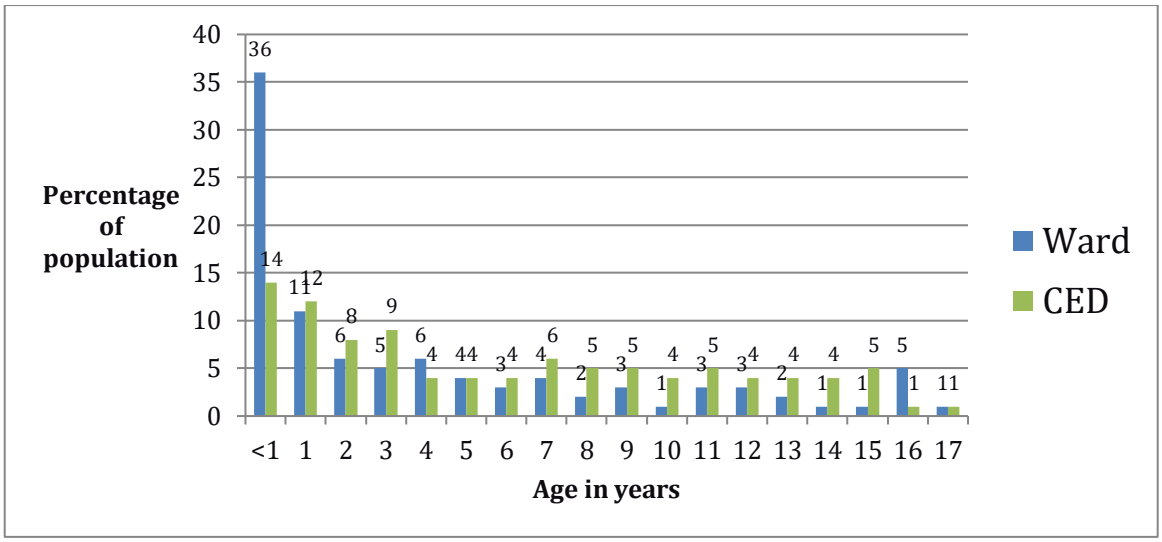

Figure 4-3: Age of recruited participants

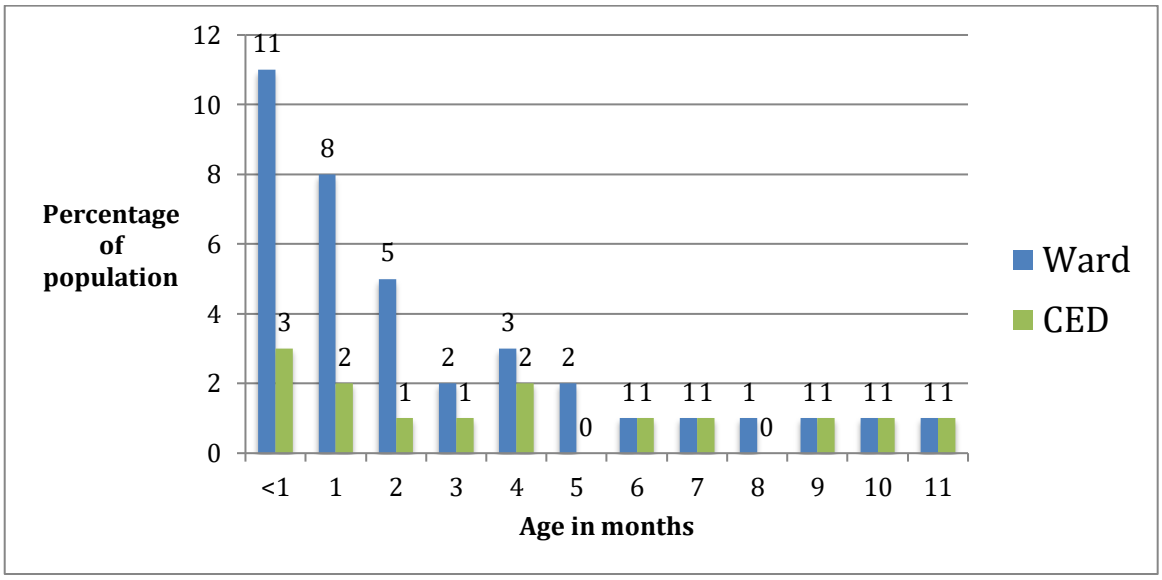

Figure 4-4: Age of recruited participants under 1 year

The mean age in the inpatient group was 4 years and 4 months, the mean age in the ED group was 6 years and 2 months, with an overall mean for the population of 5 years and 3 months. The median age in the inpatient group was 2 years, the median in the ED group was 5 years, and the overall median age was 3 years.

The most common clinical category from POPI UK observed in the population was pain or fever, affecting 373 participants. Corresponding with this finding, the two most common prescriptions were paracetamol and ibuprofen, prescribed to 316 and 205 participants respectively. Alongside analgesia, common medication groups included antibiotics, bronchodilators and antiemetics, as well as prednisolone and oral fluids. The latter, oral fluids, are not prescription-only or even medication in the usual definition. However, documentation of oral fluid challenges or treatment was documented alongside prescribing data in order to assess relevant criteria related to oral rehydration solution for diarrhoea or vomiting.

Prescriber background could not be recorded for all prescriptions, but prescribers included a range of backgrounds and experience including paediatric consultants, paediatric specialty trainees, GP trainees, and nurse practitioners.

4.6.2 Evaluation of POPI UK criteria: relevance to study population

The primary aim of this study was to identify what proportion of children received prescriptions that can be assessed using the POPI UK criteria.

Out of 598 patients, 574 had at least one documented symptom or diagnosis included in the POPI UK criteria; 292 patients in the inpatient group and 282 in the emergency department group. The most frequent was pain or fever (373), with other frequent indications being vitamin supplements and antibiotic prophylaxis (242), nausea, vomiting or gastro-oesophageal reflux (162), cough (102), and ENT infections (51). Some patients had symptoms or diagnoses that related to multiple categories. Six categories were not relevant to any patients in the study population. The number of patients presenting with symptoms or diagnoses relevant to each of the categories in the tool is shown over page in Table 4-B.

Table 4-B: Patients with symptoms or diagnoses related to each POPI UK category

POPI UK tool category	Number of patients presenting with related symptoms or diagnosis (by setting)		
	Inpatient	**ED**	**Total**
Pain and fever	183	190	373
Vitamin supplements and antibiotic prophylaxis	115	127	242
Nausea, vomiting, or gastrooesophageal reflux	97	65	162
Cough	65	37	102
ENT infections	20	31	51
Diarrhoea	29	17	46
Urinary infections	17	3	20
Bronchiolitis	13	2	15
Asthma	7	4	11
Atopic eczema	4	3	7
Epilepsy	5	1	6
Herpes simplex	1	0	1
Depression	0	1	1
Anorexia	1	0	1
ADHD	1	0	1
Acne vulgaris	0	0	0
Scabies	0	0	0
Lice	0	0	0
Ringworm	0	0	0
Impetigo	0	0	0
Nocturnal enuresis	0	0	0

There were a number of frequent diagnoses that are not contained within any of the categories of the POPI UK criteria. Uncoded diagnoses with at least fifteen cases in the study population were: lower respiratory tract infections (LRTI), viral-induced wheeze, appendicitis, sepsis, soft tissue injury, and fracture. These are listed in Table 4-C.

Table 4-C: Common diagnoses in study population that are not contained in the POPI UK criteria

Diagnosis	Number of cases in study population
Viral-induced wheeze	50
Sepsis	46
Soft tissue injury	39
Lower respiratory tract infection	34
Appendicitis	20
Head injury	18
Meningitis	16
Jaundice	15

The most common uncoded diagnosis found in the study population was viral-induced wheeze, followed by sepsis and soft tissue injury. Only seven of the original categories in the tool had more cases than those listed in Table 4-C.

4.6.3 Potentially inappropriate medicines and omissions detected by the POPI UK criteria

One secondary aim was to identify any instances of PIMs or PIOs in the study population. There were 282 instances of PIMs and PIOs identified in 261 of the 598 (44%) participants, with more than one PIP/PIO for some participants. The categories of identified potentially inappropriate prescribing are shown in Table 4-D.

Table 4-D: Categories of identified PIMs and PIOs

Clinical category	Number
Vitamins and Antibiotic Prophylaxis	242
Pain and fever	30
Bronchiolitis	4
Nausea, vomiting and gastro-oesophageal reflux	2
Atopic eczema	2
ENT infection	1
Asthma	1
Total	282

As shown in Table 4-D, the majority of PIMs and PIOs fell within just two categories: 242 related to vitamins and antibiotics prophylaxis, 30 related to pain and fever. The related clinical categories of all identified PIMs/PIOs are further broken down in Table 4-E.

Table 4-E: Specific PIMs and PIOs detected

Clinical category	Criterion	Nº of cases
Vitamins and Antibiotic Prophylaxis	Omission: Healthy Start vitamins for infants and children 6 months- 5 years or having less than 500mL infant formula per day	242
Pain and fever	Omission: Failure to give an osmotic laxative to patients being treated with morphine for a period of more than 48 hours	22
	Inappropriate prescription: Prescription of two alternating antipyretics as a first-line treatment	7
	Inappropriate prescription: Prescription of a medication other than paracetamol or ibuprofen as a first-line treatment for pain (except in the case of migraine)	1
Bronchiolitis	Inappropriate prescription: Antibiotics, ß2 agonists or corticosteroids to treat bronchiolitis	4
Nausea, vomiting and gastro-oesophageal reflux	Inappropriate prescription: Acid-suppressing drugs to treat overt regurgitation in the absence of feeding difficulties, distress, or faltering growth	1
	Omission: Oral rehydration solution (ORS) for dehydrated children unless IV fluid therapy is indicated (shock, red flag symptoms despite ORS, persist vomiting of ORS)	1
Atopic eczema	Inappropriate prescription: More than one application per day of a dermocorticoid, except in cases of severe lichenification	1
	Inappropriate prescription: Prescription of antihistamines except as a trial for severe itching or where sleep disturbance has a significant impact on the child or carers	1
ENT infection	Inappropriate prescription: An antibiotic for < 4 days symptoms of acute upper respiratory tract infection except: • bilateral acute otitis media in children younger than 2 years • acute otitis media in children with otorrhoea • acute sore throat/acute pharyngitis/acute tonsillitis when three or more Centor criteria are present.	1
Asthma	Omission: Preventative treatment (inhaled corticosteroids) in the case of persistent asthma	1

As Table 4-E shows, a single criterion relating to vitamins dominated, with 242 cases related to that criterion alone. There were several other criterion with multiple identified instances, two in the category of pain and fever, and one relating to bronchiolitis.

In 38 prescriptions, it was not possible to determine whether or not an inappropriate prescription or omission had occurred according to the POPI UK criteria. In some cases, there was uncertainty about a PIM or PIO in more than one category. The specific criteria cited and reasons for uncertainty are listed in Table 4-F.

Table 4-F: Cases where it was not possible to determine whether a PIM/PIO had been made according to the POPI UK criteria

Clinical category	Criterion	Reason for uncertainty	Number of cases
Nausea, vomiting, or gastro-oesophageal reflux	Omission: Oral rehydration solution (ORS) for dehydrated children unless IV fluid therapy is indicated (shock, red flag symptoms despite ORS, persist vomiting of ORS) distress, or faltering growth	Types of oral fluids used for oral fluid challenge not specified	12
		Indication for GORD treatment not documented	3
	Inappropriate prescription: Acid-suppressing drugs to treat overt regurgitation in the absence of feeding difficulties,	Hydration status not specified	2
		Subjective: "distress"	1
Diarrhoea	Omission: Oral rehydration solution (ORS) for dehydrated children unless IV fluid therapy is indicated (shock, red flag symptoms despite ORS, persist vomiting of ORS)	Type of oral fluids used for oral fluid challenge not specified	4
		Hydration status not documented	2
ENT infections	Inappropriate prescription: An antibiotic for < 4 days symptoms of acute upper	Centor criteria not documented	4
		Duration of symptoms not documented	1

	respiratory tract infection (except: • bilateral acute otitis media in children younger than 2 years • acute otitis media in children with otorrhoea acute sore throat/acute pharyngitis/acute tonsillitis when three or more Centor criteria are present.	Specific indication for antibiotics not clear from documentation	1
	Inappropriate prescription: Antibiotic treatment for a sore throat except in severe cases (anticipated to be no more than 20% of cases)	Subjective: definition of "severe"	1
Pain and fever	Omission: Failure to give an osmotic laxative to patients being treated with morphine for a period of more than 48 hours	On-going loose stools	4
		Duration morphine not specified	1
Bronchiolitis in infants	Inappropriate prescription: Antibiotics, ß2 agonists or corticosteroids to treat bronchiolitis	Antibiotics given but indication documented as chest infection although only listed diagnosis bronchiolitis	2
Atopic eczema	Inappropriate prescription: More than one application per day of a dermocorticoid, except in cases of severe lichenification	Frequency of application not documented	1
Attention deficit disorder with hyperactivity	Omission: Recording a growth chart (height and weight) if the patient is taking methylphenidate	Not documented whether growth chart being completed for patient	1
Total			40

In some of the instances described in Table 4-F, the reason for the case being documented as "Uncertain" was due to clinical reasoning making the criterion irrelevant, while the proposition itself did not give room for subjective reasoning. For instance, laxatives would clearly be inappropriate in the context of diarrhoea, despite ongoing prescription of potentially constipating opiates. In other instances, overview of clinical documentation and prescriptions did not provide adequate information, such as frequency of application of a topical prescription, or the presence or absence of growth documentation elsewhere.

4.6.4 Settings of prescribing and rates of potentially inappropriate prescribing

Another secondary aim of this study was to evaluate whether there was any difference in rates of rational prescribing between settings. A null hypothesis of no difference was not assessed with statistical testing as it was deemed that the numbers were not sufficient for meaningful testing. However, the rates of PIMs and PIOs detected did differ between the two settings studied, a children's emergency department and an inpatient ward.

As discussed above, the distribution of age of participants presenting to the two settings was quite different, as illustrated in Figure 4-3 and Figure 4-4, with many more patients aged less than 1 year in the inpatient population (36%) compared with the emergency department (14%). Another important difference between settings was the number of medicines prescribed. A total of 1,608 medications were prescribed for the study population as a whole. 1,279 were prescribed for patients in the Inpatient setting, and only 329 for patients in the ED. The rates of potentially irrational prescribing in each setting therefore need to be evaluated in the context of the number of children with relevant indications and the total number of medicines prescribed.

In total, 14 PIMs were identified in the inpatient setting and two in the ED. These are further subdivided by clinical category in Table 4-G. PIOs were again affected by the high rates in the vitamins category, with 138 PIOs in the inpatient setting and 128 in the ED. Excluding the vitamins category, there were 23 PIOs identified in the inpatient group and one in the ED.

Table 4-G: Inappropriate prescriptions and omissions by setting

	Inappropriate prescriptions		Inappropriate omissions	
Clinical category	**Inpatient**	**ED**	**Inpatient**	**ED**
Vitamins and antibiotic prophylaxis	0	0	115	127
Pain and fever	7	1	21	1
Bronchiolitis	4	0	0	0
Nausea, vomiting and gastro-oesophageal reflux	1	0	1	0
Atopic eczema	2	0	0	0
ENT infection	0	1	0	0
Asthma	0	0	1	0
Total (excluding vitamins)	14	2	138 (23)	128 (1)

As this shows, the inpatient population had more potentially inappropriate prescribing identified in both categories, whether the vitamins category was included or not. Most striking were the higher number of PIMs, half of which were due to PIMs relating to pain and fever.

In order to take into account the different numbers of patients within relevant categories in the different settings, the numbers of PIMs/PIOs identified need to be considered in the context of total numbers of prescriptions. The number of PIMs/PIOs as compared with total number of medicines prescribed is shown below in Table 4-H.

Table 4-H: Numbers of prescriptions and potential irrational prescribing by setting

Setting	Number of prescriptions	PIMs	PIOs	Total PIMs and PIOs
Inpatient	1,279	14	138	152
ED	329	2	128	130

The higher rates of potentially inappropriate describing identified in the inpatient group and possible reasons for this finding are discussed further in 4.7.2.3.

4.6.5 Age of participants and potentially inappropriate describing

Identified instances of either type of potentially inappropriate prescribing were not evenly distributed across the age groups, with a much higher proportion occurring in the 1 to 5 year age group, as shown in Table 4-I below.

Table 4-I: Rates of potentially inappropriate prescribing by age group

Age group	Number of participants	Number with potentially inappropriate prescribing identified (%)
<1 year	152	38 (25)
1 to 5 years	208	208 (100)
6 to 10 years	115	6 (5)
11 to 15 years	97	5 (5)
> 15 years	26	4 (15)

Clearly, this result is significantly affected by the fact that the vitamin criterion related to all participants between age 6 months and 5 years. Excluding this criterion, rates by age group are shown in Table 4-J.

Table 4-J: Rates of potentially inappropriate prescribing excluding vitamin criterion by age group

Age group	Number of participants	Number with potentially inappropriate prescribing (%)
<1 year	152	8 (5)
1 to 5 years	208	14 (7)
6 to 10 years	115	6 (5)
11 to 15 years	97	5 (5)
> 15 years	26	4 (15)

This shows that while potentially inappropriate prescribing occurred most often in the 1-5 years age group, as a proportion of the population the group over 15 years was more affected, with 15% of this group having either a PIP or PIO.

4.7 Discussion

4.7.1 Appropriateness of clinical categories in the POPI UK criteria to the study population

This study demonstrated that the POPI UK criteria were applicable to a large majority of patients (574/598, 96%). However, two categories contributed a large number of patients to this finding. The category of vitamin supplements and antibiotic prophylaxis was relevant to 242 patients, all of which were due to patient age (with one criterion stating that an inappropriate omission would be the omission of Healthy Start vitamins for infants and children aged 6 months to 5 years or having less than 500mL infant formula per day). This captured a large proportion of the study population, of which a quarter were aged under 1 year and 60% under 6 years. Forty-three of these patients presented with vitamin supplements and antibiotic prophylaxis as their only relevant clinical condition, while 199 had concurrent symptoms or diagnoses relevant to other categories.

Pain and fever was also a category relevant to many patients (373/598) with a range of diagnoses that presented with the symptoms of pain or fever. Of these, 232/373 presented with other categories included in the criteria and 141/373 presented with pain and fever as their only included clinical condition.

Excluding these two categories, only 35% (390/598) still had a symptom or condition that is included in the tool.

In the category of vitamins and antibiotic prophylaxis, every patient between 6 months and 5 years of age was considered as having a PIO, in that Healthy Start vitamins were not prescribed for any child in this study, as per the criterion. However, in collecting data from clinical notes, it was not possible to determine whether patients were receiving infant formula, or the volume if so. Coding this as a PIO unknown for all patients under two years was considered, as a diet high in infant formula was considered possible, but the precise cut-off would have been chosen without good evidence base. Absence of recording adequate infant formula in the diet was therefore accepted as evidence that the omission was not a rational decision and so falls within irrational prescribing.

While alternative data collection methods would be able to access detailed dietary information, for instance via data collection from parents, this is a serious limitation for a tool aiming to assess quality of prescribing, as it cannot be scored from prescribing and clinical coding data. This limitation is also true of a number of other criteria, for instance the omission "Recording a growth chart (height and weight) if the patient is taking methylphenidate" for patients with ADHD as shown in Table 4-F. A full list of criteria that may not be measurable from prescribing and clinical coding data alone is shown in Table 4-K. Some of these criteria could have been coded as PIOs on the same basis, for the 102 patients presenting with cough, one with anorexia and one with ADHD.

Table 4-K: POPI UK criteria that cannot be scored using only prescribing and clinical coding data

Clinical category	Criterion
Vitamin Supplements and Antibiotic Prophylaxis	Healthy Start vitamins for infants and children 6 months- 5 years or having less than 500mL infant formula per day
Cough	Failure to propose a whooping cough vaccine for pregnant women.
Scabies	Decontamination of household linen and clothes and same day treatment of all members of the household
Anorexia	Prescription of medications as a sole or primary treatment for anorexia nervosa
ADHD	Recording a growth chart (height and weight) if the patient is taking methylphenidate

In the case of the criterion related to scabies, no patients were recorded with this indication. The one patient with anorexia nervosa did not have any medications prescribed, making it clear the PIM of "Prescription of medications as a sole or primary treatment for anorexia nervosa" did not apply. In other cases, the decision against this approach was subjective. For instance, in no instance was the presence of a pregnant woman noted in the patient records of cases of cough, therefore it seemed unreasonable to record absence of documentation about advice for whooping cough vaccine as a PIO.

The results demonstrate that pain and fever are highly prevalent conditions in the paediatric population attending the emergency department and those admitted as inpatients and are therefore appropriate targets for studying rational prescribing.

However, when the categories of pain and fever and vitamin supplements and antibiotic prophylaxis are excluded, approximately two-thirds (65%) of patients in this population had no presenting symptoms or diagnoses that are contained within the tool.

The diagnoses in Table 4-C may represent further appropriate conditions to consider when assessing quality of prescribing, if a broadly inclusive strategy such as POPI is being used. For example, viral-induced wheeze is a condition for which the management has changed substantially and repeatedly in recent years (163, 164). While controversy remains around some approaches to treatment, other treatments are known to be ineffective but continue to be prescribed (165). Sepsis is also a frequent condition observed in the study population that is not included in POPI UK. This is a condition known to be time-critical in terms of pharmaceutical management with antimicrobial therapy in both adults (166) and children (167), with strong evidence for reduced mortality and organ failure resulting from optimal prescribing (i.e. antimicrobial therapy within one hour of recognition of sepsis), suggesting this would be a valuable target for improving prescribing practice.

4.7.2 Potentially inappropriate medicines and omissions detected in this study

In total, 282 PIOs or PIOS were detected, out of 1,607 prescriptions, with a rate of 17.5%. These occurred in 258 of the 598 participants (43%), with more than one PIM/PIO in some cases.

However, the "rate" must be interpreted with the understanding that it is possible for there to be more than one PIM/PIO for a single prescription within the POPI UK criteria. For example, a patient prescribed morphine as the only treatment for pain for several days would have both a PIM and a PIO (Inappropriate medicine: *Prescription of a medication other than paracetamol or ibuprofen as a first-line treatment for pain (except in the case of migraine)* and Omission: *Failure to give an osmotic laxative to patients being treated with morphine for a period of more than 48 hours*). If this patient were the only participant studied, this would generate a PIM/PIO rate of 200%.

4.7.2.1 Comparing potentially inappropriate medicines and potentially inappropriate omissions

Of the 282 PIM/PIOs, only sixteen comprised PIMs, while 266 were PIOs. Out of 1,607 prescriptions, this represents a 1% rate of PIMs and 16.4% rate of PIOs. However, a large majority of omissions related to a single vitamin-related criterion (discussed in detail below); excluding the Health Start vitamin criterion, there were 24 PIOs, a rate of 1.5%.

4.7.2.2 Comparing potential irrational prescribing within each clinical category

The most common category in which potentially irrational prescribing was detected was vitamin supplements and antibiotic prophylaxis, specifically in prescription of Healthy Start vitamins (239 cases). There were no prescriptions of Healthy Start vitamins to any patient in the study population. Given this complete omission, it seems possible that rather than this representing a 100% PIO rate in the study population, this may instead demonstrate that the criterion is not appropriate for evaluation of prescriptions. The NHS website with patient and healthcare professional information about Healthy Start vitamins (168) describes distribution points in England, Scotland, Wales, and Northern Island, including inviting parents to apply for coupons by post or by contacting midwives or health visitors. This highlights that the usual source of Healthy Start vitamins is unlikely to be via prescription and might not therefore be detected in an inpatient setting if parents continue to give these to their children even in hospital. Alternatively, this may demonstrate a genuine deficit; it would be useful to evaluate the nutritional guidelines of UK paediatric hospitals to assess whether nutritional supplements are considered and whether vitamins are provided as non-prescribed nutritional supplements, intentionally omitted during inpatient stays, or unintentionally omitted during inpatient stays.

Excluding the vitamin PIO from analysis, there were 40 PIMs/PIOs identified, with a rate of 2.5%. Thirty-seven of these were in the inpatient group (a rate of 2.9%) and three in the emergency department (a rate of 0.9%).

The second most frequently detected potentially irrational prescribing was the PIO of "Failure to give an osmotic laxative to patients being treated with morphine for a period of more than 48 hours", which occurred in 22 cases. Of those cases, 21 occurred in the

inpatient setting and one in the emergency department, which may reflect the increased likelihood of strong analgesia being given as a "stat" or one-off prescription in the emergency setting, as compared with patients receiving more than 48 hours of care in the inpatient setting.

The third most frequent potentially irrational prescribing was also in the category of Pain and Fever, "Prescription of two alternating antipyretics as a first-line treatment". All seven instances of this PIM occurred in the inpatient setting, which may again highlight that this is a type of irrational prescribing to which patients may be more vulnerable during on-going periods of treatment compared to periods of assessment and initial management. However, this may also reflect difficulty in capturing data about use of non-prescribed medicines in an outpatient population, as two commonly used antipyretics in the UK, ibuprofen and paracetamol, are both available without prescription. Therefore parental use of these medications would be important contributors to their use, both rational and irrational, but would not be captured through analysis of prescribing.

The only other potentially irrational prescribing detected more than once was in the category of Bronchiolitis, the PIM of "Antibiotics, ß2 agonists or corticosteroids to treat bronchiolitis". This was detected in four cases, again all in the inpatient setting. The specific potentially inappropriate medicines prescribed for patients with the diagnosis of bronchiolitis were antibiotics (cefuroxime, amoxicillin, azithromycin, clarithromycin, and co-amoxiclav) and salbutamol (ß2 agonist). This may relate to the diagnostic uncertainty between severe bronchiolitis and bacterial lower respiratory tract infection, however these cases were only coded as potentially irrational prescribing if there were no alternative diagnoses listed in the patient's case notes that demonstrated clinician diagnostic uncertainty. For example, two cases were coded as "possible G1" but rejected due to patient diagnoses including in one case "? sepsis, ? bronchiolitis" and in the second case, "? chest infection, ? bronchiolitis", documenting clinical uncertainty around the diagnosis.

4.7.2.3 Comparing inpatient versus emergency department populations

There was a substantial difference in the number of prescriptions between the two populations. There were 1,279 prescriptions for the patients in the inpatient population, compared with 329 prescriptions for the patients in the emergency department. This may

reflect the higher complexity and morbidity of children who require inpatient admission, as well as some participants being on regular medications that were not required to be prescribed while in the emergency department, but which would have appeared in their prescriptions once admitted.

There were 152 PIMs/PIOs in a total 1,279 prescriptions (12%) in the inpatient population, and 130 PIMs/PIOs in the emergency department out of 329 prescriptions (40%). This shows that while there were more PIMs/PIOs detected in the inpatient group, there was a much higher rate in the emergency department when the lower number of prescriptions per patient is taken into account.

However, excluding the vitamin category, there were only 37 instances of potentially irrational prescribing in the inpatient population and three in the emergency department population. This is due to the effect of differences in the age of participants in the different settings, as the vitamin-related PIO applied to all patients age 6 months to 5 years. There were many more participants in this category in the inpatient compared with the emergency department population.

The clinical categories in which potentially irrational prescribing was detected also differed between the populations. These are shown below in Table 4-L.

Table 4-L: Clinical categories of potential PIMs and PIOs in the inpatient and emergency department populations

Clinical category	Number of PIMS and PIOs/number of patients with relevant clinical category (%)	
	Inpatient	Emergency department
Vitamin supplements and antibiotic prophylaxis	115/206 (56)	127/154 (82)
Pain and fever	28/174 (16)	2/199 (1)
Bronchiolitis	4/7 (57)	0/8 (0)
Nausea, vomiting, or gastroesophageal reflux	2/93 (2)	0/69 (0)
Atopic eczema	2/3 (67)	0/4 (0)
ENT infections	0/24 (0)	1/27 (4)
Asthma	1/8 (13)	0/3 (0)

These data demonstrate that the higher rate of identified potentially irrational prescribing in the inpatient population (excluding the vitamin category) does not correlate with higher numbers of patients with a relevant clinical indication. That is to say that there are patients present in the emergency department population with the same indications for prescribing in whom potentially irrational prescribing has not been detected. There are several possible explanations for this observation.

The higher numbers of medicines prescribed in the inpatient population may have increased observed rates of PIMs. In addition, it may be that children in this group had greater morbidity, e.g. anti-emetics for nausea or vomiting may be considered clinically indicated for patients whose severity warrants admission, or inpatients may be more likely to have other causes for nausea and vomiting besides gastroenteritis, thereby justifying use of anti-emetics. Bronchiolitis was an area with a 57% rate of PIM compared with none in the ED group; again, more severe morbidity may account for patients having been prescribed antibiotics, for example, in case of an alternative diagnosis of bacterial infection. However, cases were only rated as PIMs if bacterial infection was not stated as a diagnosis, which may suggest these are cases of true inappropriate prescribing.

4.7.3 Usefulness of the POPI UK criteria in identifying potentially inappropriate prescribing

This study demonstrated the POPI UK criteria were used to successfully identify a number of PIMs and PIOs in the study population. However, 242/282 of these related to the single vitamin criterion, with 39 other PIMs or PIOs identified. In addition, there were 30 cases where it was undeterminable whether or not a PIM or PIO had occurred.

In most cases where a PIM or PIO could not be determined, this was due to the highly detailed nature of the POPI UK's implicit criteria, such as requiring knowledge of the patient's complete diet, or documentation not included on either electronic or paper prescribing nor in clinical notes. These included examples such as the presence or absence of a growth chart, the hydration status of the patient at the time of prescribing, or all examination features needed to calculate a Centor score in tonsillitis. In other cases, the issue was subjectivity of terms in the criteria such as "severe" and "distress", which, if

not explicitly documented by the prescribing clinician, could not readily be inferred by the POPI UK coder.

These cases of indeterminate criteria highlighted that a comprehensive view of patient data is required to code patient data using the POPI UK criteria. In comparison, explicit criteria such as the STOPP/START criteria for geriatric medicine can be applied to more limited datasets such as prescribing databases with only coded diagnoses and prescriptions(169). This facilitates application of the criteria to potentially very large datasets, including previously acquired data and data matched to patient outcome measures, such as a 2015 population-based cohort study of older adults in Ontario using Beers and STOPP/START criteria(110). PIPc was also designed to be applicable to retrospective prescribing datasets, although there may be limitations in their application, as discussed in Section 2.5.4.

The highly detailed criteria of the POPI UK tool are also likely to necessitate a clinically trained coder who is able to understand the specific clinical terminology of inclusions and exclusions described within criteria. Some criteria require good knowledge of technical language, e.g. "otorrhoea", and others specific knowledge of symptoms, e.g. the presentation of "overt regurgitation" in infants, or "red flag symptoms" of dehydration.

The fact that indeterminate cases almost equalled identified PIMs and PIOs appears to highlight a significant limitation to the POPI UK tool. However, as discussed in 4.1.1, this is a limitation that may be expected in highly detailed implicit criteria, where the detail allows for more accurate results but makes scoring the tool more challenging. It may be expected that therefore the precision, or repeatability, of the POPI UK tool might be low, given the difficulty of coding using the POPI UK criteria as revealed in this study.

4.7.4 Comparison with published clinical evaluation of French POPI criteria

There is one published validation study of the French POPI criteria, published as an abstract (129) and subsequently in the British Medical Journal Open (123).

Similar to this clinical evaluation of the POPI UK criteria, the POPI criteria were evaluated in their usefulness to detect potential irrational prescribing, without directly

studying association with adverse drug effects or patient outcomes. Unlike the evaluation of the POPI UK criteria, the French POPI criteria were conducted as retrospective analysis of prescription data. Patient data were drawn from two study populations: an emergency department and a community pharmacy. A total of 18,562 prescriptions for 15,973 patients in the emergency department and 4,780 prescriptions for 2,225 patients in the community pharmacy were analysed.

One important difference in study protocol was that, despite the POPI criteria assessing for PIOs, their clinical validation study inclusion criteria mandated inclusion only of children who had been prescribed one or more medications. This is in contrast to the approach to the validation of the POPI UK tool, where participants were eligible even without any prescriptions, in order to enable greater capture of potentially inappropriate omissions. As the tools both assess for PIOs as well as PIMs, this may cause a falsely low rate of omissions being identified. In addition, in the original POPI study only primary diagnoses and their related prescriptions were evaluated, rather than all diagnoses and prescriptions (123).

In the French POPI study, PIMs and PIOs were analysed separately. The rate of PIMs was 2.9% in the emergency department and 12.3% in the community pharmacy. PIOs were detected in 2.3% of prescriptions in the emergency department and 6.1% in the community pharmacy.

In comparison, the UK POPI UK criteria study demonstrated overall rates of PIMs in 1% and PIOs in 16.4%, which falls to 1.5% excluding the criterion mandating Healthy Start vitamins.

The close equivalent criterion in the original POPI criteria to the Healthy Start vitamin criterion in the POPI UK tool is a criterion advising a PIO of vitamin D supplementation. These are compared in Table 4-M.

Table 4-M: Comparison of original POPI and POPI UK criteria relating to vitamins

Original POPI criterion	POPI UK criterion
Insufficient intake of vitamin D. Minimum vitamin D intake: Breastfed baby = 1,000 to 1,200 IU/day; Infant, 18 months of age (milk enriched in vitamin D) = 600 to 800 IU/day; Child aged between 18 months and 5 years, and adolescents aged between 10 and 18 years: two quarterly loading doses of 80,000 to 100,000 IU/day in winter (adolescents can take this dose in one go)	Healthy Start vitamins for infants and children 6 months- 5 years or having less than 500ml infant formula per day

This criterion was excluded from analysis in both populations of the original POPI clinical study, meaning that the comparison between studies is more pertinent when excluding the vitamin criterion from the POPI UK study results.

The categories with the most frequent potentially irrational prescribing in the study of the original POPI tool were in respiratory and digestive medicine, in contrast with the study of the POPI UK criteria, where vitamins and antibiotic prophylaxis and pain and fever were the most common categories of potentially irrational prescribing. This difference is likely due to the original POPI study only including three of the criteria related to pain and fever—in fact, only one was applied to the hospital population (a PIM relating to opiates used to treat migraine) and two in the community population (relating to dosage of ibuprofen and the combined use of two NSAIDs).

The selective use of criteria in the study using the original POPI tool therefore limits the usefulness of direct comparisons.

4.7.5 Study population and risk of bias

As stated in section 4.3.3, fluency in the English language was a mandatory inclusion criterion due to resource constraints. As demographic data around ethnicity was not collected, it is not possible to state to what extent the study population was representative of the catchment population of the Royal Derby Hospital. However, the three groups likely to have been excluded by this criterion- first- or second-generation immigrants, international travellers and children of parents with disability (e.g. native sign language users) – are likely to have relevant characteristics that affect the results of the study.

In terms of evaluating the applicability of the POPI UK criteria to a population, some heritable conditions are more prevalent in people of particular ethnic origins, for instance African or Caribbean origins in the case of sickle cell anaemia (of which no cases were identified in the study population). Other acquired conditions, such as malaria (not included in POPI UK), are likely to be acquired in endemic regions and may therefore be more common in international travellers or immigrant families with travel from such areas.

In addition, all recruitment and data collection were conducted during the day. Although patients admitted overnight to the inpatient ward were likely to be captured, this will have excluded patients seen in the ED overnight. It is possible that certain conditions were over- or under-represented as a result, if they are more likely to present at night. Recruitment was undertaken between August and February and therefore captured both summer and winter populations.

In future work using POPI UK, further evaluation of the applicability of the criteria to the full population would be valuable to ascertain whether the criteria are equally applicable without these limitations.

4.8 Conclusions

4.8.1 Strengths and limitations of the POPI UK criteria

These results demonstrate that the POPI UK criteria have reasonably broad scope and are relevant to the majority of children presenting to the Emergency Department and admitted to the inpatient paediatric ward in this study. Even excluding the PIO related to vitamins, the criteria related to at least one condition seen in the majority patients in the population. The criteria were able to detect a number of potentially clinically significant inappropriate PIMs or PIOs that might have adverse effects on patients, such as omission of laxatives with over 48 hours of morphine administration (which may lead to constipation with both patient discomfort and the risk of secondary complications), PIMs of non-indicated therapies such as acid-suppressing medications, antibiotics, or inhaled ß2

agonists (which therefore carry the risk of adverse effects of therapy without likelihood of patient benefit).

The findings also highlighted a number of prevalent symptoms and conditions that are not included within the POPI UK, including sepsis and viral-induced wheeze. As discussed in Section 4.7.1, these are areas where there is evidence suggesting that they may be valuable areas in which to study irrational prescribing.

This study also exposed a significant weakness in the POPI UK criteria in that the degree of specificity in the criteria required access to very detailed patient information, which was not always available from written patient records even contemporaneously. This limitation would limit the ability to apply the POPI UK criteria to any retrospective dataset and even with contemporaneous data collection it was not possible to code all criteria for all patients, with 38 cases with indeterminate coding. This limitation would apply equally to the original POPI criteria, and the published evaluations of the original POPI criteria have not addressed this limitation.

In addition, the complexity of the criteria makes them time-consuming to apply. In each case, data collection required review of all of the patient's clinical notes as well as their current and historic prescriptions since the time of admission in order to identify potential indications or contra-indications to medications, or clinical reasoning that might influence interpretation of criteria. Depending on the length of the patient's admission at the time of data collection, this took up to 45 minutes per patient. Analysis with cross-reference to the POPI UK codes became quicker with experience using the tool and once experienced with the tool took approximately ten minutes per patient.

4.8.2 Further research needs identified

This study highlighted several limitations in the clinical application of the POPI UK criteria. Several frequent clinical indications are not included within the tool, and as discussed some of the complex implicit criteria were challenging to apply to the data. The high degree of complexity and nuance in implicit criteria may increase their accuracy but compromise their precision. To test this hypothesis, and evaluate the precision of the POPI UK criteria, an inter-rater and intra-rater repeatability study was felt to be of great

value. This study is detailed in Chapter 5. Other future work could address the clinical areas not covered by the POPI UK criteria, either by further modifying the tool or considering alternative approaches to evaluate rational prescribing in these areas.

5 Inter- and intra-rater repeatability study of the POPI UK criteria

5.1 Introduction

5.1.1 Repeatability studies

As discussed in Section 1.4.2 and in more detail in Section 4.1, a test's reliability can be described through two aspects: repeatability, which evaluates precision, and accuracy, which describes closeness to a true value.

Repeatability studies evaluate the similarity of results between different observers, or by the same observer when the test is performed multiple times. A high degree of precision is therefore reflected in a high degree of agreement between observers (inter-rater variability) or between scores by the same observer (intra-rater variability).

Repeatability studies do not provide any measure of the accuracy of a test. Supposing a true value is known, even if both raters gave incorrect answers, if their responses were in agreement then this would support a high level of repeatability.

Cohen's Kappa (κ) coefficient is an index of inter-observer agreement in categorical data. Although there is no universally accepted value of Kappa that equates to an acceptable degree of agreement, by one widely used convention a Kappa of < 0.4 is considered poor, 0.4-0.7 fair to good, and > 0.7 excellent (170).

5.1.2 Repeatability studies of other rational prescribing tools

Repeatability studies have often been used to evaluate the precision of rational prescribing tools, including the MAI (171), STOPP/START criteria (72), and ACOVE criteria (172). Precision is a valuable characteristic of a rational prescribing tool as it increases the likelihood that values obtained in different studies, settings, or simply by

different raters are comparable, and therefore enables the tool to be used to make valid comparisons.

A 2013 review of the MAI provides a cross-section of different methodologies that have been used in eight separate repeatability studies of the MAI. These are summarised in Table 5-A, adapted from Hanlon et al, 2013 (171).

Table 5-A: Methodology of inter-rater reliability studies of the MAI

Reference	Raters	Number of patients
Hanlon et al, 1992 (128)	Physician and pharmacist; two pharmacists Intra-rater reliability also evaluated	10
Samsa et al, 1994 (173)	Physician and pharmacist	10
Fitzgerald et al, 1997 (174)	Two pharmacists	10
Kassam et al, 2003 (175)	Two pharmacists	32
Bregnhøj et al, 2005 (176)	Two clinical pharmacologists, a clinical pharmacologist and a pharmacist (in pairs) Intra-rater reliability also evaluated	30
Spinewine et al, 2006 (177)	Physician and pharmacist	16
Stuijt et al, 2009 (178)	Three pairs of pharmacists Intra-rater reliability also evaluated	15
Gallagher et al, 2011 (179)	Two physicians	40

The original POPI tool has also been evaluated in terms of inter-rater reliability in a study published as a conference abstract (180). In this study, twenty cases from the prior clinical validation study of children treated in an emergency department were selected. This included cases with or without PIMs/PIOs, but all cases had some medicines prescribed. One doctor and one pharmacist, who were involved in the creation of the POPI tool, evaluated the cases and composed "standard answers". The cases were then reviewed separately by eleven clinicians (including generalists, paediatricians, pharmacists, residents, and general practitioners) not experienced with the tool. Inter-rater agreement was tested by calculating Cohen's Kappa coefficient.

In the evaluation of the original POPI inter-rater reliability, the results were analysed separately for PIMs and PIOs, with Kappas of 0.8 and 0.71 respectively (180). Intra-rater reliability was not tested.

5.2 Aims

The aims of this study were to measure the inter-rater and intra-rater reliability of the POPI UK tool.

5.3 Methods

5.3.1 Study design

The methodology chosen was designed for similarity to other studies assessing the reliability of rational prescribing tools in order to allow comparisons. The majority of studies assessing the MAI used the methodology of two raters, with a range of patient numbers from ten to 40. For this study, two junior doctors from relevant specialties (emergency medicine and general practice) were selected as raters. This meant that each worked in roles with paediatric patients. The junior doctors had trained and worked in different locations and were both ST1 grade at the time of the study. Junior doctors were chosen as the POPI UK criteria contain technical language and are likely to require both clinical knowledge and familiarity with medical notes and terminology to apply. Furthermore, as junior doctors are often highly involved in audit and quality improvement work(181), junior doctors are a group that is likely to make use of the POPI UK criteria in future.

Twenty cases were selected at random from the data collected for the clinical validation study of the POPI UK tool (see Chapter 4), with ten cases drawn from each clinical setting of a paediatric emergency department and a paediatric inpatient ward. These case data were transcribed to new Case Report Forms to match the form of data that users of the tool might be using to evaluate prescribing; these case report forms were anonymous and the only patient identity information provided was age and sex.

The cases were selected according to Participant Identification Numbers using a random number generator from 1-300 for ten cases and from 301-600 for ten cases, in order to select ten cases from each clinical setting. In order to ensure these cases were representative of the dataset as a whole and gave an opportunity for raters to apply a range of the POPI UK criteria, the rates of PIMs or PIOs in these cases was checked and was proportionate to the overall results of the dataset. This meant that there were some cases with no identified PIMs or PIOS, some cases with identified PIMs or PIOs, and some cases which had been rated as 'unknown' due to subjectivity or insufficient information. The case information was supplied in the form of a completed Case Report Form (see Figure 4-2).

Both raters were provided with the POPI UK criteria and given the opportunity to read through the criteria in advance. They were then provided with the twenty case details and asked to identify PIMs or PIOs as defined in the POPI UK criteria. The order of cases was randomised.

After a two-week interval, the raters were asked to repeat the same exercise, again with randomised case order, in order to evaluate intra-rater reliability.

5.3.2 Characteristics of selected cases

The twenty randomly selected cases are shown over page in Table 5-B.

The average number of medications per patient in the group was 3.1, compared with 2.7 in the population of the POPI UK clinical study as a while. Thirteen (65%) of the group had no PIMs/PIOs detected in the original study, which is comparable to the 66% of the whole population in the original study with no possible PIMs/PIOs identified. The median age of the selected cases was 4 years 6 months, slightly older than the overall population, which had a median age of 3 years.

Table 5-B: Characteristics of selected cases for the reliability study of POPI UK

PIN	Setting	Age	Number of prescribed medications	PIM/PIO detected by original rating
286	1	3y	6	Y
89	1	1y	4	Y
181	1	5m	8	N
144	1	2m	3	Y
27	1	9y	0	N
180	1	11y	6	N
57	1	12y	7	N
188	1	6y	5	Y
76	1	6y	7	Y
83	1	8y	4	U
500	2	12y	1	N
477	2	3y	2	U
448	2	3m	2	N
322	2	3y	0	N
381	2	15y	1	N
418	2	1y	2	N
554	2	13y	1	N
457	2	2y	1	N
471	2	12y	0	N
348	2	2m	2	N

5.4 Statistical analysis

Results were assessed for both inter-rater and intra-rater agreement. The indicator used for each case was whether the rater identified a PIM or PIO according to the POPI UK criteria. The outcomes were recorded as "Yes" (PIM/PIO detected), "No" (no PIM/PIO detected), or "Uncertain" (with free text provided to explain the source of uncertainty). As there were two raters and two sessions, this produced two Kappa figures for each inter- and intra-rater agreement, of which the mean was taken.

Statistical analysis was carried out in Microsoft Excel by calculating Cohen's Kappa.

5.5 Results

5.5.1 Inter-rater reliability

The Kappas for session one and session two were substantially different, 0.58 and 0.30 respectively, with a mean of 0.44. This corresponds to a "fair to good" rate of agreement. The results for each session are shown in Table 5-C. The category and potential irrational prescribing codes were provided (see Appendix 8).

Table 5-C: Results of each session

Session 1			Session 2		
Case	**Rater**	**Potentially irrational prescribing identified?**	**Case**	**Rater**	**Potentially irrational prescribing identified?**
1	1	N	1	1	N
	2	N		2	U
2	1	U	2	1	U
	2	U		2	Y
3	1	N	3	1	N
	2	N		2	N
4	1	N	4	1	N
	2	N		2	N
5	1	N	5	1	N
	2	N		2	N
6	1	N	6	1	N
	2	N		2	N
7	1	U	7	1	N
	2	U		2	U
8	1	U	8	1	U
	2	U		2	U
9	1	U	9	1	N
	2	N		2	N
10	1	N	10	1	N
	2	N		2	N
11	1	N	11	1	N
	2	N		2	U
12	1	N	12	1	N

	2	N		2	N
13	1	N	13	1	N
	2	N		2	N
14	1	Y	14	1	Y
	2	Y		2	U
15	1	N	15	1	N
	2	U		2	U
16	1	N	16	1	N
	2	N		2	N
17	1	Y	17	1	Y
	2	Y		2	Y
18	1	Y	18	1	N
	2	U		2	N
19	1	Y	19	1	U
	2	U		2	Y
20	1	U	20	1	U
	2	Y		2	Y

(Y=yes, N=no, U=uncertain)

The table shows the cases and each rater's identification of a PIM/PIO with 'Y', no PIM/PIO with 'N', or uncertainty with 'U'.

Results were then tabulated to count instances of agreement and disagreement in order to calculate Cohen's Kappa, as demonstrated for session one in Table 5-D below.

Table 5-D: Session one inter-rater reliability results

	Rater 2			
Rater 1	**Y**	**N**	**U**	**Total**
Y	2	0	2	4
N	0	10	1	11
U	1	1	3	5
Total	3	11	6	20
Agreement	2	10	3	0.75
By Chance	0.03	0.3025	0.075	0.4075
Kappa	0.58			

In Table 5-D, instances of agreement are counted in the cells running diagonally from top left to bottom right, showing two instances where raters agreed there was a PIM/PIO present, ten where they agreed there was no PIM/PIO, and three where both raters were uncertain. The rates of counted agreement as compared to what would be expected by chance are used to calculate Cohen's Kappa by the formula:

$$\text{Cohen's Kappa} = \frac{\rho_o - \rho_e}{1 - \rho_e}$$

Where P_o is the observed agreement and P_e is the hypothetical probability of agreement by chance.

Using the data from session one as a worked example, P_o is calculated as the number of cases in agreement divided by the total number of cases, shown as the total in the agreement row, i.e.

$$P_o = 15 / 20 = 0.75$$

P_e is calculated as the probability that instances of yes, no, or uncertain were in agreement by chance. These are calculated individually and then summed. Again, using the data from session one:

'Yes'	$P_e = (4 / 20)$ x $(3 / 20) = 0.03$
'No'	$P_e = (11 / 20)$ x $(11 / 20) = 0.3025$
'Uncertain'	$P_e = (5 / 20)$ x $(6 / 20) = 0.075$
Total	$P_e = 0.4075$

Therefore, Kappa can be calculated for the inter-rater reliability of session one as:

$$\kappa = \frac{\rho_o - \rho_e}{1 - \rho_e} = \frac{0.75 - 0.4075}{1 - 0.4075} = 0.58$$

The results for session two are shown in Table 5-E.

Table 5-E: Session two inter-rater reliability results

	Rater 2			
Rater 1	**Y**	**N**	**U**	**Total**
Y	1	0	1	2
N	0	10	4	14
U	3	0	1	4
Total	4	10	6	20
Agreement	1	10	1	0.6
By Chance	0.02	0.35	0.06	0.43
Kappa	0.30			

5.5.2 Intra-rater reliability

The full results for each rater are shown in Table 5-F and Table 5-G respectively.

Table 5-F: Intra-rater reliability of rater 1

	Session 2			
Session 1	**Y**	**N**	**U**	**Total**
Y	2	1	1	4
N	0	11	0	11
U	0	2	3	5
Total	2	14	4	20
Agreement	2	11	3	0.8
By Chance	0.02	0.385	0.05	0.455
Kappa	0.63			

Table 5-G: Intra-rater reliability of rater 2

	Session 2			
Session 1	**Y**	**N**	**U**	**Total**
Y	2	0	1	3
N	0	9	2	11
U	2	1	3	6
Total	4	10	6	20
Agreement	2	9	3	0.7
By Chance	0.03	0.275	0.09	0.395
Kappa	0.50			

The Kappa for intra-rater agreement was on average higher than that of inter-rater agreement, at 0.63 for rater 1 and 0.50 for rater 2, with a mean of 0.57. Like the inter-rater reliability figure, this corresponds with "fair to good" agreement.

5.5.3 Criteria rated as uncertain

Free text responses were requested for codings of 'uncertain'. The responses that highlighted the reason for uncertainty are shown over page in Table 5-H with the related POPI UK criterion, grouped into four categories of reasons for rater uncertainty.

As Table 5-H shows, the free-text comments could be grouped into the categories: more information required; subjective criterion; undefined timing or duration of prescription, and; specialist knowledge required. These categories highlight the challenges that prevented raters being able to apply the POPI UK criteria to the clinical information and prescriptions provided to them.

Table 5-H: Free text responses explaining responses of uncertainty

Category	Free text response	Related POPI UK criteria
More information required	No past medical history, ?risk factors	Nausea, vomiting and gastroesophageal reflux (inappropriate prescription): The combined use of proton pump inhibitors and NSAIDs, for a short period of time, in patients without risk factors
	Not enough information	Nausea, vomiting and gastroesophageal reflux (omission): Oral rehydration solution (ORS) for dehydrated children unless IV fluid therapy is indicated (shock, red flag symptoms despite ORS, persist vomiting of ORS)
	Don't know if they have risk factors for pavilizumab	Bronchiolitis (omission): Palivizumab in high-risk cases, defined as: 1) children < 2 years with chronic lung disease on home oxygen or who have prolonged use of oxygen 2) infants < 6 months with left-to-right shunt haemodynamically significant congenital heart disease and/or pulmonary hypertension children < 2 years with severe congenital immunodeficiency
	Need more information.	
	Not enough information	
	Unclear indication as more than one diagnosis	Bronchiolitis (inappropriate prescription): H_1-antagonists, cough suppressants, mucolytic drugs, or ribavirin to treat bronchiolitis
	Cannot know if this was proposed.	Cough (omission): Failure to propose a whooping cough vaccine for pregnant women.
	Not enough information	
	No information on accompanying family members.	
Subjective criterion	Unclear if symptom of limp = pain	Pain and fever (inappropriate prescription): Prescription of a medication other than paracetamol as a first line treatment (except in the case of migraine
	Unclear whether this qualifies as "severe"	ENT infections (inappropriate prescription): Antibiotic treatment for a sore throat except in severe cases (anticipated to be no more than 20% of cases)
	Unclear how severe.	
Undefined timing or duration of prescription	Unclear time on morphine	Pain and fever (omission): Failure to give an osmotic laxative to patients being treated with morphine for a period of more than 48 hours
	Morphine and paracetamol prescribed, looks like morphine was first-line?	Pain and fever (inappropriate prescription): Prescription of a medication other than paracetamol or ibuprofen as a first-line treatment for pain (except in the case of migraine)
Specialist knowledge required	I don't know this brand name, is it a steroid?	Atopic eczema: A potent topical corticosteroid applied to the face, or for > 14 days applied to the axilla or groin

Two criteria were mentioned three times by raters as requiring more information than was available to them, in the case of the criterion relating to bronchiolitis, the full past medical history of the child was required to rate it. In the criterion relating to pertussis vaccination, information was required about all adults accompanying the child in consultations.

Two criteria were mentioned twice, relating to analgesia and antibiotics prescribing. In these cases, raters highlighted areas of subjectivity and the high level of details required specifying indications and intended timings of prescriptions.

5.6 Discussion

5.6.1 Reliability of the POPI UK criteria

Both the inter-rater and intra-rater agreement in this study were > 0.4, being 0.44 and 0.57 respectively. In the review of reliability studies of the MAI by Hanlon et al, a Kappa of > 0.4 was considered "good" reliability (171).
Table 5-I shows the inter-rater and, where it was measured, intra-rater Kappa scores for the MAI in the eight studies they reviewed.

Table 5-I: Kappa score for the inter-rater and, where it was measured, intra-rater reliability of the MAI in eight studies (171)

Reference	Raters	Kappa	
		Inter-rater	Intra-rater
Hanlon et al, 1992 (128)	Physician and pharmacist; two pharmacists	0.83 0.59	0.92
Samsa et al, 1994 (173)	Physician and pharmacist	0.74*	
Fitzgerald et al, 1997 (174)	Two pharmacists	0.64	
Kassam et al, 2003 (175)	Two pharmacists	0.65	
Bregnhøj et al, 2005 (176)	Two clinical pharmacologists, a clinical pharmacologist and a pharmacist (in pairs)	0.50	0.71
Spinewine et al, 2006 (177)	Physician and pharmacist	0.84	
Stuijt et al, 2009 (178)	Three pairs of pharmacists	0.47	0.84
Gallagher et al, 2011 (179)	Two physicians	> 0.85	

*The intra-class correlation coefficient was calculated rather than Kappa in one study.

Like the POPI UK repeatability study, these results show higher intra-rater compared to inter-rater reliability. A higher intra-rater agreement may be expected, as a rater may have an individual interpretation of criteria, which they reliably apply, compared to a different interpretation by another rater.

The MAI is an apposite comparator to the POPI UK because it also had three different outcomes or ratings, "A" indicating appropriate, "B" marginally appropriate, and "C" inappropriate (171). However, the MAI consists of only ten criteria, which makes it much simpler for raters to apply compared with the 80 criteria of POPI UK. This may account, at least in part, for the higher levels of reliability found in the studies of the MAI.

5.6.2 Comparison with the reliability of the original POPI tool

The original POPI tool was reported to have inter-rater reliability of 0.8 (for PIMs) and 0.71 (for PIOs) (180). The study also reported a median time of use of 2 mins 45s per case and user satisfaction with the tool (82%). Given the very close similarity between the POPI UK and the original POPI criteria, it is not clear how this very fast rate of use was achieved compared with the time taken to apply the POPI UK (from 10 to 45 minutes) as discussed in 4.8.1, although this may be partly due to differences in methodology.

It is not stated in the report of the inter-rater reliability study, however in the clinical validation study of the original POPI criteria from which the cases were selected, it was stated that only 82 of the POPI criteria were applied to the emergency department population. Furthermore, other criteria were only applied selectively, for instance only three of five criteria related to analgesia and antipyrexics were evaluated, and not all prescriptions of amoxicillin were assessed according to the relevant criterion (123). A selective approach to application of criteria would likely decrease the time taken to apply the criteria and would also be likely to increase the observed repeatability due to there being fewer opportunities for disagreement between raters.

In addition, only primary diagnoses and their related prescriptions were evaluated in the original POPI study, as opposed to all prescriptions and documented indications in the POPI UK study. Furthermore, the clinical study of POPI UK showed greater complexity

in the inpatient group studied. While the original POPI was tested against an emergency department population only, the POPI UK was tested against both emergency and inpatient populations. This is supported by the measure of number of prescriptions evaluated. In total, 57 medication prescriptions were evaluated in the original POPI repeatability study, as compared with 62 in the POPI UK study (including three cases with no prescriptions, meaning some more complex cases with greater polypharmacy).

The inter-rater reliability study of the original POPI tool also used different methodology to that of other rational prescribing tools discussed above. As the repeatability study for the original POPI tool was published after the POPI UK repeatability study was carried out, it was not possible to match methodologies for closer comparison. Developers of the original POPI tool rated twenty cases, and these ratings were used as a gold standard against which eleven other raters were individually compared. This is in contrast to the usual application of Cohen's Kappa as a statistical measure, which assumes that no 'true' value can be identified and that all raters' judgements are equally valid (182). The reported reliability figures are therefore median values of eleven Kappa values comparing each rater against the gold standard answer, rather than comparing raters with one another. Inter-rater reliability for PIMs ranged between 0.61-0.96, while reliability for PIOs ranged between 0.41-1.0.

There are a number of factors that could contribute to the POPI UK criteria scoring less highly for inter-rater reliability than the original POPI criteria.

Firstly, it should be considered whether there is evidence that the modifications to the tool have reduced its reliability. Compared with the original tool. Forty-nine criteria are unchanged, 29 modified, four simplified into two, and 23 omitted altogether. As a result, over half (49/80) of the modified criteria are identical to the original tool. Of the criteria associated with raters' uncertainty, in Table 5-J, five were associated with unchanged criteria, eight associated with criteria where modifications did not affect the cause for uncertainty (needing additional information related to severity, risk factors or people accompanying the child), and two associated with modifications that may have introduced cause for uncertainty due to subjectivity in the criterion. This is shown below in Table 5-J.

Table 5-J: POPI UK criteria associated with uncertainty in comparison to the original POPI criteria

Related POPI UK criteria	Comparison to original POPI criterion	Expected impact on rater uncertainty
Nausea, vomiting and gastroesophageal reflux (potentially inappropriate): The combined use of proton pump inhibitors and NSAIDs, for a short period of time, in patients without risk factors	Unchanged	Unchanged
Bronchiolitis (potentially inappropriate): H_1-antagonists, cough suppressants, mucolytic drugs, or ribavirin to treat bronchiolitis	Unchanged	Unchanged
Pain and fever (potentially inappropriate): Prescription of a medication other than paracetamol as a first line treatment (except in the case of migraine) (x2)	Unchanged	Unchanged
Pain and fever (omission): Failure to give an osmotic laxative to patients being treated with morphine for a period of more than 48 hours	Unchanged	Unchanged
Bronchiolitis (omission): Palivizumab in high-risk cases, defined as: 1) children < 2 years with chronic lung disease on home oxygen or who have prolonged use of oxygen 2) infants < 6 months with left-to-right shunt haemodynamically significant congenital heart disease and/or pulmonary hypertension	Modified from: Palivizumab in the following cases: (1) babies born both at less than 35 weeks of gestation and less than six months prior to the onset of a seasonal RSV epidemic; (2) children less than two years old who have received treatment	Unchanged

children < 2 years with severe congenital immunodeficiency (x3)	for bronchopulmonary dysplasia in the past six months; (3) children less than two years old suffering from congenital heart disease with hemodynamic abnormalities	
Cough (omission): Failure to propose a whooping cough vaccine for pregnant women. (x3)	Modified from: Failure to propose a whooping cough booster vaccine for adults who are likely to become parents in the coming months or years (only applicable if the previous vaccination was more than 10 years ago). This booster vaccination should also be proposed to the family and entourage of expectant parents (parents, grand-parents, nannies/child minders)" to "Failure to propose a whooping cough vaccine for pregnant women.	Unchanged
Atopic eczema (potentially inappropriate): A potent topical corticosteroid applied to the face, or for >14 days applied to the axilla or groin	Modified from: A strong dermocorticoid (clobetasol propionate 0.05% Dermoval, betamethasone dipropionate Diprosone) applied to the face, the armpits or groin, and the backside of babies or young children	Unchanged
Nausea, vomiting and gastroesophageal reflux (omission): Oral rehydration solution (ORS) for dehydrated children unless IV fluid therapy is indicated (shock, red flag symptoms despite ORS, persist vomiting of ORS)	Modified from: Oral rehydration solution (ORS)	Increased (subjective assessment of indications for IV fluids)

ENT infections (potentially inappropriate): Antibiotic treatment for a sore throat except in severe cases (anticipated to be no more than 20% of cases) (x2)	Modified from: Antibiotic treatment for a sore throat, without a positive rapid diagnostic test result, in children less than three years old	Increased (subjective assessment of severity of case)

Given that seven out of the nine criteria for which uncertainty was rated had not been modified in a way that increased their subjectivity or complexity, the changes made to develop POPI UK do not seem adequate to explain the difference in inter-rater reliability between the original POPI tool and the POPI UK tool.

An alternative explanation for the difference in agreement between this study and that of the original POPI tool is the different settings of patients. All cases used in the original POPI study were drawn from an emergency department population, whereas in this study, half were from the emergency department and half from an inpatient group. It is not possible to calculate whether agreement differed for the emergency department compared with inpatient group in this study due to the anonymisation and randomisation process.

There are a number of ways in which these populations differ. In particular, the average number of prescriptions was much higher for inpatient cases (4.3 per patient) than emergency department cases (1.1 per patient) in the POPI UK clinical validation study (see Chapter 4), introducing a higher number of medications that need to be reviewed by the rater. By comparison the figures in the original POPI tool study were 1.1 prescriptions per patient in the emergency department setting and 2.1 in the community pharmacy setting. Their data excluded patients who had no prescriptions, as per their exclusion criteria.

The higher number of prescriptions per patient in the inpatient setting of the POPI UK tool validation study as compared to any of the other settings tested may suggest a higher degree of complexity, which could contribute to less reliability between raters.

In addition, in the report of the original POPI tool validation study, the detection of potentially irrational prescribing was measured as a binary outcome as compared with

three options in this study (Y/N/U). This would increase inter-rater agreement as measured in the original study. Indeed, omitting the "U" responses in this study results in complete agreement (Kappa=1) on cases where neither rater scored their response as "U". Of course, this does not indicate that the results of this study would have been Kappa of 1 for inter-rater reliability of the POPI UK criteria if raters were asked to rate all responses Y/N, as the cases of uncertainty may have resulted in guessing and therefore introduced disagreement. However, even assuming entirely divergent guesses between raters or between sessions, this would have resulted in an increased Kappa value.

Lastly, the methodology used in the study of the original POPI tool was to compare each rater back to a fixed gold standard result. It did not, therefore, directly compare raters who were unpractised with the tool against each other. It is possible that there was less disagreement between each rater and the gold standard results than there might have been between raters.

It is therefore not possible to directly compare the results between the reliability testing of the original POPI criteria and the POPI UK criteria.

5.6.3 Limitations of the study

Like several of the studies reviewed by Hanlon et al (171), this study evaluated inter-rater reliability between two similar raters (in this case, both junior doctors). Given the highly technical clinical information included in the POPI criteria, it may be that raters with different clinical backgrounds would show more disagreement while more experienced clinicians or pharmacists might show more agreement.

The inclusion of the coding of "uncertain" added both complexity to the analysis of this study and greater information regarding the users' experience of the POPI UK tool. A more in-depth interview of users of the tool would provide more detail on which areas of the tool are challenging to use, whether due to subjectivity, technical knowledge requirements, or need for detailed information that may not be readily available in patient notes or retrospective datasets.

5.7 Conclusions

This study demonstrated fair to good inter-rater and intra-rater reliability for the POPI UK tool, suggesting that it has comparable precision to other widely accepted rational prescribing tools such as the MAI for older adults.

The relative complexity of the POPI UK criteria likely contributes to a lower precision than they might otherwise have, as well as meaning they are time-consuming to apply (15). Many of the criteria require technical knowledge such as good working knowledge of drug groups and symptomatology, and there are subjective areas in some criteria such as evaluating the severity of a sore throat. In addition, several criteria require detailed information to be available about the patient, such as co-morbidities or discussions that were had ("failure to propose whooping cough" does not require a prescription, per se, only a discussion). This level of detail is comparable between the original and POPI UK criteria. While these detailed criteria have some advantages in increasing the clinical validity of the tool in terms of aiming for truly rational prescribing, they also increase the difficulty of using the tool. For instance, while there are large prescribing datasets available such as GP practice prescribing data, these are unlikely to contain sufficient detail to evaluate against all of the POPI UK criteria. However, for prospectively collected data, the high level of detail in the criteria may increase their sensitivity and specificity for identifying genuinely irrational prescribing.

Avenues for future research include a direct comparison between the original POPI tool and POPI UK using the same data and methodology or evaluation of inter-rater reliability of the POPI UK with raters from different clinical backgrounds and levels of experience. It would also be interesting and may inform further development of the POPI UK to re-test the criteria with the removal of all criteria that were rated as uncertain, to test the hypothesis that this would increase inter- and intra-rater reliability. If so, this could guide the development of a more reliable rational prescribing tool.

6 Conclusions

6.1 Introduction

Rational prescribing by definition should achieve an optimum balance between the therapeutic benefits of prescribed medicines and minimal harms to individuals, communities, and healthcare systems in the form of adverse effects, medication resistance, and excess cost (12). Inappropriate prescribing has both economic and human costs (183). Prescribing for children is complicated by the need for individualised calculated dosing regimens and a dearth of high-quality evidence on which to base practice (5).

Rational prescribing tools provide a means of studying quality of prescribing with a quantitative approach. These allow assessment by prescribers of their own prescribing, service-level evaluations of prescribing for quality improvement purposes, research into influences on decision-making in prescribing, and comparison between patterns of irrational prescribing across different clinical settings, regions, or times, or between groups of prescribers.

Prior to this thesis, there was no rational prescribing tool for evaluating the quality of prescribing for children across a range of clinical settings in the UK. The work as described in this thesis has identified all available paediatric rational prescribing tools, developed a new rational prescribing tool that can be used to evaluate and compare quality of prescribing for children in any clinical setting within UK practice, and also provided evidence for the accuracy and precision of this tool.

6.2 Summary of findings

6.2.1 Systematic review of paediatric rational prescribing tools

Chapter 2 reports a systematic review of medical, nursing and pharmaceutical literature for paediatric rational prescribing tools. The original search resulted in three publications all relating to a single rational prescribing tool, the POPI (Pediatrics: Omissions of Prescriptions and Inappropriate prescriptions) tool. This tool was developed using French, UK and USA guidelines relating to paediatric prescribing, using the Delphi consensus method. The tool is designed to address frequent paediatric pathology categories according to physiological systems, meaning that it can be applied in a wide range of clinical settings.

An update of the systematic review in 2019 demonstrated a further paediatric rational prescribing tool that has been published since the systematic review was completed. This tool, the PIPc (Potentially Inappropriate Prescribing in children) is designed specifically for use in primary care settings in the UK (117). It comprises twelve indicators across four physiological categories. These were also designed by Delphi consensus and are intended to be used to evaluate prescribing where clinical data were unavailable, such as dispensing datasets. The updated search also identified the POPI UK.

Analysis of the systematic review included exploring the characteristics of the rational prescribing tools that were found. A number of limitations were identified in both tools, including barriers to applying the criteria to the types of clinical data they were designed to assess.

6.2.2 Developing POPI UK

The original POPI tool was developed using a combination of national guidelines from France, the UK, and the US. A number of criteria could not be readily applied to UK practice, due to references to medications outwith the British national formulary or criteria that were contradicted by UK clinical guidelines. In order to develop a tool applicable to paediatric practice across the UK, a study was undertaken to modify the original POPI criteria, with the aim of retaining as much as possible of the criteria

developed through the Delphi consensus method while ensuring that the criteria would provide a justified evaluation of rational prescribing in the context of UK paediatric practice.

Overall, no change was made to 49 criteria. Twenty-nine criteria were modified to concord more closely with UK guidelines. Four criteria were condensed into two criteria due to being linked within single UK guidelines. Twenty-three were omitted due to the absence of relevant UK guidance or conflicting UK guidance. One category title was amended to concord with terminology in use in the UK.

The novel POPI UK tool comprises 80 criteria that can be used to evaluate rational prescribing for children in UK practice.

6.2.3 Clinical evaluation of the POPI UK tool

In order to evaluate the usefulness of the POPI UK tool, two studies were undertaken to assess its validity as a measure of rational prescribing. The first of these studies was an evaluation of the tool in terms of accuracy, by testing whether it was of appropriate scope and sensitivity to detect instances of potentially irrational prescribing in UK paediatric practice. Clinical and prescribing data on 598 paediatric cases were collected prospectively in two different clinical contexts, a children's emergency department and a children's inpatient ward.

This study demonstrated that 96% of patients in the study population had at least one documented clinical symptom, sign, or diagnosis that falls within the scope of the POPI UK tool. Even excluding the highly prevalent vitamins criterion, relevant to 242 cases, the majority of patients (89%) had at least one relevant clinical indication, suggesting that the tool has broad enough scope to be used to evaluate prescriptions in both studied settings. Furthermore, 262 instances of potentially irrational prescribing were detected, suggesting that the criteria are relevant to UK paediatric practice in at least the two settings studied.

The study also highlighted some drawbacks to the POPI UK criteria. In 38 prescriptions, it was not possible to determine whether or not prescribing was rational according to the

modified criteria due to subjectivity or a higher level of clinical information being required than was accessible even through prospective collection of data. The comparison of results of this study to the published use of the original POPI criteria showed that exclusion of patients with no medicines prescribed may have caused a falsely low rate of omissions detected in the French study, as well as raising concern about how criteria requiring highly detailed and sometimes non-clinical information were scored on retrospective data. Lack of discussion of these issues in reports about the original POPI criteria mean that its limitations may not have been fully illustrated in those studies.

In addition, there were a number of common diagnoses in the POPI UK study population that are not included within the criteria, including viral-induced wheeze, sepsis, and soft tissue injuries. These may present future targets for subsequent modification of the tool or development of other tools aimed at detecting irrational prescribing.

6.2.4 Inter- and intra-rater reliability study of the POPI UK tool

The second study to evaluate the POPI UK tool was a repeatability study to test its precision. An inter- and intra-rater reliability study measures the closeness of results when the test is applied to the same data either by two different raters or by the same rater at different times. Higher precision may increase the usefulness of the tool for use in both quality improvement and research.

The study methodology was designed to be similar to the studies of precision of other rational prescribing tools to facilitate clearer interpretation of the results. The measured inter- and intra-rater repeatability of the POPI UK criteria were 0.44 and 0.57 respectively. These correspond to "good" reliability according to the classifications used for other rational prescribing tools (171) but were significantly lower than those reported for the original POPI criteria of 0.8 and 0.71 respectively. This is in spite of the fact that over half of the modified criteria are identical to the original tool and may relate to the differing study populations and study designs. The POPI UK tool was tested against both an emergency department population and inpatient population, whereas the original tool was only tested in emergency department patients. The clinical evaluation study of the

POPI UK tool, showed that the inpatient population had a much higher number of prescriptions per patient compared with the emergency department group, and may therefore present greater complexity to a rater.

6.3 Practical implications

The POPI UK tool is a novel paediatric rational prescribing tool that has practical applications in a variety of areas. In all of these applications, the limitations of the tool in terms of its complexity, time-consuming nature, and the need for detailed patient information would be challenges that would need to be overcome to achieve the greatest benefit. This is considered in more detail in Section 7.5 Future research.

6.3.1 Research

The tool can also be used to facilitate research into paediatric rational prescribing. This field has been described as an "evidence based desert" (101) and the POPI UK criteria provide a means of quantitative and qualitative analysis that can be applied in a variety of settings. Rational prescribing tools have been used extensively in research in other fields, for instance Beers' criteria have been used to investigate rational prescribing for older adults in a variety of settings (67, 110, 184-186).

The POPI UK tool could be used in a similar way to explore whether there is a difference in quality of prescribing for children in non-specialist settings such as undifferentiated emergency departments and general practice as compared to paediatric departments. It could also be used to investigate whether there are differences in prescribing between different groups of prescribers, including non-medical prescribers, and examine factors associated with better prescribing. Equally, the tool could be used to investigate the relationship between rational prescribing and patient outcomes, to identify the impact of higher and lower quality prescribing on patients. However, it is the author's view that significant changes to the tool would greatly improve its usefulness and effectiveness, as discussed in Section 6.5.

6.3.2 Quality improvement

As a measure of rational prescribing, the POPI UK criteria can be used in audit by or on behalf of prescribers to evaluate rational prescribing or guide targets for interventions to improve quality of prescribing.

Medical audits are systematic and quantitative assessments of clinical care that require a standard against which to compare contemporary practice (187), (188). Audits have been demonstrated to be an effective component of prescribing education for both medical and non-medical prescribers (189) and a prescribing audit has recently become a mandatory component of general practitioner training in the UK. In a pilot of this scheme, positive feedback from trainees on the impact upon their practice included quotations such as, "An excellent way of spending more time on my prescribing and identifying errors which I didn't think I was making", and "I always look at prescribing when debriefing but doing a batch enabled themes to appear" (190).

More broadly within medicine, audits have been found in a Cochrane review of evidence to have moderate evidence for improvement in adherence of practitioners with desired standards, and are more effective when clear targets are set out for health professionals(191). The evidence for improvement in patient outcomes was weaker but remained favourable.

Rational prescribing also accommodates system-level considerations of high-quality prescribing such as cost-effectiveness and community impact. One of the tenets of rational prescribing is that "Patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community" (42). Using prescribing indicators and audit to guide interventions has been a successful strategy not only in decreasing the rate of antibiotic use, and thus expenditure on antibiotics, but this reduction in use has been associated with decreased antibiotic resistance(192), which would have substantial beneficial ramifications for the wider community.

POPI UK have the advantage of being designed to be applicable to paediatric practice whether in hospital or primary care and could be used in such settings as an audit tool to evaluate rational prescribing or to test quality of prescribing before and after interventions.

In the case of applying POPI UK for the purposes of an audit, where a target or gold standard rate of compliance may be set against which to compare data, users of the tool should consider that detection of potentially irrational prescribing by a tool does not

necessarily indicate poor prescribing, nor would a "perfect score" indicate that there is no poor prescribing occurring. All that is being tested is adherence to the specific criteria in the tool.

In this context, the tool can be used to identify patterns or types of potentially irrational prescribing and provide an opportunity for reflection and consideration of factors contributing to what is detected, as well as to measure rates before and after an intervention. It is often the case that the standard set in an audit, aiming for 100% compliance, may have good clinical reasons for deviation and less than 100% is identified both before and after an intervention. This does not necessarily reduce the usefulness of the exercise.

The appropriate target compliance level may vary from criterion to criterion. The case of contraception for women of child-bearing potential on isotretinoin would seem to be a case for 100% compliance, but the Pregnancy Prevention programme does "allow" for the exclusion of women who are not sexually active, which could mean incorrect assessment of a potentially inappropriate omission were such a case audited. In the case of antibiotic prophylaxis for children with sickle cell anaemia, the criteria do accommodate penicillin allergy with the alternative of erythromycin, but of course allergy to both is possible and would mandate deviation. However, the same provisos are true of many targets set in audits (i.e. there may be a reason beneficial to the patient for non-adherence to other targets). So long as audits are used to study a phenomenon, and not as a tool to judge or punish a department or group, 100% compliance could certainly be used as a target, accepting that no measure is perfect. The setting of this standard may well depend on settings and factors like how much clinical information they will be able to gather about the patient and would be for the individual or organisation undertaking the audit to consider.

6.3.3 Education

Rational prescribing tools can also be used in medical education. Prescription audit has been demonstrated to improve prescribing skills in medical students(193). Other rational prescribing tools, including Beers' criteria and STOPP (Screening Tool of Older Persons' Potentially Inappropriate Prescriptions) criteria, have been used as educational tools (194, 195). In a single-blind study using rational prescribing tools to teach medical students about age-related pharmacokinetics, pharmacodynamics, and how to elicit the goals of drug treatment, student feedback was positive and students in the intervention group using the tools were able to identify significantly more potentially inappropriate medicines than those in the control group(194).

As the POPI UK criteria cover many categories of irrational prescribing, including overprescribing, underprescribing and different types of misprescribing, in an educational setting the criteria could be used to identify if there were particular types of irrational prescribing that were more prevalent. This could guide further education into rational decision-making around prescribing.

6.3.4 Reflection on impact upon my own practice

This section is the personal reflection of the author on the impact of this work on her own clinical practice.

While undertaking the research contained within this thesis, I have continued clinical practice as a General Practice Specialist Trainee in settings with paediatric prescribing, including emergency departments, inpatient wards, and in general practice.

The primary purpose of this work was not personal clinical development, however the value of the work to my own practice has been significant. The principles of rational prescribing are essential to the principles of good medical practice and engagement in this research strengthened my understanding of the practical applications of rational prescribing to practice. The General Medical Council ethical guidance to doctors in "Good medical practice: Duties of a doctor" commends doctors to "prescribe drugs, including repeat prescriptions, only when you have adequate knowledge of the patient's health and are satisfied that the drugs or treatment serve the patient's needs" and to "provide effective treatments based on the best available evidence"(196).

I have learnt a great deal through studying rational prescribing for children in so much depth, and have been aware of both in terms of prescribing practices directly applicable to my clinical work and more subtle transformation of my attitude and approach to prescribing. Examples of specific learning points have been an increased awareness of the guidelines reflected in the POPI UK criteria, such as the recommendation for vitamin supplementation for children, the need to advocate for whooping cough vaccination to pregnant women, the importance of oral rehydration therapy for diarrhoea and vomiting, and the reminder to think of analgesia when prescribing antibiotics for ear infections.

The subtler but perhaps more meaningful change I have taken from my work has been in evaluating the value of what I prescribe beyond the simple question, "Will this treat the disease I have diagnosed?" The necessity of a treatment being effective for a given condition is only one part of that treatment being rational. Other aspects, such as wider system and societal considerations around cost effectiveness and drug resistance, are essential in general practice, where 300 million consultations take place every year, compared to 23 million ED attendances (197).

The importance of high-quality prescribing has been recognised by the Royal College of General Practitioners, who have introduced a mandatory prescribing assessment to the training of GPs. I was in a cohort completing the first mandatory prescribing assessment, which highlights many of the principles of rational prescribing by asking trainees to reflect on the quality of a randomly collected sample of their prescriptions not only according to the right choice of drug, but dosage, duration, instructions, follow-up, documentation, and review. In both my personal reflection and detailed discussion with my clinical supervisor, my prescribing for paediatric patients was highlighted as very good; I believe this is in a large part due to the amount of thought and research I have been involved in in this area of practice.

In addition, the academic collaboration with paediatric research nurses, paediatric clinical pharmacologists, and paediatric pharmacists has given me access to a wealth of paediatric pharmacological expertise, which has fostered my development in this area. By seeking to disseminate my research to a broader audience, I have benefited from the process of peer review of my publications and have also been fortunate to present the work to two

different audiences in the Royal College of Paediatrics and Child Health, which has helped me to better articulate my research findings and their relevance to clinical practice, provided further critical analysis of the results, and led me to ask more questions of my work.

6.4 Strengths, challenges and limitations

This thesis has a number of strengths. The systematic literature review demonstrated a relative paucity of rational prescribing tools for use in paediatric practice and identified two paediatric rational prescribing tools, PIPc, which was developed for application to primary care settings and POPI, designed to be used in any paediatric setting but founded in French clinical guidelines.

The POPI UK criteria comprise a tool using up-to-date British clinical guidelines, and the subsequent validation studies demonstrated relevance to UK paediatric practice, the ability to detect potentially irrational prescribing using the tool, and a good degree of repeatability. These new findings have direct applicability to both clinical and academic medicine as discussed in 6.3. Practical Implications.

The clinical validation study protocol was modelled on WHO recommendations of rational prescribing studies (54). Data were gathered from two different areas of paediatric practice, taking in a range of prescribers including GP trainees, paediatric trainees, nurse practitioners, and consultant paediatricians.

The protocol for the repeatability study was modelled after similar studies that have been used to evaluate rational prescribing tools for older adults, facilitating direct comparison of results and providing a foundation for future in-depth research.

A limitation of this work was the development of the UK tool through modification of the French POPI criteria. As discussed in Sections 1.4 and 3.1, rational prescribing tools have often been developed through Delphi consensus method, with other examples of tools being updated, as in this work, for application of criteria developed in one country to be used in another.

As the original POPI criteria were selected through French prevalence data, it is possible that the criteria may be of less relevance to UK practice. On the other hand, British guidelines were applied to the development of the original tool and 49 of the 80 criteria comprising POPI UK are unchanged from the original criteria. This shows a significant degree of agreement in practice. Only 22 of the 105 POPI criteria were omitted due to absence of evidence in UK guidelines which, as discussed in Section 3.4.2,, does not necessarily reflect irrelevance to UK practice.

Ultimately, the clinical study of POPI UK demonstrated a high degree of relevance of the criteria to UK clinical practice, but with some areas of potentially valuable study excluded, such as viral-induced wheeze and sepsis. Further study of the applicability of POPI UK in community settings, including general practice, is needed It is unlikely a single rational prescribing tool would have the scope to apply to all areas of interest and is probable that there will always be value in having several different tools available to study rational prescribing in children in the UK, as is now the case with both PIPc and POPI UK.

A second limitation of the thesis is limited direct comparison to the studies that have been undertaken for the original POPI tool, which were published after completion of the studies of POPI UK.

Resource and time constraints applied limitations to study design. For instance, screening for the systematic review was by a single researcher for title and abstract, with a second reviewer only included for full-text screening due to such constraints and the high number of articles eligible for screening.

An area where this limitation had particular impact is the fact that all data were gathered from a single hospital, and therefore there may be some factors affecting patient populations or prescribing practices that are not more broadly generalisable, or missed factors which relate to prescribing in other settings such as primary care. Further research using the POPI UK POPI criteria would be valuable not only to study differences in rational prescribing in different settings across the UK, but also to further validate the use of the tool in a wider variety of settings.

Similarly, the fact that the large majority of data were collected by a single researcher may have affected evaluation of the tool. As a result of this, as both developer of the tool and rater of the findings, the author was extremely familiar with the POPI UK criteria throughout the process. This is somewhat mitigated by the inclusion of two different raters for the repeatability study, however it would be beneficial to evaluate whether there were unidentified obstacles to other prescribers or researchers making use of the tool, particularly non-medical prescribers given the high degree of clinical detail contained within the tool.

One challenge that was identified early in the research process was designing patient information leaflets for the study that were accessible to parents and children. As discussed in Chapter 1, the additional complexity of informed family decision-making is one of the perceived barriers to research involving children (87). In fact, it is important to develop information resources accessible to both children and adults of varying literacy levels and cognitive ability (92). However, ethical and legal issues mean that institutions may have mandatory language that must be included in participant information materials, which sometimes necessitates inclusion of technical language that reduces the readability of content.

As discussed in Chapter 2, in the case of designing participant information material for this study both readability scoring tools and families' feedback were used during the design process to maximise their accessibility and usefulness. Following review by University governance, it was necessary to include certain mandatory text, which provided additional and important information to participants but unfortunately increased the reading age grade of the documents. This was partly overcome by agreement that mandatory text must be available to all participants in the parent/carer information sheets and for participants aged over 16 who could give consent, in the 16-18 years information sheets, but did not need to be included in age-specific leaflets for younger ages, which were aimed at communicating with younger people in the study in order to facilitate informed assent. Further small amendments were made following review by the ethics committee, some of which included simplification of language.

This demonstrates the challenge in developing research literature that is accessible to a large majority of stakeholders while also having sufficient detail and clarity to

communicate information about the research and provide the foundation for truly informed consent. This is not an issue unique to paediatric research, but developing literature that is explicitly aimed at a range of ages brought the issue into greater visibility. One essential and effective resolution of this issue is ensuring that researchers provide time for full discussion of all information that is provided in writing. Not only does this provide participants with an important opportunity to ask questions, this also gives the researcher an opportunity to ensure that the information has been understood before seeking consent. This was a key part of the protocol for obtaining informed consent for the clinical validation study for the POPI UK criteria.

6.5 Future research

There are a number of avenues that invite further research building upon the work of this thesis.

Despite its limitations, as discussed in section 6.3 there are a number of research applications for the POPI UK criteria. The tool could be used to investigate independent factors associated with higher quality rational prescribing for children and to test interventions designed to improve quality of prescribing. It could further be used in research investigating to what extent irrational prescribing is associated with poorer patient outcomes, and whether there are particular settings or types of irrational prescribing where the impact may be more harmful.

It would be useful to directly compare the existing tools evaluating the same prescribing data with unmodified original POPI criteria, the PIPc, and the POPI UK criteria to explore whether the tools have different sensitivities for detecting different categories or types of irrational prescribing. It would also be useful to compare the inter- and intra-rater reliability of the tools within a controlled setting where similar patient data and raters were used.

However, this work has shown that while there are extant paediatric rational prescribing tools, and one product of this work is a tool that can be used in any paediatric practice setting in the UK, the limitations and complexities of the existing tools currently reduce

their effectiveness. It is recommended that the criterion related to ibuprofen prescribing be modified to more accurately reflect UK guidelines, which recommend three to four times daily prescribing. To advance the study of paediatric rational prescribing, further modification of the POPI UK tool could be undertaken to reduce its complexity. Options that might increase its reliability and reduce the time taken to apply the criteria would include: significantly reducing the number of criteria; removing all subjective criteria, and; targeting areas of prescribing that are highly prevalent and likely to be detected in most areas of practice, such as management of fever and pain, nausea and vomiting, and respiratory tract infections.

For example, the POPI UK criteria could be modified into a short paediatric prescribing tool of a similar size to the WHO prescribing indicators or the MAI, between five to ten criteria. Preferably, selected criteria would be explicit, in order to be readily applicable to varied sources of data. This would ideally be guided by a Delphi consensus method involving experts from a variety of paediatric practice settings including general, emergency, and community paediatrics as well as general practice, and involving both physicians and pharmacists. Further work would then also be required to validate such a tool.

Regardless of which tool is considered, whether the POPI UK in its current form or another modified or novel tool, rational prescribing tools require regular updating to maintain currency against evidence and prevalent practices. This process can be seen through the stepwise updates of the Beers criteria over time (63, 65, 66). This would therefore be an important element of future work involving POPI UK.

6.6 Final conclusions

This thesis has identified the absence of a rational prescribing tool for the evaluation of paediatric rational prescribing in non-general practice settings in the UK, and the research herein: i) reports the development of a novel paediatric rational prescribing tool, POPI UK, for use in a range of UK paediatric settings; ii) demonstrates clinical relevance, real-world detection of irrational prescribing by the POPI UK; iii) demonstrates the POPI UK has an acceptable level of reliability, and; iii) presents the POPI UK criteria as a

rational prescribing tool for future application to educational, clinical governance, and research purposes, and for further development.

References

1. WHO. WHO Twelfth General Programme of Work 2014-2019. Geneva. Geneva, Switzerland: World Health Organisation; 2014.
2. WHO. WHO Medicines Strategy 2008-2013, Draft 8. 2008.
3. Kathleen Holloway LvD. Rational Use of Medicines. The World Medicines Situation 2011. 3 ed. Geneva: World Health Organisation; 2011.
4. Wong ICK, Wong LY, Cranswick NE. Minimising medication errors in children. Archives of Disease in Childhood. 2009;94(2):161-4.
5. Bartelink IH, Rademaker CM, Schobben AF, van den Anker JN. Guidelines on paediatric dosing on the basis of developmental physiology and pharmacokinetic considerations. Clinical pharmacokinetics. 2006;45(11):1077-97.
6. National Institute for Health and Care Excellence. Bronchiolitis: diagnosis and management of bronchiolitis in children. NICE guideline. 2015;NG 9.
7. National Institute for Health and Care Excellence. Gastro-oesophageal reflux disease in children and young people. NICE guideline. 2015;NG1.
8. National Institute for Health and Clinical Excellence. Diagnosis and management of ADHD in children, young people and adults. NICE guideline. 2009;CG72.
9. Caldwell PH, Murphy SB, Butow PN, Craig JC. Clinical trials in children. The Lancet. 2004;364(9436):803-11.
10. Kanthimathinathan HK, Scholefield BR. Dilemmas in undertaking research in paediatric intensive care. Archives of disease in childhood. 2014;99(11):1043-9.
11. Anzelewicz S, Garnier H, Czauderna P, Rangaswami A. Cultural, geographical and ethical questions when looking to enroll pediatric patients in rare disease clinical trials. Expert Opinion on Orphan Drugs. 2017(just-accepted).
12. WHO. The rational use of drugs. Report of the Conference of Experts. Geneva, Switzerland: World Health Organisation; 1985.
13. Aronson J. Rational prescribing, appropriate prescribing. British journal of clinical pharmacology. 2004;57(3):229-30.
14. Le Grand A, Hogerzeil HV, Haaijer-Ruskamp FM. Intervention research in rational use of drugs: a review. Health policy and planning. 1999;14(2):89-102.
15. Spinewine A, Schmader KE, Barber N, Hughes C, Lapane KL, Swine C, et al. Appropriate prescribing in elderly people: how well can it be measured and optimised? The Lancet. 2007;370(9582):173-84.
16. WHO. Using indicators to measure country pharmaceutical situations: fact book on WHO Level I and Level II monitoring indicators. Geneva, Switzerland2006.
17. Fletcher-Lartey S, Yee M, Gaarslev C, Khan R. Why do general practitioners prescribe antibiotics for upper respiratory tract infections to meet patient expectations: a mixed methods study. BMJ open. 2016;6(10):e012244.
18. Meyer M. The perils of opioid prescribing during pregnancy. Obstetrics and Gynecology Clinics of North America. 2014;41(2):297-306.
19. Gulliford M, Figueroa-Munoz J, Morgan M, Hughes D, Gibson B, Beech R, et al. What does access to health care mean? Journal of health services research & policy. 2002;7(3):186-8.
20. Holloway KA. Combating inappropriate use of medicines. Expert review of clinical pharmacology. 2011;4(3):335-48.
21. Modi AC, Quittner AL. Barriers to treatment adherence for children with cystic fibrosis and asthma: what gets in the way? Journal of pediatric psychology. 2006;31(8):846-58.
22. Drotar D, Bonner MS. Influences on adherence to pediatric asthma treatment: a review of correlates and predictors. Journal of Developmental & Behavioral Pediatrics. 2009;30(6):574-82.
23. Conroy S, Carroll W. Prescribing in paediatrics. Archives of Disease in Childhood-Education and Practice. 2009;94(2):55-9.

24. Burridge AM, Terry D, Wilson K. Support for paediatric prescribers: what is discussed at hospital board level? Eur J Hosp Pharm. 2014;21(6):330-4.
25. Denne SC, Davis JM. Improving pharmaceutical trials for children: a call to the pediatric academic community. Pediatr Res. 2018;84:319-20.
26. Oscanoa T, Lizaraso F, Carvajal A. Hospital admissions due to adverse drug reactions in the elderly. A meta-analysis. European journal of clinical pharmacology. 2017;73(6):759-70.
27. Laroche ML, Charmes JP, Nouaille Y, Picard N, Merle L. Is inappropriate medication use a major cause of adverse drug reactions in the elderly? British journal of clinical pharmacology. 2007;63(2):177-86.
28. Scondotto G, Pojero F, Pollina Addario S, Ferrante M, Pastorello M, Visconti M, et al. The impact of polypharmacy and drug interactions among the elderly population in Western Sicily, Italy. Aging Clinical and Experimental Research. 2018;30(1):81-7.
29. Trumic E, Pranjic N, Begic L, Becic F, Asceric M. Idiosyncratic adverse reactions of most frequent drug combinations longterm use among hospitalized patients with polypharmacy. Medicinski arhiv. 2012;66(4):243-8.
30. Elliott R, Camacho E, Campbell F, Jankovic D, St James MM, Kaltenthaler E, et al. Prevalence and economic burden of medication errors in the NHS in England. Rapid evidence synthesis and economic analysis of the prevalence and burden of medication error in the UK. 2018.
31. Howard R, Avery A, Slavenburg S, Royal S, Pipe G, Lucassen P, et al. Which drugs cause preventable admissions to hospital? A systematic review. British journal of clinical pharmacology. 2007;63(2):136-47.
32. Bouvy JC, De Bruin ML, Koopmanschap MA. Epidemiology of adverse drug reactions in Europe: a review of recent observational studies. Drug safety. 2015;38(5):437-53.
33. Hitchen L. Adverse drug reactions result in 250 000 UK admissions a year. BMJ: British Medical Journal. 2006;332(7550):1109.
34. Gallagher RM, Mason JR, Bird KA, Kirkham JJ, Peak M, Williamson PR, et al. Adverse drug reactions causing admission to a paediatric hospital. PLoS One. 2012;7(12).
35. Pokhrel S, Quigley M, Fox-Rushby J, McCormick F, Williams A, Trueman P, et al. Potential economic impacts from improving breastfeeding rates in the UK. Archives of Disease in Childhood. 2015;100(4):334-40.
36. Lundkvist J, Jönsson B. Pharmacoeconomics of adverse drug reactions. Fundamental & clinical pharmacology. 2004;18(3):275-80.
37. Warner EL, Kirchhoff AC, Nam GE, Fluchel M. Financial burden of pediatric cancer for patients and their families. Journal of oncology practice. 2014;11(1):12-8.
38. Laxminarayan R, Duse A, Wattal C, Zaidi AKM, Wertheim HFL, Sumpradit N, et al. Antibiotic resistance-the need for global solutions. The Lancet Infectious Diseases. 2013;13(12):1057-98.
39. Laxminarayan R, Matsoso P, Pant S, Brower C, Røttingen J-A, Klugman K, et al. Access to effective antimicrobials: a worldwide challenge. The Lancet. 2016;387(10014):168-75.
40. Albrich WC, Monnet DL, Harbarth S. Antibiotic selection pressure and resistance in Streptococcus pneumoniae and Streptococcus pyogenes. Emerg Infect Dis. 2004;10(3):514-7.
41. Co-operation OfE, Development. Stemming the superbug tide: just a few dollars more: OECD publishing; 2018.
42. WHO. Promoting rational use of medicines: core components. WHO Policy Perspectives on Medicines. Geneva, Switzerland: World Health Organisation; 2002.
43. Barber N, Bradley C, Barry C, Stevenson F, Britten N, Jenkins L. Measuring the appropriateness of prescribing in primary care: are current measures complete? Journal of clinical pharmacy and therapeutics. 2005;30(6):533-9.
44. Kunin CM, Tupasi T, Craig WA. Use of AntibioticsA Brief Exposition of the Problem and Some Tentative Solutions. Annals of Internal Medicine. 1973;79(4):555-60.
45. Rana DA, Malhotra SD, Patel VJ. Inappropriate surgical chemoprophylaxis and surgical site infection rate at a tertiary care teaching hospital. Brazilian Journal of Infectious Diseases. 2013;17(1):48-53.
46. Van der Meer J, Gyssens I. Quality of antimicrobial drug prescription in hospital. Clinical Microbiology and Infection. 2001;7:12-5.
47. Britten N, Jenkins L, Barber N, Bradley C, Stevenson F. Developing a measure for the appropriateness of prescribing in general practice. BMJ Quality & Safety. 2003;12(4):246-50.
48. Neubert A, Sturkenboom MC, Murray ML, Verhamme KM, Excellence TN, et al. Databases for pediatric medicine research in Europe-assessment and critical appraisal. Pharmacoepidemiology & Drug Safety. 2008;17(12):1155-67.
49. Ovretveit J. Health service quality: an introduction to quality methods for health services: Blackwell Scientific; 1992.
50. Endeshaw B. Healthcare service quality-measurement models: a review. Journal of Health Research. 2020.

51. Campbell S, Braspenning Ja, Hutchinson A, Marshall M. Research methods used in developing and applying quality indicators in primary care. Qual Saf Health Care. 2002;11(4):358-64.
52. Coenen S, Ferech M, Haaijer-Ruskamp FM, Butler CC, Vander Stichele RH, Verheij TJ, et al. European Surveillance of Antimicrobial Consumption (ESAC): quality indicators for outpatient antibiotic use in Europe. BMJ Quality & Safety. 2007;16(6):440-5.
53. Dang CPL, Toh LS, Cooling N, Jackson S, Curtain C, Thompson A, et al. Updating and validating quality prescribing indicators for use in Australian general practice. Australian journal of primary health. 2020;26(1):31-42.
54. WHO. How to investigate drug use in health facilities: selected drug use indicators. Geneva, Switzerland; 1993.
55. Ofori-Asenso R, Brhlikova P, Pollock AM. Prescribing indicators at primary health care centers within the WHO African region: a systematic analysis (1995–2015). BMC public health. 2016;16(1):724.
56. Mao W, Vu H, Xie Z, Chen W, Tang S. Systematic review on irrational use of medicines in China and Vietnam. PloS one. 2015;10(3):e0117710.
57. Holloway KA, Ivanovska V, Wagner A, Vialle‐Valentin C, Ross‐Degnan D. Have we improved use of medicines in developing and transitional countries and do we know how to? Two decades of evidence. Trop Med Int Health. 2013;18(6):656-64.
58. World Health Organization. Using indicators to measure country pharmaceutical situations: fact book on WHO level I and level II monitoring indicators. Geneva: WHO. 2006.
59. Shelton PS, Fritsch MA, Scott MA. Assessing medication appropriateness in the elderly. Drugs & aging. 2000;16(6):437-50.
60. Kaufmann CP, Tremp R, Hersberger KE, Lampert ML. Inappropriate prescribing: a systematic overview of published assessment tools. European journal of clinical pharmacology. 2014;70(1):1-11.
61. Chang C-B, Chan D-C. Comparison of published explicit criteria for potentially inappropriate medications in older adults. Drugs & aging. 2010;27(12):947-57.
62. Beers MH. Explicit criteria for determining potentially inappropriate medication use by the elderly: an update. Archives of internal medicine. 1997;157(14):1531-6.
63. Beers MH, Ouslander JG, Rollingher I, Reuben DB, Brooks J, Beck JC. Explicit criteria for determining inappropriate medication use in nursing home residents. Archives of internal medicine. 1991;151(9):1825-32.
64. Campanelli CM. American Geriatrics Society updated beers criteria for potentially inappropriate medication use in older adults: the American Geriatrics Society 2012 Beers Criteria Update Expert Panel. Journal of the American Geriatrics Society. 2012;60(4):616.
65. Fick DM, Cooper JW, Wade WE, Waller JL, Maclean JR, Beers MH. Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. Archives of internal medicine. 2003;163(22):2716-24.
66. Fick DM, Semla TP. 2012 American Geriatrics Society Beers Criteria: new year, new criteria, new perspective. Journal of the American Geriatrics Society. 2012;60(4):614-5.
67. Jano E, Aparasu RR. Healthcare outcomes associated with beers' criteria: a systematic review. Annals of Pharmacotherapy. 2007;41(3):438-48.
68. Opondo D, Eslami S, Visscher S, De Rooij SE, Verheij R, Korevaar JC, et al. Inappropriateness of medication prescriptions to elderly patients in the primary care setting: a systematic review. PloS one. 2012;7(8):e43617.
69. Guaraldo L, Cano FG, Damasceno GS, Rozenfeld S. Inappropriate medication use among the elderly: a systematic review of administrative databases. BMC geriatrics. 2011;11(1):79.
70. Barry P, Gallagher P, Ryan C, O'mahony D. START (screening tool to alert doctors to the right treatment)—an evidence-based screening tool to detect prescribing omissions in elderly patients. Age and ageing. 2007;36(6):632-8.
71. Ryan C, O'mahony D, Byrne S. Application of STOPP and START criteria: interrater reliability among pharmacists. Annals of Pharmacotherapy. 2009;43(7-8):1239-44.
72. Gallagher P, Baeyens J-P, Topinkova E, Madlova P, Cherubini A, Gasperini B, et al. Inter-rater reliability of STOPP (Screening Tool of Older Persons' Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment) criteria amongst physicians in six European countries. Age and ageing. 2009;38(5):603-6.
73. Klassen TP, Hartling L, Craig JC, Offringa M. Children are not just small adults: the urgent need for high-quality trial evidence in children. PLoS medicine. 2008;5(8):e172.
74. Cohen E, Uleryk E, Jasuja M, Parkin PC. An absence of pediatric randomized controlled trials in general medical journals, 1985–2004. Journal of clinical epidemiology. 2007;60(2):118-23.
75. Saint Raymond A, Brasseur D. Development of medicines for children in Europe: ethical implications. Paediatric respiratory reviews. 2005;6(1):45-51.

76. Anderson BJ, Holford NH. Understanding dosing: children are small adults, neonates are immature children. Archives of disease in childhood. 2013:archdischild-2013-303720.
77. Loh TP, Metz MP. Trends and physiology of common serum biochemistries in children aged 0–18 years. Pathology-Journal of the RCPA. 2015;47(5):452-61.
78. Impicciatore P, Choonara I. Status of new medicines approved by the European Medicines Evaluation Agency regarding paediatric use. British journal of clinical pharmacology. 1999;48(1):15-8.
79. Choonara I, Conroy S. Unlicensed and off-label drug use in children. Drug safety. 2002;25(1):1-5.
80. Council Directive 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use, (2006).
81. European Medicines Agency. 5-year Report to the European Commission. London; 2012 8 July 2012.
82. European Medicines Agency. State of Paediatric Medicines in the EU - 10 years of the EU Paediatric Regulation. Brussels; 2017 26 October 2017.
83. Sammons H. Ethical issues of clinical trials in children: a European perspective. Archives of disease in childhood. 2009;94(6):474-7.
84. Shirkey H. Editorial comment: therapeutic orphans. The Journal of pediatrics. 1968;72(1):119-20.
85. Steinbrook R. Testing medications in children. The New England journal of medicine. 2002;347(18):1462.
86. Modi N, Clark H, Wolfe I, Costello A, Budge H. A healthy nation: strengthening child health research in the UK. The Lancet. 2013;381(9860):73-87.
87. Field MJ, Behrman RE, Children IoMCoCRI. The necessity and challenges of clinical research involving children. 2004.
88. Laventhal N, Tarini BA, Lantos J. Ethical issues in neonatal and pediatric clinical trials. Pediatric Clinics. 2012;59(5):1205-20.
89. UNCRC. Article 12, United Nations Convention on the Rights of the Child. 1989.
90. Nuffield Council on Bioethics. Children and clinical research: ethical issues. London; 2015 May 2015.
91. Kripalani S, Bengtzen R, Henderson LE, Jacobson TA. Clinical research in low-literacy populations: using teach-back to assess comprehension of informed consent and privacy information. IRB: Ethics & Human Research. 2008;30(2):13-9.
92. Shippee ND, Domecq Garces JP, Prutsky Lopez GJ, Wang Z, Elraiyah TA, Nabhan M, et al. Patient and service user engagement in research: a systematic review and synthesized framework. Health Expectations. 2015;18(5):1151-66.
93. Kodish E. Ethics and research with children: a case-based approach: Oxford University Press; 2005.
94. Habicht D, Witham M, McMurdo M. The under-representation of older people in clinical trials: barriers and potential solutions. The Journal of Nutrition Health and Aging. 2008;12(3):194-6.
95. McMurdo ME, Witham MD, Gillespie ND. Including older people in clinical research: Benefits shown in trials in younger people may not apply to older people. BMJ: British Medical Journal. 2005;331(7524):1036.
96. Scher KS, Hurria A. Under-representation of older adults in cancer registration trials: known problem, little progress. Journal of Clinical Oncology. 2012;30(17):2036-8.
97. Kuczera M, Field S, Windisch HC. Building Skills for All: A Review of England. OECD Skills Studies. 2016.
98. Sachs GA, Stocking CB, Stern R, Cox DM, Hougham G, Sachs RS. Ethical aspects of dementia research: informed consent and proxy consent. Clinical Research. 1994;42(3):403-12.
99. Jongsma K, Bos W, Vathorst S. Morally Relevant Similarities and Differences Between Children and Dementia Patients as Research Subjects: Representation in Legal Documents and Ethical Guidelines. Bioethics. 2015;29(9):662-70.
100. Wright DW, Clark PL, Pentz RD, Hertzberg V, Kellermann AL. Enrolling subjects by exception from consent versus proxy consent in trauma care research. Annals of emergency medicine. 2008;51(4):355-60. e3.
101. Sutcliffe AG, Wong ICK. Rational prescribing for children: In an evidence based desert, safe and appropriate treatment is difficult and too easily exploited. BMJ: British Medical Journal. 2006;332(7556):1464.
102. Menson EN, Walker AS, Sharland M, Wells C, Collaborative HIVPSS, et al. Underdosing of antiretrovirals in UK and Irish children with HIV as an example of problems in prescribing medicines to children, 1997-2005: cohort study. BMJ British Medical Journal. 2006;332(7551):1183-6.
103. Størdal K, Wyder C, Trobisch A, Grossman Z, Hadjipanayis A. Overtesting and overtreatment—statement from the European Academy of Paediatrics (EAP). European journal of pediatrics. 2019;178(12):1923-7.

104. Puntis JW. Gastro-oesophageal reflux in young babies: Who should be treated? Archives of Disease in Childhood. 2015;100(10):989-93.
105. De Bruyne P, Ito S. Toxicity of long-term use of proton pump inhibitors in children. Archives of disease in childhood. 2018;103(1):78-82.
106. Rutter N, Doyal L, editors. Neonatal care and management of pain: Historical and ethical issues. Seminars in neonatology; 1998: Elsevier.
107. Ali S, Chambers A, Johnson DW, Newton AS, Curtis SJ, et al. Reported practice variation in pediatric pain management: a survey of Canadian pediatric emergency physicians. CJEM Canadian Journal of Emergency Medical Care. 2014;16(5):352-60.
108. Attallah-Wasif ES. Pain in Infants, Children, and Adolescents. Pain: Springer; 2019. p. 1109-11.
109. Tanne JH. Children are often undertreated for pain. BMJ: British Medical Journal. 2003;327(7425):1185.
110. Bjerre LM, Ramsay T, Cahir C, Ryan C, Halil R, Farrell B, et al. Assessing potentially inappropriate prescribing (PIP) and predicting patient outcomes in Ontario's older population: a population-based cohort study applying subsets of the STOPP/START and Beers' criteria in large health administrative databases. BMJ open. 2015;5(11):e010146.
111. Corrick F, Conroy S, Sammons H, Choonara I. Paediatric Rational Prescribing: A Systematic Review of Assessment Tools. International journal of environmental research and public health. 2020;17(5):1473.
112. Moher D LA, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Medicine. 2009;6(7).
113. Kastner M, Wilczynski NL, Walker-Dilks C, McKibbon KA, Haynes B. Age-specific search strategies for Medline. Journal of medical Internet research. 2006;8(4).
114. Prot-Labarthe S, Vercheval C, Angoulvant F, Brion F, Bourdon O. POPI: A tool to identify potentially inappropriate prescribing practices for children. [French]. Archives de Pediatrie. 2011;18(11):1231-2.
115. Prot-Labarthe S, Weil T, Angoulvant F, Boulkedid R, Alberti C, Bourdon O. POPI (Pediatrics: Omission of Prescriptions and Inappropriate prescriptions): development of a tool to identify inappropriate prescribing.[Erratum appears in PLoS One. 2014;9(9):e108007]. PLoS ONE [Electronic Resource]. 2014;9(6):e101171.
116. Prot-Labarthe S, Weil T, Nguyen NPK, Berthe-Aucejo A, Angoulvant F, Boulkedid R, et al. Consensus validation of a tool to identify inappropriate prescribing in pediatrics (POPI). [French]. Archives de Pediatrie. 2016;23(5):481-90.
117. Barry E, O'Brien K, Moriarty F, Cooper J, Redmond P, Hughes CM, et al. PIPc study: development of indicators of potentially inappropriate prescribing in children (PIPc) in primary care using a modified Delphi technique. BMJ open. 2016;6(9):e012079.
118. Corrick FJ, Conroy S, Choonara I, Sammons H. Developing paediatric rational prescribing criteria. Archives of Disease in Childhood. 2017;102 (Supplement 1):A84.
119. Singh SP, Anderson B, Liabo K, Ganeshamoorthy T. Supporting young people in their transition to adults' services: summary of NICE guidance. bmj. 2016;353:i2225.
120. BNF for Children (online) [Internet]. London: BMJ Group, Pharmaceutical Press, and RCPCH Publications. [cited 01/04/2020]. Available from: http://www.medicinescomplete.com.
121. O'Mahony D, Gallagher P, Ryan C, Byrne S, Hamilton H, Barry P, et al. STOPP & START criteria: a new approach to detecting potentially inappropriate prescribing in old age. European Geriatric Medicine. 2010;1(1):45-51.
122. Gallagher P, Ryan C, Byrne S, Kennedy J, O'Mahony D. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. International journal of clinical pharmacology and therapeutics. 2008;46(2):72-83.
123. Berthe-Aucejo A, Nguyen PKH, Angoulvant F, Bellettre X, Albaret P, Weil T, et al. Retrospective study of irrational prescribing in French paediatric hospital: prevalence of inappropriate prescription detected by Pediatrics: Omission of Prescription and Inappropriate prescription (POPI) in the emergency unit and in the ambulatory setting. BMJ open. 2019;9(3):e019186.
124. Sloane PD, Zimmerman S, Brown LC, Ives TJ, Walsh JF. Inappropriate medication prescribing in residential care/assisted living facilities. Journal of the American Geriatrics Society. 2002;50(6):1001-11.
125. Oborne CA, Batty GM, Maskrey V, Swift C, Jackson S. Development of prescribing indicators for elderly medical inpatients. British journal of clinical pharmacology. 1997;43(1):91-7.
126. Rognstad S, Brekke M, Fetveit A, Spigset O, Wyller TB, Straand J. The Norwegian General Practice (NORGEP) criteria for assessing potentially inappropriate prescriptions to elderly patients: a modified Delphi study. Scandinavian journal of primary health care. 2009;27(3):153-9.
127. Wenger NS, Roth CP, Shekelle P. Introduction to the Assessing Care of Vulnerable Elders - 3 Quality Indicator Measurement Set. Journal of the American Geriatrics Society. 2007;55(s2).

128. Hanlon JT, Schmader KE, Samsa GP, Weinberger M, Uttech KM, Lewis IK, et al. A method for assessing drug therapy appropriateness. Journal of clinical epidemiology. 1992;45(10):1045-51.
129. Khanh NHP, Aurore BA, Francois A, Xavier B, Thomas W, Rym B, et al. Potentially inappropriate prescription and omissions in pediatrics: Detection by POPI in the emergency unit and in the ambulatory setting. POPI (Pediatrics: Omission of Prescription and Inappropriate prescription). International Journal of Clinical Pharmacy. 2016;38 (6):488-9.
130. Berthe-Aucejo A, Nguyen NK, Angoulvant F, Boulkedid R, Bellettre X, Weil T, et al. Interrater reliability of a tool to assess omission of prescription and inappropriate prescriptions in paediatrics. International journal of clinical pharmacy. 2019:1-7.
131. Barry E, Moriarty F, Boland F, Bennett K, Smith SM. The PIPc Study - Application of indicators of potentially inappropriate prescribing in children (PIPc) to a national prescribing database in Ireland: A cross-sectional prevalence study. BMJ Open. 2018;8 (10) (no pagination)(e022876).
132. McKean MC, Ducharme F. Inhaled steroids for episodic viral wheeze of childhood. Cochrane Database of Systematic Reviews. 2000(1).
133. Chavasse RJ, Seddon P, Bara A, McKean MC. Short acting beta2 - agonists for recurrent wheeze in children under two years of age. Cochrane Database of Systematic Reviews. 2002(2).
134. National Institute for Health and Care Excellence. Lyme disease. NICE guideline. 2018;NG 95.
135. Cairns V, Wallenhorst C, Rietbrock S, Martinez C. Incidence of Lyme disease in the UK: a population-based cohort study. BMJ open. 2019;9(8):e025916.
136. Health Protection Surveillance Centre. Lyme disease 2019 [Available from: https://www.hpsc.ie/a-z/vectorborne/lymedisease/factsheet/.
137. Laroche M-L, Charmes J-P, Merle L. Potentially inappropriate medications in the elderly: a French consensus panel list. European journal of clinical pharmacology. 2007;63(8):725-31.
138. Maio V, Canale SD, Abouzaid S. Using explicit criteria to evaluate the quality of prescribing in elderly Italian outpatients: a cohort study. Journal of clinical pharmacy and therapeutics. 2010;35(2):219-29.
139. Lechevallier-Michel N, Gautier-Bertrand M, Alpérovitch A, Berr C, Belmin J, Legrain S, et al. Frequency and risk factors of potentially inappropriate medication use in a community-dwelling elderly population: results from the 3C Study. European journal of clinical pharmacology. 2005;60(11):813-9.
140. Isah A, Laing R, Quick J, Mabadeje A, Santoso B, Hogerzeil H, et al. The development of reference values for the WHO health facility core prescribing indicators. West African Journal of Pharmacology and Drug Research. 2001;18(1):6-11.
141. Unwin B. Implementation of the Beers criteria: sticks and stones-or throw me a bone. Academy of Managed Care Pharmacy; 2005.
142. Corrick F, Choonara I, Conroy S, Sammons H, editors. Modifying a paediatric rational prescribing tool (POPI) for use in the UK. Healthcare; 2019: Multidisciplinary Digital Publishing Institute.
143. Reed GM, First MB, Kogan CS, Hyman SE, Gureje O, Gaebel W, et al. Innovations and changes in the ICD - 11 classification of mental, behavioural and neurodevelopmental disorders. World Psychiatry. 2019;18(1):3-19.
144. Sanchez LA, Holdsworth M, Bartel SB. Stratified administration of serotonin 5-HT 3 receptor antagonists (setrons) for chemotherapy-induced emesis. Pharmacoeconomics. 2000;18(6):533-56.
145. Das RR, Sankar J, Naik SS. Efficacy and safety of diosmectite in acute childhood diarrhoea: a meta-analysis. Archives of disease in childhood. 2015;100(7):704-12.
146. European Medicines Agency. Guideline on pharmaceutical development of medicines for paediatric use.2013 October 24, 2015. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/07/WC500147002.pdf.
147. East Cheshire NHS Trust. Paediatric Antibiotic Policy for Children 1 month - 18 years2014 October 24, 2015. Available from: http://www.eastcheshire.nhs.uk/About-The-Trust/policies/A/Antibiotic%20Policy%20-%20Paediatric%20ECT2037.pdf
148. Nottingham University Hospitals. The investigation and management of Urinary Tract Infection in Children2013 October 24, 2015.
149. Nottingham University Hospitals. Oral Sucrose for the Management of Procedural Pain2013 October 24, 2015. Available from: http://www.nuh.nhs.uk/handlers/downloads.ashx?id=61221.
150. Calderdale and Huddersfield NHS Trust. Protocol for the Administration of Sucrose2014 October 24, 2015. Available from: http://www.formulary.cht.nhs.uk/pdf,_doc_files_etc/MMC/055_Sucrose.076.pdf
151. Maraninchi D. Nitrofurantoïne et risque de survenue d'effets indésirables hépatiques et pulmonaires lors de traitements prolongés. In: AFSSAPS, editor. France2011.
152. National Institute for Health and Care Excellence. Urinary tract infections (lower): antimicrobial prescribing. NICE guideline. 2018;NG 109.

153. Traitement de l'acné par voie locale et générale - Recommandations de bonne pratique In: AFSSAPS, editor. France2007.
154. Utilisation du fluor dans la prévention de la carie dentaire avant l'âge de 18 ans. In: AFSSAPS, editor. France2008.
155. Bresee JS, Duggan C, Glass RI, King CK. Managing acute gastroenteritis among children; oral rehydration, maintenance, and nutritional therapy. MMWR - Morbidity and Mortality Weekly Report, Centers for Disease Control. 2003.
156. Streiner DL, Norman GR. "Precision" and "accuracy": two terms that are neither. Journal of clinical epidemiology. 2006;59(4):327-30.
157. Goodwin LD, Leech NL. The meaning of validity in the new standards for educational and psychological testing: Implications for measurement courses. Measurement and evaluation in Counseling and Development. 2003;36(3):181-91.
158. Franck L, Winter I. Research participant information sheets are difficult to read. Bulletin of medical ethics. 2004(195):13-6.
159. Kis V, Field S. Time for the US to reskill? What the survey of adult skills says. Retrieved from the Organization for Economic Cooperation and Development website: http://skills. oecd. org/Survey_of_Adult_Skills_US. pdf; 2013.
160. Paasche-Orlow MK, Taylor HA, Brancati FL. Readability standards for informed-consent forms as compared with actual readability. New England journal of medicine. 2003;348(8):721-6.
161. Roberts H, Zhang D, Dyer GS. The readability of AAOS patient education materials: evaluating the progress since 2008. JBJS. 2016;98(17):e70.
162. Eltorai AE, Sharma P, Wang J, Daniels AH. Most American Academy of Orthopaedic Surgeons' online patient education material exceeds average patient reading level. Clinical Orthopaedics and Related Research®. 2015;473(4):1181-6.
163. Barr R, Carande EJ, Pollard AJ, Drysdale SB. Change in viral bronchiolitis management in hospitals in the UK after the publication of NICE guideline. Journal of Clinical Virology. 2018.
164. Davis E, Carranza A, Carlin V, Keller S. Changing Practice Across the Care Continuum to Increase Evidence-based Management of Patients with Acute Viral Bronchiolitis. Am Acad Pediatrics; 2018.
165. Carande EJ, Galiza EP, Nickless A, Pollard AJ, Drysdale SB. Viral bronchiolitis management in hospitals in the UK. Journal of Clinical Virology. 2018;104:29-33.
166. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Critical care medicine. 2006;34(6):1589-96.
167. Weiss SL, Fitzgerald JC, Balamuth F, Alpern ER, Lavelle J, Chilutti M, et al. Delayed antimicrobial therapy increases mortality and organ dysfunction duration in pediatric sepsis. Critical care medicine. 2014;42(11):2409.
168. NHS. Healthy Start vitamins 2011 [Available from: https://www.healthystart.nhs.uk/healthy-start-vouchers/healthy-start-vitamins/.
169. Nauta KJ, Groenhof F, Schuling J, Hugtenburg JG, van Hout HP, Haaijer‐Ruskamp FM, et al. Application of the STOPP/START criteria to a medical record database. Pharmacoepidemiology and drug safety. 2017;26(10):1242-7.
170. Fleiss J. Statistical methods for rates and proportions 2nd edition. New York: John Wiley; 1981 1981.
171. Hanlon JT, Schmader KE. The medication appropriateness index at 20: where it started, where it has been, and where it may be going. Drugs & aging. 2013;30(11):893-900.
172. San-José A, Agustí A, Vidal X, Barbé J, Torres OH, Ramírez-Duque N, et al. An inter-rater reliability study of the prescribing indicated medications quality indicators of the Assessing Care Of Vulnerable Elders (ACOVE) 3 criteria as a potentially inappropriate prescribing tool. Archives of gerontology and geriatrics. 2014;58(3):460-4.
173. Samsa GP, Hanlon JT, Schmader KE, Weinberger M, Clipp EC, Uttech KM, et al. A summated score for the medication appropriateness index: development and assessment of clinimetric properties including content validity. Journal of clinical epidemiology. 1994;47(8):891-6.
174. Fitzgerald LS, Hanlon JT, Shelton PS, Landsman PB, Schmader KE, Pulliam CC, et al. Reliability of a modified medication appropriateness index in ambulatory older persons. Annals of Pharmacotherapy. 1997;31(5):543-8.
175. Kassam R, Martin LG, Farris KB. Reliability of a modified medication appropriateness index in community pharmacies. Annals of Pharmacotherapy. 2003;37(1):40-6.
176. Bregnhøj L, Thirstrup S, Kristensen MB, Sonne J. Reliability of a modified medication appropriateness index in primary care. European journal of clinical pharmacology. 2005;61(10):769-73.

177. Spinewine A, Dumont C, Mallet L, Swine C. Medication appropriateness index: reliability and recommendations for future use. Journal of the American Geriatrics Society. 2006;54(4):720-2.
178. Stuijt CC, Franssen EJ, Egberts AC, Hudson SA. Reliability of the medication appropriateness index in Dutch residential home. Pharmacy world & science. 2009;31(3):380-6.
179. Gallagher P, O'connor M, O'mahony D. Prevention of potentially inappropriate prescribing for elderly patients: a randomized controlled trial using STOPP/START criteria. Clinical Pharmacology & Therapeutics. 2011;89(6):845-54.
180. Nguyen HPK, Berthe-Aucejo A, Angoulvant F, Boulkedid R, Bellettre X, Weil T, et al. POPI-(Pediatrics: Omission of Prescriptions and Inappropriate Prescriptions) criteria amongst physicians and pharmacists: Interrater reliability. International Journal of Clinical Pharmacy. 2017;39 (1):297.
181. Gillian Vance BB, Sharmila Jandial, Jon Scott. Identifying the work activities performed by doctors in the Foundation Programme. Newcastle University; 2015.
182. Sun S. Meta-analysis of Cohen's kappa. Health Services and Outcomes Research Methodology. 2011;11(3-4):145-63.
183. Moriarty F, Cahir C, Bennett K, Fahey T. Economic impact of potentially inappropriate prescribing and related adverse events in older people: a cost-utility analysis using Markov models. BMJ open. 2019;9(1):e021832.
184. Saastamoinen LK, Verho J. Register-based indicators for potentially inappropriate medication in high-cost patients with excessive polypharmacy. Pharmacoepidemiology & Drug Safety. 2015;24(6):610-8.
185. Heininger-Rothbucher D, Daxecker M, Ulmer H, Gritsch W, Pechlaner C, Wiedermann CJ. Problematic drugs in elderly patients presenting to a European emergency room. European Journal of Internal Medicine. 2003;14(6):372-6.
186. Pinto MCX, Ferre F, Pinheiro MLP. Potentially inappropriate medication use in a city of Southeast Brazil. Brazilian Journal of Pharmaceutical Sciences. 2012;48(1):79-86.
187. Shaw CD, Costain DW. Guidelines for medical audit: seven principles. BMJ. 1989;299(6697):498-9.
188. Hogerzeil HV. Promoting rational prescribing: an international perspective. British journal of clinical pharmacology. 1995;39(1):1-6.
189. Kamarudin G, Penm J, Chaar B, Moles R. Educational interventions to improve prescribing competency: a systematic review. BMJ open. 2013;3(8):e003291.
190. RCGP. Prescribing assessment: Royal College of General Practitioners; [Available from: https://www.rcgp.org.uk/training-exams/training/mrcgp-workplace-based-assessment-wpba/prescribing-assessment.aspx.
191. Ivers N, Jamtvedt G, Flottorp S, Young JM, Odgaard‐Jensen J, French SD, et al. Audit and feedback: effects on professional practice and healthcare outcomes. Cochrane database of systematic reviews. 2012(6).
192. Yang J, Zheng L, Guan Y, Song C. Analysis of the impact of antimicrobial management and rational use of antibiotics. European Journal of Hospital Pharmacy. 2019:ejhpharm-2018-001609.
193. Akici A, Gören MZ, Aypak C, Terzioğlu B, Oktay Ş. Prescription audit adjunct to rational pharmacotherapy education improves prescribing skills of medical students. European journal of clinical pharmacology. 2005;61(9):643-50.
194. Cheng HY, Bradley E. Improving Identification of Potentially Inappropriate Medications among Older Patients: a Preliminary Report of a Single-Blind, Controlled Trial Teaching Fourth Year Medical Students Value-and Preference-Based Prescribing/De-Prescribing. Medical Science Educator. 2016;26(3):431-5.
195. Wahab MSA. The relevance of educating doctors, pharmacists and older patients about potentially inappropriate medications. International journal of clinical pharmacy. 2015;37(6):971-4.
196. General Medical Council. Good Medical Practice. London: GMC; 2014.
197. England N. Next steps on the NHS five year forward view. London: NHS England. 2017.

Appendices

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2. Corrick F, Choonara I, Conroy S, Sammons H, editors. Modifying a paediatric rational prescribing tool (POPI) for use in the UK. Healthcare; 2019;7(1)
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4. Corrick FJ, Conroy S, Choonara I, Sammons H. Developing paediatric rational prescribing criteria. Archives of Disease in Childhood. 2017;102 (Supplement 1):A84. (Oral presentation)
5. Corrick F, Smith C, Choonara I, Sammons HM. Rational Prescribing for Children: Evaluating the modified POPI criteria. RCPCH Annual QI Conference; 2016 (Poster and oral presentation) – awarded best trainee project
6. Corrick, F, Sammons HM. Assessment Tools of Rational Prescribing in Children. Trent Paediatric Society Meeting; 2016 (Poster)
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International Journal of *Environmental Research and Public Health*

MDPI

Review

Paediatric Rational Prescribing: A Systematic Review of Assessment Tools

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Abstract: Rational prescribing criteria have been well established in adult medicine for both research and quality improvement in the appropriate use of medicines. Paediatric rational prescribing has not been as widely investigated. The aims of this review were to identify and provide an overview of all paediatric rational prescribing tools that have been developed for use in paediatric settings. A systematic literature search was made of MEDLINE, Embase, CINAHL and IPA from their earliest records until July 2019 for all published paediatric rational prescribing tools. The characteristics of the tools were recorded including method of development, types of criteria, aspects of rational prescribing assessed, and intended practice setting. The search identified three paediatric rational prescribing tools: the POPI (Pediatrics: Omissions of Prescriptions and Inappropriate Prescriptions) tool, the modified POPI (UK) tool, and indicators of potentially inappropriate prescribing in children (PIPc). PIPc comprises explicit criteria, whereas POPI and the modified POPI (UK) use a mixed approach. PIPc is designed for use in primary care in the UK and Ireland, POPI is designed for use in all paediatric practice settings and is based on French practice standards, and the modified POPI (UK) is based on UK practice standards and is designed for use in all paediatric practice settings. This review describes three paediatric rational prescribing tools and details their characteristics. This will provide readers with information for the use of the tools in quality improvement or research and support further work in the field of paediatric rational prescribing.

Keywords: rational prescribing; paediatrics; rational use of medicines

1. Introduction

Rational prescribing has been defined by the World Health Organisation as "when patients receive the appropriate medicines, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost both to them and the community" [1]. It has been poorly studied in paediatric patients; a field that has been described as "an evidence based desert" [2]. Irrational prescribing has wide-ranging impacts, from adverse drug reactions and progression of inappropriately managed disease to additional system healthcare costs and antimicrobial resistance. The use of criteria lists as tools to quantify rational prescribing in adult medicine is well established [3]. There are a number of potential benefits to rational prescribing tools; assessment tools enable quantification of the quality of prescribing, which facilitates research into interventions aiming to improve prescribing and allows prescribing in different settings to be compared. This facilitates deeper research into root causes of problematic prescribing or excellent prescribing and fosters collaboration between different groups.

A 2014 systematic review of rational prescribing tools for adults by Kaufmann et al. identified 46 published tools [4]. Of these, 22% did not have a stated target population, while 78% were specifically targeted to prescribing for older adults. Older adults have been identified as a group vulnerable to irrational prescribing due to a variety of factors, including the frequent existence of co-morbidities, polypharmacy, care taking place in a number of different settings, and the effect of ageing on the selection of appropriate medications [5]. Many similar challenges exist in paediatric medicine, with well-recognised developmental changes in physiology and metabolism having a significant impact on pharmacokinetics in children of different ages [6]. In addition, children may receive medications in a number of different settings, including general practice, undifferentiated emergency departments, walk-in centres, paediatric wards in district general hospitals, and specialist paediatric hospital settings. This means that prescribers with varied levels of paediatric experience and expertise may be responsible for prescribing.

Kaufmann et al. explicitly excluded tools targeted to children in their 2014 review. The aim of this review was to carry out a systematic review of paediatric rational prescribing tools in order to produce a comprehensive overview of current tools available to measure rational prescribing in children. This will hopefully facilitate others studying this area.

2. Methods

The systematic literature search was designed to identify articles describing tools to assess rational (or inappropriate) prescribing for children.

Inclusion criteria were: articles describing tools targeted at evaluating the rationality or appropriateness of prescriptions for children (aged less than or equal to 18 years), updated and revised versions of previously published tools, and including tools limited to specific drugs, drug groups, diseases or disease groups.

Exclusion criteria were: tools targeting adults, tools without specified target patient groups, indicators that assess rates or percentages of prescription types in a population, articles describing a validation study of a previously published tool, educational interventions aimed at improving prescribing, and guidelines describing recommended prescribing.

Search Strategy

The search was conducted in four databases in order to attempt to capture relevant medical, nursing and pharmaceutical research. These were: Ovid MEDLINE, Embase, International Pharmaceutical Abstracts (IPA) and CINAHL. Databases were searched from their earliest records possible until the start of July 2019.

Search terms to capture studies including children were derived from the recommended search strategy described by Kastner et al. 2006 [7], as these have demonstrated high sensitivity. The MeSH term "inappropriate prescribing" was introduced in 2011, and was previously incorporated in the broad term "Drug therapy". Search terms for rational prescribing were derived from the systematic review of adult rational prescribing tools by Kaufmann et al. 2014 [4]. The combined terms were:

(inappropriate prescribing or suboptimal prescribing or inappropriate medication or inappropriate practices or drug prescriptions or Medication Appropriateness Index) and (child* or children* or p*ediatric* or infant* or adolescent*).

All potentially relevant publications were screened by title and abstract and articles that met the exclusion criteria were excluded. The remaining articles were retrieved in full. Full-texts were examined by FC and a second researcher who performed independent full-text screening, independently assessing articles according to the inclusion and exclusion criteria. After this process, any articles without consensus were resolved by discussion and mutual agreement. A manual search of the bibliographies of included texts was completed.

Included articles were analysed by FC to extract the development process and characteristics of the rational prescribing tool.

3. Results

The search produced 2142 potentially relevant publications. 234 duplicated articles were removed. 1908 articles were screened by title and abstract and 1736 were excluded (Figure 1). One hundred seventy-two articles were selected for full-text review by two reviewers of which 163 were excluded. The excluded articles screened at full-text did not meet the inclusion criterion of describing rational prescribing tools. Four full-texts were unavailable online from University library resources, and from the British Library. In the case of the four full-texts that were unavailable the abstracts suggested that these articles would not meet the inclusion criteria, although this could not be determined with certainty. Five articles met the inclusion criteria. Bibliography mining of the included articles did not identify any further relevant articles.

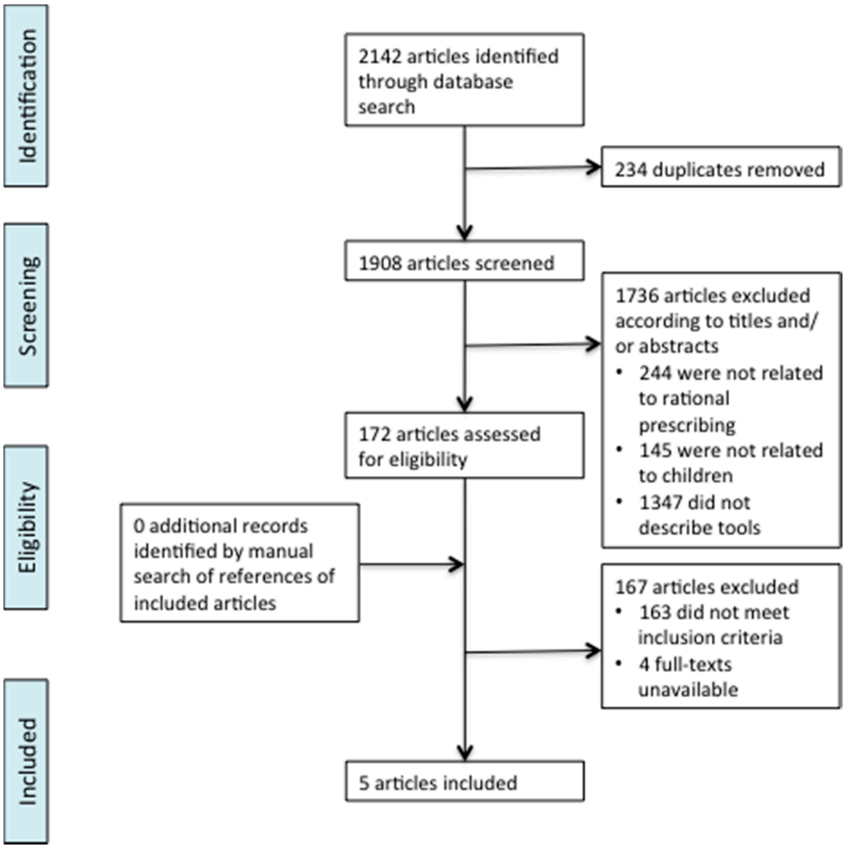

Figure 1. Flowchart of screening process for literature search. Adapted from the PRISMA group statement [8].

3.1. Rational Prescribing Tools Identified

In total, five relevant articles were identified, relating to three paediatric rational prescribing tools. These are shown in Table 1.

Table 1. Results of systematic literature search.

Authors	Title	Year of Publication	Country	Name of Rational Prescribing Tool	Number of Criteria
Prot-Labarthe et al. [8]	POPI: A tool to identify potentially inappropriate prescribing practices for children (French).	2011	France	POPI	9 (partial list)
Prot-Labarthe et al. [9]	POPI (Pediatrics: Omission of Prescriptions and Inappropriate prescriptions): development of a tool to identify inappropriate prescribing.	2014	France	POPI	105
Prot-Labarthe et al. [10]	Consensus validation of a tool to identify inappropriate prescribing in pediatrics (POPI) (French).	2016	France	POPI	101
Corrick et al. [11]	Developing paediatric rational prescribing criteria.	2017	UK	Modified (UK) POPI	80
Barry et al. [12]	PIPc study: development of indicators of potentially inappropriate prescribing in children (PIPc) in primary care using a modified Delphi technique.	2016	Ireland and UK	PIPc	12

Three relevant articles were identified relating to a single tool: POPI (Pediatrics: Omissions of Prescriptions and Inappropriate Prescriptions) tool [9–11]. All three included articles are very similar, two in French and one in English, and describe the process of developing the POPI tool. The earliest, from 2011, is a letter describing the tool, giving nine examples of the gastro-intestinal criteria. The 2014 and 2016 articles are English and French language, respectively. They report the consensus validation of the tool and give full details of the criteria. The number of criteria listed differs due to the combination of several criteria together in the latter publication. Note that the 2014 article states there are 104 criteria but lists 105. For the purposes of clarity, from this point reference to the POPI criteria is specifically to the wording and numbering in the English 2014 publication unless otherwise stated.

The other two relevant articles relate to two additional rational prescribing tools. One of these describes the modified (UK) POPI tool [12], a modification of the above POPI tool for application to use in the UK published by the authors of this review in 2017. The other relates to the development of a rational prescribing tool for the evaluation of paediatric prescribing in primary care, indicators of potentially inappropriate prescribing in children (PIPc) [13]. This was developed in Ireland and the UK and published in September 2016.

3.2. Characteristics of the Identified Paediatric Rational Prescribing Tools

All three tools are examples of explicit or mixed rational prescribing tools and are comprised of a number of explicit criteria defining potentially inappropriate prescriptions (PIPs) and potentially inappropriate omissions (PIOs). Both POPI and the modified POPI (UK) also contain some criteria with implicit features.

The POPI tool comprises 105 criteria (80 PIPs and 25 PIOs) categorised by the authors according to broadly grouped clinical conditions: diverse illnesses, digestive problems, ENT-pulmonary problems, dermatological problems, and neuropsychiatric disorders. The groups are further subdivided into particular symptoms or conditions. The criteria cover a range of aspects of inappropriate prescribing, including overprescribing, underprescribing, and almost all areas of misprescribing except drug-food interactions.

The modified (UK) POPI tool comprises 80 criteria under the same categories as the original POPI tool, except for the removal of one subcategory (Mosquitos [sic]). The criteria include 60 PIPs and 20 PIOs across the same aspects of inappropriate prescribing as the original POPI criteria.

PIPc comprises twelve criteria of potentially inappropriate prescribing or omissions, categorised according to four physiological systems: respiratory, gastrointestinal, dermatological, and neurological. Seven criteria describe PIPs with potential overprescribing or misprescribing practices, five relate to PIOs.

The characteristics of the identified tools are summarised in Table 2, where bullet points identify aspects of irrational prescribing that are covered by each tool.

3.3. Development of the Popi Tool

The methodology used to develop the POPI tool was designed to closely match the development of the STOPP/START criteria, according to the authors [10]. The STOPP/START criteria are criteria for rational prescribing in older people developed in 2008 [14] comprising two lists; the "STOPP" list of PIPs, and the "START" list of PIOs. In the STOPP/START tool, the authors structured their criteria according to physiological systems to mirror the usual organisation of drug formularies. The propositions were validated using an 18-member panel Delphi consensus where agreement was determined by the kappa-statistic for agreement and participants were able to suggest additional criteria if desired [15].

The POPI tool was developed in part by the Delphi consensus method. Prior to the Delphi consensus process, the authors compiled a list of possible propositions.

The authors structured POPI around 100 propositions classified according to biological systems and divided into omissions and inappropriate prescriptions. The number of propositions was chosen as "a good compromise between the number of major biological system to explore, the number of items in the geriatric lists and the maximum number of items compatible with a tool easy use" [8] (p. 2). The authors then compiled a list of health problems frequently encountered in paediatric practice, according to frequency in the general population (source not specified), prevalence (derived from data from the French National Insurance Fund for Employers for long term conditions), and frequency as cause for hospitalisation (per French hospital medico-administrative records). The authors identified health problems from this list, referred to as "themes", that would either require drug intervention or where pharmacological intervention would be considered inappropriate.

For each selected theme, the authors conducted a literature search to identify recommendations on management. There was a requirement for recommendations to be evidence-based but the authors did not specify the level of evidence. Only recommendations published after 2000 were accepted and these were then weighted by date of publication. Accepted sources of recommendations were the French Health Products Safety Agency (Agence Française de Sécurité Sanitaire des Produits de Santé), the French National Authority for Health (Haute Autorité de Santé Française), the French Society for Paediatricians (Sociétè Française de Pédiatrie), the American Academy of Pediatrics (National Guideline Clearing House), and the National Institute for Health and Clinical Evidence (NICE) Cochrane Library [sic]. They also used the MEDLINE database to search for examples of medication error and inappropriate prescription (search strategy unpublished).

The propositions were then validated by a two-round Delphi consensus. Sixteen experts, including pharmacists and paediatricians, were included, of whom ten responded to both rounds. The process of recruitment of experts is not described, only that most pharmacists were members of the French Society of Clinical Pharmacy and most paediatricians were members of the French Society of Pediatricians.

Table 2. Characteristics of the paediatric rational prescribing tools.

Rational Prescribing Tool	Development Method	Healthcare Setting	Patient Group	Aspects of Inappropriate Prescribing								
				Misprescribing							Overprescribing	Underprescribing
				Drug Choice	Dosage	Duration	Duplication	Drug-Disease Interaction	Drug-Drug Interaction	Drug-Food Interaction		
POPI (Pediatrics: Omissions of Prescriptions and Inappropriate Prescriptions), Prot-Labarthe et al. [9–11]	Delphi consensus	Not specified	Children	♦	♦	♦	♦	♦	♦		♦	♦
Modified POPI (UK), Corrick et al. [8]	Modification of prior tool	Not specified	Children	♦	♦	♦	♦	♦	♦		♦	♦
PIPc (indicators of potentially inappropriate prescribing in children), Barry et al. [13]	Delphi consensus	Primary care	Children < 16 years	♦				♦	♦		♦	♦

Initially, 108 propositions were presented to the experts. There is inconsistency between the 2014 (English) compared with the 2016 (French) publication in that the 2014 paper states 104 criteria were validated, whereas the 2016 paper states 101 criteria were validated. Furthermore, while it is stated in the 2014 paper that 104 propositions were validated, in fact 105 propositions are included in their final list. The difference between the two papers is due to three instances of combining two statements into a single criterion, and the omission of one proposition in the 2016 (French) publication. Specifically, two propositions about desmopressin for nocturnal enuresis are combined into one and six propositions about atopic eczema are combined into four. A proposition about benzyl benzoate for scabies is omitted. Other than this, the described process and criteria are the same.

Two propositions were removed following the consensus study due to new contraindications having been published for the use of these drugs in children, therefore 102 propositions were ultimately validated. In the 2016 French language publication describing the consensus validation of the POPI tool [11], the authors state that 101 of 108 criteria were validated. For the purposes of evaluation and discussion below, the English language published list of 105 validated propositions in the 2011 report is used.

3.4. Development of the Modified Popi UK) Tool

The modified POPI (UK) tool was developed in order to apply the POPI tool, which was based on a mixture of French, UK, and US guidelines, to UK practice [12]. A number of medications identified in the original POPI criteria are either not in usual use or unavailable in the UK, while some criteria directly conflicted with national UK clinical guidelines.

Each of the 105 criteria in the English language publication of the POPI tool were compared to relevant UK clinical guidelines from NICE, the Scottish Intercollegiate Guideline Network (SIGN), and the British National Formulary for Children (BNFc). In cases where there were no relevant guidelines or directly contradictory guidelines, criteria were removed. If guidelines differed, criteria were modified to reflect UK guidelines.

In comparison to the original criteria, 49 criteria were not changed. 29 were modified to meet UK guidelines, four criteria were combined into two, and 23 were omitted altogether. Omitted criteria included the removal of the clinical category of "Mosquitos", which comprised seven criteria.

3.5. Development of the PIPc

Like the POPI tool, the PIPc was developed by a two-round Delphi consensus method. Initial propositions were selected via a systematic literature search for previously developed indicators for paediatric prescribing.

Inclusion criteria were:

- Describe prescribing that is hazardous or known to be ineffective
- Describe prescribing in keeping with best practice/current guidelines
- Apply to the population of children < 16 years

Exclusion criteria were:

- Medications unavailable in the study setting
- Criteria that could not be applied in the absence of clinical information
- Criteria containing medications with a low prevalence of use

A steering group of academic and clinical general practitioners (GPs), academic and clinical pharmacists, a pharmacoepidemiologist/statistician, and a postdoctoral researcher, assessed each criterion. Those that were not felt to meet the above conditions were excluded. In some cases, criteria were modified to meet the need to be applicable without access to clinical information, for example when evaluating data from a dispensing database.

The panel for the Delphi consensus comprised eighteen specialists, nine from the Republic of Ireland (three GPs, three paediatricians, and three pharmacists) and nine from the UK (three GPs, three paediatricians, and three pharmacists).

The two-round Delphi consensus resulted in twelve criteria being accepted into the final PIPc.

3.6. Characteristics of the Tools

The use of the POPI tool is not specifically limited to any particular clinical setting. The propositions were selected from paediatric health problems in the general population and as causes for hospitalisation, suggesting the tool would be relevant to both primary and secondary care. However, no primary care specialists or general practitioners were involved in the development of the tool. The paediatric population is not explicitly defined by the authors but some propositions are age-specific, for instance pharmacological treatment for attention deficit disorder is described as inappropriate "before age six (before school)" [8] (p. 7) and topical 0.1% tacrolimus is considered inappropriate for atopic eczema "before 16 years of age" [8] (p. 6).

The criteria of the POPI tool cover a wide range of the aspects of rational prescribing, including all three categories of underprescribing, overprescribing, and misprescribing. Underprescribing errors are specifically identified in the tool as omissions. The inappropriate prescription propositions include some examples of overprescribing and misprescribing.

The modified POPI (UK) tool shares the characteristics of the original POPI tool.

The PIPc is a tool that has been designed specifically for application in primary care settings. Unlike the POPI tool, it has been developed to be applicable without access to clinical information, meaning that it can be used to evaluate data from large previously collected prescribing databases where clinical information is often either omitted or concealed.

The authors of the PIPc define their paediatric population as children under 16 years of age. The age at which young people transition from paediatric to adult healthcare services can vary depending on health needs, social circumstances such as attendance in full-time education, and availability of specialist services [16]. In addition to the population specified for the tool, some criteria further specify particular age ranges, for example, "Loperamide should not be prescribed to children under 4 years" [11] (p. 8).

The PIPc criteria describe almost as broad a range of types of potentially irrational prescribing as POPI despite having far fewer criteria. The only aspects of irrational prescribing not contained within the PIPc that are covered by POPI are misprescribing of dosage, duration, and duplication.

3.7. Validation studies

The POPI tool has been evaluated in both a clinical validation [17] and repeatability study [18] (Table 3). The very high rate of PIPs in the community pharmacy is not further analysed in the published report.

Table 3. Validation or repeatability studies.

Tool	Setting	Number of Children	Prevalence of PIPS	Prevalence of PIOs	Reference
POPI	Emergency department	15973	3.3%	2.6%	17
	Community	2225	26.4%	2.6%	
POPI	Emergency department	20	N/A (repeatability study)	N/A (repeatability study)	18
PIPc	Primary care	414,856	3.5%	2.5%	19
POPI(UK)	Emergency department and inpatient	400	32 in total		20

The published repeatability study of the POPI tool [18] found good repeatability despite the high complexity and mixed implicit and explicit approach of the tool.

The POPI tool was developed using French, American and UK guidelines and has been validated in clinical practice, with the above study showing that it is able to detect some potentially irrational prescribing in French settings. It is not yet known whether it detects irrational prescribing that correlates to adverse events or patient outcomes, or whether it could be used to evaluate prescribing outside French practice.

Although not published as a clinical validation study, there is a published study using the PIPc criteria to detect potentially irrational prescribing [19] (Table 3). In this study, the criteria were applied to a national pharmacy claims database in Ireland, the Primary Care Reimbursement Service (PCRS) with a cross-sectional methodology. The database records pharmacy claims for medicines for eligible patients prescribed by general practitioners or transcribed from hospital prescriptions by general practitioners, with limited patient demographic data (age, gender and region). No clinical details of the patients are recorded. The rate of PIO rose to 11.5% when including the criterion relating to co-prescription of a space device. Similarly, a single criterion had a large impact on PIPs and when this criterion, relating to carbocisteine, was removed the PIP rate fell to 0.29%.

One significant limitation in this study was that it highlighted the difficulty in applying even the intentionally simple and explicit criteria of PIPc to retrospective anonymised data. The age of patients in the PCRS database was recording in age bands of 0–4 years, 5–11 years, and 12–15 years. In several cases, these bands overlapped age limits described in PIPc criteria. In order to analyse the data, the authors made calculations to estimate the number of children of a certain age. For example, to calculate the number of children under 2 years in the 0–4 years band, the total number of children in the band was divided by 5 and multiplied by 2. This assumes a normal distribution of ages, which may not be the case.

There is no published repeatability study of PIPc.

A clinical validation study of the modified POPI (UK) tool has only been published in abstract form [12] (Table 3). There is currently no published repeatability study for the modified POPI (UK) tool.

3.8. Comparison with Existing Adult Rational Prescribing Tools

All of the paediatric tools identified cover a range of types of rational prescribing, with the POPI and modified POPI (UK) tools covering a particularly broad range. By comparison, the majority of adult tools identified by Kaufmann et al. [4] had a narrower focus.

Of the 46 adult tools identified by Kaufmann et al., the median number of aspects of rational prescribing covered by each tool was 4.5, similar to the PIPc, which covers five aspects. However, four tools did cover eight or nine categories of prescribing, which is comparable to the POPI and modified POPI (UK), which cover eight.

The PIPc is designed for use in primary care settings, while the POPI tool and modified POPI (UK) are developed for application in a range of settings. The breadth of applications of both the POPI tool and modified POPI (UK) tool is similar to a number of rational prescribing tools for older adults, which have been used in settings including nursing homes, emergency departments, and primary care.

Of the adult tools evaluated by Kaufmann et al., the majority of tools (28) were explicit, a minority (8) were implicit, and the remaining 10 used a mixed approach like POPI. Implicit criteria may be more accurate, as they can take into account individual patient requirements, but this may come at the cost of reliability as they are more dependent on the rater's knowledge and judgement [5]. The reverse is true of explicit tools, which are less reliant on rater judgement and therefore might be expected to have greater repeatability and reliability and be less time-consuming to apply, with concomitant lower accuracy. Therefore, mixed tools may stand to inherit both the advantages and disadvantages of each approach.

The authors of the original POPI state that the tool comprises explicit criteria; however, in both the POPI and modified POPI (UK) tools a number of criteria contain judgement-based and patient-specific

considerations. Other propositions require taking into account the patient's co-morbidities and entire medication regimen, characteristics that are usually considered components of implicit (patient-specific) criteria. For example, several propositions require the rater to make subjective judgements, such as in the theme of Attention Deficit Disorder, which includes "Pharmacological treatment before age six . . . except in severe cases" [7] (p. 7).

In some cases, the modified POPI (UK) amended criteria replace subjective judgements with explicit quantified cut-offs to reflect similarly precise recommendations in the UK guidelines. For instance where the original POPI tool lists a PIO of "Asthma inhaler appropriate for the child's age", the modified POPI (UK) criterion reads, "Asthma inhaler appropriate for the child's age (aged < 5 years, either Metered Dose Inhaler with spacer system or nebuliser; age 3–5 years Dry Powder Inhaler may be appropriate)" [12].

The PIPc criteria are entirely explicit and do not require evaluation of a patient's condition or subjective judgements. One criterion that may require non-anonymised data for full evaluation, however, is the recommendation in the Respiratory System theme, that "Children under 12 years who are prescribed a pressurised metered-dose inhaler should also be prescribed a spacer device at least every 12 months" [11] (p. 8). In order to assess this with certainty, the rater would need to be able to see all prescriptions for the child within the prior twelve months. Nonetheless, these criteria are all explicit.

4. Discussion

This systematic literature review identified three rational prescribing tools for use in paediatric practice, the PIPc, the POPI tool, and the modified POPI (UK) tool.

There are a number of research and clinical applications for rational prescribing tools.

The varying characteristics of the three paediatric rational prescribing tools identified have implications for their use and impact in future work. PIPc is intended only for primary care settings, while the POPI and modified (UK) POPI tools can be applied in any paediatric setting.

All three tools could be used for both clinical governance and research purposes to identify areas of problematic prescribing, compare rates of irrational prescribing between settings, grades or specialties of prescribers, or regions. Because the tools provide a means to quantify rational prescribing, they may also facilitate the evaluation of educational or quality improvement interventions. The tools could also be used to assess factors associated with problematic prescribing.

In terms of structure and complexity, the POPI tool comprises a relatively high number of criteria compared with many other tools, although there is one published tool targeted at older adults with 392 quality indicators (not all of which relate to rational prescribing), ACOVE-3 [20]. The PIPc has closer to the lowest number of criteria of the adult tools. Some of the tools detailed in the Kaufmann systematic review have as few as ten criteria, for instance the Medication Appropriateness Index (MAI) [21], which is also targeted at older adults. A simple count of criteria is not necessarily a useful measure of complexity however. For example, in the case of the MAI, it is intended that all ten criteria are applied to each drug a patient is prescribed, where some systems simply list medications that are contraindicated or essential.

The high number of propositions and mixed implicit and explicit approach of the POPI tool makes it quite high in complexity, thus it requires a high level of clinical knowledge to apply. Some patients may fall within multiple themes, for instance Pain and fever might be expected alongside a number of other themes with an infectious focus, such as Urinary Infections and ENT Infections, and other themes describe long-term conditions that any child might have as co-morbidity. The theme of Vitamin Supplements and Antibiotic Prophylaxis includes a proposition describing minimum vitamin D intake, which would need to be assessed for every child. This would therefore require a high level of familiarity with the tool for accurate use and necessitates access to a high level of information about each patient.

By contrast, the PIPc is by design a tool that is simpler to apply and that requires minimal clinical information about a patient. The only clinical diagnosis specified in the tool is a presumed diagnosis

of asthma in two criteria, which it appears that a rater is intended to presume on the basis of the prescriptions described, e.g., "An inhaled short-acting beta-2 agonist should be prescribed to children under 5 years who are also taking a leukotriene receptor antagonist for presumed asthma" [11] (p. 8). The PIPc is likely to be quicker to apply and does not require the high level of clinical information required by the POPI tool. However, it is also less broad and therefore it will not identify some aspects of irrational prescribing such as duplication, inappropriate drug duration, or incorrect drug dosage. There are also fewer clinical conditions included within the PIPc as compared with POPI, which may not reduce its efficacy as a screening tool in general settings but might reduce its usefulness in more specialist settings.

Further work comparing the sensitivity of the tools to detect rational prescribing and their utility in different clinical settings would be informative. In addition, it would be valuable to assess whether higher rates of irrational prescribing as detected by the tools is associated with poorer clinical outcomes or increased rates of adverse drug events.

As electronic prescribing becomes increasingly widespread, algorithmic clinical decision support systems have been developed to help alert clinicians to potentially inappropriate prescribing. In the older adult population where the Beers criteria and STOPP/START criteria are well-established, a computerised clinical decision support system integrating these rational prescribing tools has been developed [22]. This may be another avenue for further development towards greater rational prescribing for children by integrating one or more of the identified rational prescribing tools in a similar model.

The study of rational prescribing in children is a neglected area of research [23,24]. Studies of the value of these tools in different clinical settings by different investigators is needed to evaluate how useful the tools are. Such studies are essential to improve rational prescribing in different paediatric populations.

5. Conclusions

This systematic literature search identified three rational prescribing tools for use in assessing potentially inappropriate prescribing in paediatric settings, the PIPc, the POPI tool, and the modified POPI (UK) tool. We have outlined the characteristics of the tools, including their modes of design, aspects of rational prescribing assessed, and intended practice settings, which may assist readers in making use of the tools in their own clinical practice or for further research. The paucity of paediatric rational prescribing tools compared to adult tools shows that this remains a relatively underdeveloped field of study with great potential for future research.

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References

1. WHO. *The Rational Use of Drugs. Report of the Conference of Experts*; World Health Organisation: Geneva, Switzerland, 1985.
2. Sutcliffe, A.G.; Wong, I.C.K. Rational prescribing for children: In an evidence based desert, safe and appropriate treatment is difficult and too easily exploited. *BMJ Br. Med. J.* **2006**, *332*, 1464–1465. [CrossRef] [PubMed]

3. Kaur, S.; Mitchell, G.; Vitetta, L.; Roberts, M.S. Interventions that can reduce inappropriate prescribing in the elderly. *Drugs Aging* **2009**, *26*, 1013–1028. [CrossRef] [PubMed]
4. Kaufmann, C.P.; Tremp, R.; Hersberger, K.E.; Lampert, M.L. Inappropriate prescribing: A systematic overview of published assessment tools. *Eur. J. Clin. Pharmacol.* **2014**, *70*, 1–11. [CrossRef] [PubMed]
5. Spinewine, A.; Schmader, K.E.; Barber, N.; Hughes, C.; Lapane, K.L.; Swine, C.; Hanlon, J.T. Appropriate prescribing in elderly people: how well can it be measured and optimised? *Lancet* **2007**, *370*, 173–184. [CrossRef]
6. Bartelink, I.H.; Rademaker, C.M.; Schobben, A.F.; van den Anker, J.N. Guidelines on paediatric dosing on the basis of developmental physiology and pharmacokinetic considerations. *Clin. Pharmacokinet.* **2006**, *45*, 1077–1097. [CrossRef]
7. Kastner, M.; Wilczynski, N.L.; Walker-Dilks, C.; McKibbon, K.A.; Haynes, B. Age-specific search strategies for Medline. *J. Med Internet Res.* **2006**, *8*, e25. [CrossRef]
8. Moher, D.L.A.; Tetzlaff, J.; Altman, D.G.; The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med.* **2009**, *6*, e1000097. [CrossRef]
9. Prot-Labarthe, S.; Vercheval, C.; Angoulvant, F.; Brion, F.; Bourdon, O. POPI: A tool to identify potentially inappropriate prescribing practices for children. *Arch. Pediatrie* **2011**, *18*, 1231–1232. [CrossRef]
10. Prot-Labarthe, S.; Weil, T.; Angoulvant, F.; Boulkedid, R.; Alberti, C.; Bourdon, O. POPI (Pediatrics: Omission of Prescriptions and Inappropriate prescriptions): development of a tool to identify inappropriate prescribing. *PLoS ONE* **2014**, *9*, e101171. [CrossRef]
11. Prot-Labarthe, S.; Weil, T.; Nguyen, N.P.; Berthe-Aucejo, A.; Angoulvant, F.; Boulkedid, R.; Alberti, C.; Bourdon, O. Consensus validation of a tool to identify inappropriate prescribing in pediatrics (POPI). *Arch. Pediatrie* **2016**, *23*, 481–490. [CrossRef]
12. Corrick, F.J.; Conroy, S.; Choonara, I.; Sammons, H. Developing paediatric rational prescribing criteria. *Arch. Dis. Child.* **2017**, *102* (Suppl. 1), A84.
13. Barry, E.; O'Brien, K.; Moriarty, F.; Cooper, J.; Redmond, P.; Hughes, C.M.; Bennett, K.; Fahey, T.; Smith, S.M. PIPc study: development of indicators of potentially inappropriate prescribing in children (PIPc) in primary care using a modified Delphi technique. *BMJ Open* **2016**, *6*, e012079. [CrossRef]
14. O'Mahony, D.; Gallagher, P.; Ryan, C.; Byrne, S.; Hamilton, H.; Barry, P.; O'Connor, M.; Kennedy, J. STOPP & START criteria: a new approach to detecting potentially inappropriate prescribing in old age. *Eur. Geriatr. Med.* **2010**, *1*, 45–51.
15. Gallagher, P.; Ryan, C.; Byrne, S.; Kennedy, J.; O'Mahony, D. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. *Int. J. Clin. Pharmacol. Ther.* **2008**, *46*, 72–83. [CrossRef] [PubMed]
16. Singh, S.P.; Anderson, B.; Liabo, K.; Ganeshamoorthy, T. Supporting young people in their transition to adults' services: summary of NICE guidance. *BMJ* **2016**, *353*, i2225. [CrossRef] [PubMed]
17. Khanh, N.H.P.; Aurore, B.A.; Francois, A.; Xavier, B.; Thomas, W.; Rym, B.; Patrick, A.; Olivier, B.; Sonia, P.L. Potentially inappropriate prescription and omissions in pediatrics: Detection by POPI in the emergency unit and in the ambulatory setting. POPI (Pediatrics: Omission of Prescription and Inappropriate prescription). *Int. J. Clin. Pharm.* **2016**, *38*, 488–489.
18. Berthe-Aucejo, A.; Nguyen, N.K.; Angoulvant, F.; Boulkedid, R.; Bellettre, X.; Weil, T.; Alberti, C.; Bourdon, O.; Prot-Labarthe, S. Interrater reliability of a tool to assess omission of prescription and inappropriate prescriptions in paediatrics. *Int. J. Clin. Pharm.* **2019**, *41*, 734–740. [CrossRef]
19. Barry, E.; Moriarty, F.; Boland, F.; Bennett, K.; Smith, S.M. The PIPc Study - Application of indicators of potentially inappropriate prescribing in children (PIPc) to a national prescribing database in Ireland: A cross-sectional prevalence study. *BMJ Open* **2018**, *8*, e022876. [CrossRef]
20. Wenger, N.S.; Roth, C.P.; Shekelle, P. Introduction to the Assessing Care of Vulnerable Elders-3 Quality Indicator Measurement Set. *J. Am. Geriatr. Soc.* **2007**, *55*, S247–S252. [CrossRef]
21. Hanlon, J.T.; Schmader, K.E.; Samsa, G.P.; Weinberger, M.; Uttech, K.M.; Lewis, I.K.; Cohen, H.J.; Feussner, J.R. A method for assessing drug therapy appropriateness. *J. Clin. Epidemiol.* **1992**, *45*, 1045–1051. [CrossRef]
22. Niehoff, K.M.; Rajeevan, N.; Charpentier, P.A.; Miller, P.L.; Goldstein, M.K.; Fried, T.R. Development of the tool to reduce inappropriate medications (TRIM): A clinical decision support system to improve medication prescribing for older adults. *Pharmacother. J. Hum. Pharmacol. Drug Ther.* **2016**, *36*, 694–701. [CrossRef] [PubMed]

23. Choonara, I. Rational prescribing is important in all settings. *Arch. Dis. Child.* **2013**, *98*, 720. [CrossRef] [PubMed]
24. Van den Anker, J.; Allegaert, K. Rational Use of Antibiotics in Neonates: Still in Search of Tailored Tools. *Healthcare* **2019**, *7*, 28. [CrossRef] [PubMed]

Appendix 2:
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Article

Modifying a Paediatric Rational Prescribing Tool (POPI) for Use in the UK

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Abstract: Rational prescribing tools can be used by individual prescribers, organisations, and researchers to evaluate the quality of prescribing for research and quality improvement purposes. A literature search showed that there is only one tool for evaluating rational prescribing for paediatric patients in hospital and outpatient settings. The Pediatrics: Omission of Prescriptions and Inappropriate Prescriptions (POPI) tool was developed in France and comprises 105 criteria. The aim of this study was to modify this tool to facilitate its use in paediatric practice in the United Kingdom (UK). POPI criteria were compared to relevant UK clinical guidelines from the National Institute for Health and Care Excellence, the Scottish Intercollegiate Guideline Network and the British National Formulary for Children. Where guidelines differed, criteria were modified to reflect UK guidance. If there were no relevant guidelines or directly contradictory guidelines, criteria were removed. Overall, no change was made to 49 criteria. There were 29 modified to concord with UK guidelines. Four criteria were reduced to two criteria due to being linked in single guidelines. Twenty-three criteria were omitted, due to the absence of relevant UK guidance or directly conflicting UK practice, including one entire clinical category (mosquitos). One category title was amended to parallel UK terminology. The modified POPI (UK) tool comprises of eighty criteria and is the first rational prescribing tool for the evaluation of prescribing for children in hospital and outpatient settings in the UK.

Keywords: paediatric; children; use of medicines; rational prescribing

1. Introduction

Rational prescribing describes practices aimed to optimise the use of medicines, encompassing safety, clinical effectiveness, access, and financial considerations. The WHO has defined rational prescribing as "when patients receive the appropriate medicines, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost both to them and the community" [1]. Rational prescribing has been considered a problem mainly for low and lower middle-income countries, but it is increasingly being recognized as a problem in high-income countries [2,3].

Rational prescribing tools have been used, particularly in older adult medicine, as both research and quality improvement tools to investigate and improve rational prescribing [4]. These tools provide their users, whether individual prescribers, organizations, or research groups, with an objective measurement tool for the quality of prescribing according to rational prescribing principles. This facilitates research into factors involved in irrational prescribing, comparison across

time or between groups of prescribers, organizations, services, or geographical regions, and the assessment of the efficacy of quality improvement interventions.

Children are a population particularly vulnerable to irrational prescribing due to the relative paucity of research supporting the paediatric use of medicines, with many medicines prescribed off-label, and children often excluded from drug trials.

The Pediatrics: Omission of Prescriptions and Inappropriate Prescriptions (POPI) tool was published in 2013 [5]. It was the first rational prescribing tool for use in paediatrics worldwide. The tool comprises explicit criteria based on French, American, and UK guidelines. The selection of clinical indications was based upon French prevalence data and the criteria were selected by Delphi consensus. In total, there are 105 "propositions" in the POPI tool, which are either indicators of potentially inappropriate prescriptions (for example, ineffective treatments) or potentially inappropriate omissions (such as highly effective first-line treatments).

Given the variation in the prevalence of disease, the availability of different formularies, and the diversity in paediatric practice internationally, the tool is not applicable outside of France. The only other extant rational prescribing tool for paediatric use is the potentially inappropriate prescribing in children (PIPc) indicators [6], which was developed exclusively for use in primary care settings. We therefore sought to modify the POPI tool for the application in UK paediatric practice in hospitals and outpatient settings by amending it to concord with UK clinical guidelines.

The aims of our study were twofold.

Firstly, to evaluate the applicability of the POPI tool to practice outside France by comparing the criteria to UK formulary and clinical guidelines.

Secondly, to modify the tool, where necessary, for application to UK paediatric practice and therefore to facilitate further evaluation of the tool using UK prescribing data.

2. Materials and Methods

The 105 propositions of the POPI criteria were compared by one researcher (FC) to evidence-based UK clinical guidelines and clinical knowledge summaries from the National Institute of Health and Care Excellence (NICE) [7], the Scottish Intercollegiate Guidelines Network (SIGN) [8], the British National Formulary for Children (cBNF) [9], and the European Medicines Agency (EMA) [10]. The national guidance from NICE, SIGN and the cBNF were preferred; EMA recommendations were referred to when no national guidelines were available. This process used the most recent guidelines available on 1st October 2015. Where amendments were made, the specific related guideline is cited.

Following the comparison with the guidelines, there were three possible outcomes:

- Guidelines concurred with the POPI propositions. No change was made.
- There was partial discordance. POPI propositions were amended to match UK guidance.
- There was no guidance available or the proposition was in complete discordance with guidance, the proposition was omitted.

The final wording of the modified POPI criteria was reached as consensus in consultation with two paediatric clinical pharmacology consultants.

3. Results

Overall, no change was made to 49 propositions. There were 29 amended to concord more closely with UK guidelines. Four were reduced into two propositions, as they were closely related and the relevant guidelines referred to them together, simplifying the tool. Twenty-three were omitted altogether, which included the omission of an entire category. One category title was amended, as the diagnosis of attention deficit disorder without hyperactivity is not in use in the UK.

The most substantial single change was the omission of the category of "mosquitos". There are currently no areas in the UK where insect-borne diseases are endemic. This was not considered applicable to UK practice and therefore the category comprising of seven propositions, was removed. Some suggest that the viable habitat of mosquito vectors for vivax malaria may expand to

the UK in the future, and if this were to occur, then this might be an appropriate area to target rational prescribing.

Twelve propositions were omitted due to a lack of relevant clinical guidelines (Table 1). The majority of these related to inappropriate prescriptions for medicines that are either not used in the UK, e.g., Diosmectite, or not used by the rectal route, e.g., rectal paracetamol.

Four propositions were also omitted where UK clinical guidelines contradicted the proposition. These are listed in Table 2 with the relevant conflicting UK guideline. They included the use of nitrofurantoin for urinary tract infections in young children; fluoride supplements in infants under the age of six months: the use of setrons (5-HT3 antagonists) for nausea/vomiting in association with chemotherapy; and isotretinoin for adolescent acne.

Table 1. Propositions omitted due to the absence of relevant UK clinical guidelines.

Symptom or Illness Category	Omitted Paediatric Rational Prescribing Tool (POPI) Proposition
Pain and fever (inappropriate prescriptions).	Rectal administration of paracetamol as a first-line treatment.
Pain and fever (omission).	Failure to give sugar solution to newborn babies and infants under four months old two minutes prior to venipuncture.
Urinary infection (inappropriate prescription).	Nitrofurantoin used as a prophylactic.
Diarrhoea (inappropriate prescription).	The use of Diosmectite (Smecta) in combination with another medication [medication not approved for use in the UK]. The use of Saccharomyces boulardii (Ultralevure) in powder form, or in a capsule that has to be opened prior to ingestion, to treat patients with a central venous catheter or an immunodeficiency. Intestinal antiseptics.
Cough (inappropriate prescription).	Mucolytic drugs, mucokinetic drugs, or helicidine before two years of age. Alimemazine (Theralene), oxomemazine (Toplexil), promethazine (Phenergan, and other types). Terpene-based suppositories.
Bronchiolitis (inappropriate prescription).	0.9% NaCl to relieve nasal congestion (not applicable if nasal congestion is already being treated with 3% NaCl delivered by a nebulizer).
ENT infections (inappropriate prescription).	Ethanolamine tenoate (Rhinotrophyl) and other nasal antiseptics.
Acne vulgaris (inappropriate prescription).	Androgenic progestins (levonorgestrel, norgestrel, norethisterone, lynestrenol, dienogest, contraceptive implants or vaginal rings).

Table 2. Propositions omitted due to conflicting UK clinical guidelines.

Symptom or Illness Category	Omitted POPI Proposition	Conflicting UK Guideline
Urinary infection (inappropriate prescription).	Nitrofurantoin used as a curative agent in children under six years of age, or indeed any other antibiotic if avoidable.	NICE guidance CG54: http://www.nice.org.uk/guidance/CG54/chapter/1-Guidance (Recommends nitrofurantoin for children aged three months and over.)
Vitamin supplements and antibiotic prophylaxis (inappropriate prescription)	Fluoride supplements prior to six months of age.	SIGN guidance 138: http://www.sign.ac.uk/pdf/SIGN138.pdf (Describes risks and benefits as balanced.) NICE Delivering Better Oral Health Toolkit: http://www.nice.org.uk/guidance/ph55/chapter/context#delivering-better-oral-health-toolkit (Recommends fluoride toothpaste as soon as teeth erupt.)
Nausea, vomiting, or gastroesophageal reflux (inappropriate prescription)	The use of setrons (5-HT3 antagonists) for chemotherapy-associated nausea and vomiting.	British National Formulary for Children: https://bnfc.nice.org.uk/drug/ondansetron.html (Chemotherapy-associated nausea and vomiting listed as licensed indication for

		ondansetron.)
Acne vulgaris (inappropriate prescription)	Isotretinoin in combination with a member of the tetracycline family of antibiotics.	NICE Acne Vulgaris Clinical Knowledge Summary: http://cks.nice.org.uk/acne-vulgaris#!topicsummary (Recommended second-line for moderate acne.)

Two propositions were combined with closely related propositions, where the recommendations were linked in a single UK guideline in order to make the modified tool as concise as possible. The original and combined propositions are shown below in Table 3 with the related UK guidance. These related to the use of medicines for infants with bronchiolitis and the use of antibiotics in children with otitis media/upper respiratory tract infections.

Table 3. Propositions with shared UK guidelines and the simplified combined proposition.

Original POPI Propositions (Symptom or Illness Category)	**Relevant UK Guidance (NICE, SIGN or cBNF)**	**Combined Proposition**
Beta2 agonists, corticosteroids to treat an infant's first case of bronchiolitis. (Bronchiolitis in infants, inappropriate prescription.) Antibiotics in the absence of signs indicating a bacterial infection (acute otitis media, fever, etc.). (Bronchiolitis in infants, inappropriate prescription.)	NICE guidance NG9: http://www.nice.org.uk/guidance/ng9/chapter/1-Recommendations (Recommendation 1.4.3: Do not use any of the following to treat bronchiolitis in children: antibiotics; hypertonic saline; adrenaline (nebulised); salbutamol; montelukast; ipratropium bromide; systemic or inhaled corticosteroids; a combination of systemic corticosteroids and nebulised adrenaline.)	(Inappropriate prescription) Antibiotics, Beta2 agonists or corticosteroids to treat bronchiolitis.
An antibiotic other than amoxicillin as a first-line treatment for acute otitis media, strep throat, or sinusitis (provided that the patient is not allergic to amoxicillin). An effective dose of amoxicillin for a pneumococcal infection is 80–90 mg/kg/day and an effective dose for a streptococcal infection is 50 mg/kg/day. (ENT infections, inappropriate prescription.) Antibiotics for nasopharyngitis, congestive otitis, sore throat before three years of age, or laryngitis; antibiotics as a first-line treatment for acute otitis media showing few symptoms, before two years of age. (ENT infections, inappropriate prescription.)	NICE guidance CG69: http://www.nice.org.uk/guidance/cg69/chapter/1-Guidance (A no antibiotic prescribing strategy or a delayed antibiotic prescribing strategy should be agreed upon for patients with the following conditions: acute otitis media; acute sore throat/acute pharyngitis/acute tonsillitis; common cold; acute rhinosinusitis; acute cough/acute bronchitis. Depending on the clinical assessment of severity, patients in the following subgroups can also be considered for an immediate antibiotic prescribing strategy (in addition to a no antibiotic or a delayed antibiotic prescribing strategy): Bilateral acute otitis media in children younger than two years; acute otitis media in children with otorrhoea; acute sore throat/acute pharyngitis/acute tonsillitis when three or more Centor criteria are present. SIGN guideline 117: In severe cases, where the practitioner is concerned about the clinical condition of the patient, antibiotics should not be withheld. (Penicillin V 500 mg four times daily for 10 days is the dosage used in the majority of studies. A macrolide can be considered as an alternative first line treatment, in line with local guidance.)	(Inappropriate prescription) An antibiotic for <4 days symptoms of acute upper respiratory tract infection (except: bilateral acute otitis media in children younger than two years; acute otitis media in children with otorrhoea; acute sore throat/acute pharyngitis/acute tonsillitis when three or more Centor criteria are present).

There were 19 propositions that related to inappropriate prescriptions, and 10 propositions that related to inappropriate omissions that were amended to more closely concord with UK guidelines (Table 4 and Table 5). In some instances, the age was changed, e.g., loperamide is considered inappropriate in the UK in children under the age of four years old, whereas in France it is under the

age of three years old. Some medicines such as benzyl benzoate are not recommended at all in children in the UK. Some medicines such as sodium cromoglycate are not recommended at all in France, whereas in the UK it can be used for exercise-induced asthma. In addition, the category title of "Attention deficit disorder with or without hyperactivity" was amended to "Attention deficit hyperactivity disorder", as attention deficit disorder without hyperactivity is not recognised in UK clinical guidelines.

Others involved minor changes in relation to dosing and age for penicillin prophylaxis for children with sickle cell disease; patient groups for palivizumab: or vitamin use in infants.

Table 4. Inappropriate prescription propositions modified to concord with UK guidelines.

Original POPI Propositions—Inappropriate Prescription (Symptom or Illness Category)	**Relevant UK Guidance (NICE, SIGN or cBNF) (Recommendation)**	**Modified POPI Proposition—Inappropriate Prescription**
Prescription of a medication other than paracetamol as a first-line treatment [for pain] (except in the case of migraine). (Pain and fever)	NICE Clinical Knowledge Summary: Management of mild-to-moderate pain: http://cks.nice.org.uk/analgesia-mild-to-moderate-pain#!scenario (Prescribe either paracetamol or ibuprofen alone. Both are suitable first-line choices for treating mild-to-moderate pain in children.)	Prescription of a medication other than paracetamol or ibuprofen as a first-line treatment for pain (except in the case of a migraine).
Oral solutions of ibuprofen administered in more than three doses per day using a graduated pipette of 10 mg/kg (other than Advil). (Pain and fever)	cBNF Ibuprofen: https://bnfc.nice.org.uk/drug/ibuprofen.html (Child 1–3 months 5 mg/kg 3–4 times daily. Child 3–6 months 50 mg 3 times daily; max. 30 mg/kg daily in 3–4 divided doses. Child 6 months to 1 year 50 mg 3–4 times daily; max. 30 mg/kg daily in 3–4 divided doses. Child 1–4 years 100 mg 3 times daily; max. 30 mg/kg daily in 3–4 divided doses. Child 4–7 years 150 mg 3 times daily; max. 30 mg/kg daily in 3–4 divided doses. Child 7–10 years old 200 mg 3 times daily; max. 30 mg/kg (max. 2.4 g) daily in 3–4 divided doses. Child 10–12 years 300 mg 3 times daily; max. 30 mg/kg (max. 2.4 g) daily in 3–4 divided doses. Child 12–18 years initially 300–400 mg 3–4 times daily; increased if necessary to max. 600 mg four times daily; maintenance dose of 200–400 mg three times daily may be adequate.)	Doses of ibuprofen administered in more than three doses per day or exceeding maximum dose of 30 mg/kg daily in three doses per day.
Gastric antisecretory drugs to treat gastroesophageal reflux, dyspepsia, the crying of newborn babies (in the absence of any other signs or symptoms), as well as faintness in infants. (Nausea, vomiting, or gastroesophageal reflux)	NICE guidance NG1: http://www.nice.org.uk/guidance/NG1/chapter/1-Recommendations (Recommendation 1.3.1: Do not offer acid-suppressing drugs, such as proton pump inhibitors (PPIs) or H_2 receptor antagonists (H_2RAs), to treat overt regurgitation in infants and children occurring as an isolated symptom. Recommendation 1.3.2: Consider a four-week trial of a PPI or H_2RA for those who are unable to tell you about their symptoms (for example, infants and young children, and those with a neurodisability associated with expressive communication difficulties) who have overt regurgitation with one or more of the following: unexplained feeding difficulties (for example, refusing feeds, gagging or choking); distressed behaviour; faltering growth.)	Acid-suppressing drugs to treat overt regurgitation in the absence of feeding difficulties, distress, or faltering growth.
The use of type H2 antihistamines for long periods of treatment. (Nausea, vomiting, or gastroesophageal reflux)	NICE guidance NG1: http://www.nice.org.uk/guidance/NG1/chapter/1-Recommendations (Recommendation 1.3.4: four-week trial then stop, assess response, refer if symptoms recur.)	The use of H2 receptor antagonists for more than four weeks.

Erythromycin as a prokinetic agent. (Nausea, vomiting, or gastroesophageal reflux)	NICE guidance NG1: http://www.nice.org.uk/guidance/NG1/chapter/1-Recommendations (Do not offer metoclopramide, domperidone or erythromycin without seeking specialist advice.)	Erythromycin.
Loperamide before three years of age. (Diarrhoea)	cBNF Loperamide: https://bnfc.nice.org.uk/drug/loperamide-hydrochloride.html (Licensed from four years.)	Loperamide before four years of age
Antibiotic treatment for a sore throat, without a positive rapid diagnostic test result, in children less than three years old. (ENT infections)	SIGN guideline 117: http://www.sign.ac.uk/guidelines/fulltext/117/ (Minimises usefulness of rapid diagnostic test results in guiding therapy: In severe cases, where the practitioner is concerned about the clinical condition of the patient, antibiotics should not be withheld. (Penicillin V 500 mg four times daily for 10 days is the dosage used in the majority of studies. A macrolide can be considered as an alternative first-line treatment, in line with local guidance.)	Antibiotic treatment for a sore throat except in severe cases (where the patient's clinical condition is documented as concerning).
Antibiotics to treat otitis media with effusion (OME), except in the case of hearing loss or if OME lasts for more than three months. (ENT infections)	NICE Clinical Knowledge Summary: http://cks.nice.org.uk/otitis-media-with-effusion#!scenario (Period of active observation for 6–12 weeks: During this period, do not prescribe antibiotics, steroids, antihistamines, decongestants, or mucolytics specifically for the treatment of otitis media with effusion (OME).)	Antibiotics to treat otitis media with effusion in the first 6–12 weeks.
H1-antagonists with sedative or atropine-like effects (pheniramine, chlorpheniramine), or camphor; inhalers, nasal sprays, or suppositories containing menthol (or any terpene derivatives) before 30 months of age. (ENT infections)	cBNF: https://www.evidence.nhs.uk/formulary/bnfc/current/3-respiratory-system/34-antihistamines-immunotherapy-and-allergic-emergencies/341-antihistamines#PHP11980 (Sedating antihistamines not for use in neonates, phenothiazine sedating antihistamines not for use <2 years, chlorphenamine not licensed <1 year.) https://www.evidence.nhs.uk/formulary/bnfc/current/3-respiratory-system/38-aromatic-inhalations (Menthol inhalations permissible, no sprays or suppositories in BNF nor terpene containing medicines.)	Sedating antihistamines (pheniramine, chlorpheniramine) before two years (except for anaphylaxis).
Ketotifen and other H1-antagonists, sodium cromoglycate. (Asthma)	SIGN guidance 141 (British guideline on the management of asthma): http://www.sign.ac.uk/pdf/SIGN141.pdf (Antihistamines and ketotifen are ineffective. Sodium cromoglycate for exercise-induced asthma.)	Ketotifen and other antihistamines.
The application of benzyl benzoate (Ascabiol) for periods longer than eight hours for infants and 12 h for children or for pregnant girls. (Scabies)	Children's BNF: http://www.evidence.nhs.uk/formulary/bnf/current/13-skin/1310-anti-infective-skin-preparations/13104-parasiticidal-preparations/scabies and NICE Clinical Knowledge Summary: http://cks.nice.org.uk/scabies#!scenario (Benzyl benzoate should be avoided in children (permethrin or malathion are less irritant and more effective and should be used instead.)	Benzyl benzoate.
Treatment other than griseofulvin for Microsporum. (Ringworm)	NICE Clinical Knowledge Summary Fungal Skin infections: http://cks.nice.org.uk/fungal-skin-infection-body-and-groin#!scenario (Recommends topical treatment first-line. Gruseofulvin the only oral treatment appropriate for children.)	Oral treatment other than griseofulvin.
Any antibiotic other than mupirocin as a first-line treatment (except in cases of	NICE Clinical Knowledge Summary Impetigo: http://cks.nice.org.uk/impetigo#!scenario (For localized [sic] infection, treat with topical fusidic acid… Topical mupirocin, retapamulin, and antiseptics are not recommended initially.)	Any antibiotic other than fusidic acid as a first-line treatment (except

hypersensitivity to mupirocin). (Impetigo)		in cases of hypersensitivity to fusidic acid).
Orally administered acyclovir to treat primary herpetic gingivostomatitis. (Herpes simplex)	NICE Clinical Knowledge Summary Herpes Simplex (oral): http://cks.nice.org.uk/herpes-simplex-oral#!scenario:1 (Consider oral antivirals for immunocompetent individuals with severe gingivostomatitis.)	Orally administered aciclovir to treat severe herpetic gingivostomatitis.
A strong dermocorticoid (clobetasol propionate 0.05% Dermoval, betamethasone dipropionate Diprosone) applied to the face, the armpits or groin, and the backside of babies or young children. (Atopic eczema)	NICE guidance CG57: https://www.nice.org.uk/guidance/CG57/chapter/1-Guidance (use mild potency for the face and neck, except for short-term (3–5 days) use of moderate potency for severe flares; use moderate or potent preparations for short periods only (7–14 days) for flares in vulnerable sites such as axillae and groin; do not use very potent preparations in children without specialist dermatological advice.) Children's BNF Dermoval not listed: http://www.evidence.nhs.uk/formulary/bnf/current/13-skin/134-topical-corticosteroids/topical-corticosteroid-preparation-potencies	A potent topical corticosteroid applied to the face, or for >14 days applied to the axilla or groin.
Local or systemic antihistamine during the treatment of outbreaks. (Atopic eczema)	NICE guidance CG57: https://www.nice.org.uk/guidance/CG57/chapter/1-Guidance (Recommendation 1.5.6: Healthcare professionals should offer a 1-month trial of a non-sedating antihistamine to children with severe atopic eczema or children with mild or moderate atopic eczema where there is severe itching or urticaria. Healthcare professionals should offer a 7–14 day trial of an age-appropriate sedating antihistamine to children aged 6 months or over during an acute flare of atopic eczema if sleep disturbance has a significant impact on the child or parents or carers.)	Prescription of antihistamines except as a trial for severe itching or where sleep disturbance has a significant impact on the child or carers.
Cyproheptadine (Perlactin), clonidine. (Anorexia)	NICE guidance CG9: https://www.nice.org.uk/guidance/CG9/chapter/1-Guidance (Recommendation 1.2.3.1: Medication should not be used as the sole or primary treatment for anorexia nervosa.)	Prescription of medications as a sole or primary treatment for anorexia nervosa.
Antipsychotic drugs to treat attention deficit disorder without hyperactivity. (attention deficit disorder with or without hyperactivity)	NICE guidance CF72: https://www.nice.org.uk/guidance/cg72/chapter/1-Guidance (Recommendation 1.5.5.7: Antipsychotics are not recommended for the treatment of ADHD in children and young people.)	Antipsychotic drugs to treat attention deficit hyperactivity disorder.
Slow release methylphenidate as two doses per day, rather than only one dose. (Attention deficit disorder with or without hyperactivity)	NICE guidance CF72: https://www.nice.org.uk/guidance/cg72/chapter/1-Guidance (Recommendation 1.8.2.2: modified-release preparations should be given as a single dose in the morning.)	Modified release methylphenidate as two doses per day rather than only one dose.

Table 5. Omission of prescription propositions modified to concord with UK guidelines.

Original POPI Propositions—Inappropriate Omission (Symptom or Illness Category)	**Relevant UK Guidance (NICE, SIGN or cBNF) (Recommendation)**	**Modified POPI Proposition—Inappropriate Omission**
Insufficient intake of vitamin D. Minimum vitamin D intake: Breastfed baby = 1000 to 1200	NICE guidance PH56: http://www.nice.org.uk/guidance/ph56/chapter/1-Recommendations (Vitamin D	Healthy Start vitamins for infants and children 0.5–5 years or having less than 500

IU/day; Infant, 18 months of age (milk enriched in vitamin D) = 600–800 IU/day; Child aged between 18 months and five years, and adolescents aged between 10 and 18 years: two quarterly loading doses of 80,000 to 100,000 IU/day in winter (adolescents can take this dose in one go). (Vitamin supplements and antibiotic prophylaxis)	supplements should be available for at-risk groups, including infants and children <5 years, Healthy Start vitamins.)	mL infant formula per day.
Antibiotic prophylaxis with phenoxymethylpenicillin (Oracilline) starting from two months of age and lasting until five years of age for children with sickle-cell anaemia: 100,000 IU/kg/day (in two doses) for children weighing 10kg or less and 50,000 IU/kg/day for children weighing over 10 kg (also in two doses). (Vitamin supplements and antibiotic prophylaxis)	NICE Clinical Knowledge Summary: http://cks.nice.org.uk/sickle-cell-disease#!scenario:3 (Explain that lifelong prophylaxis is recommended, but it is particularly important that there is full adherence up to five years of age. Prescribe phenoxymethylpenicillin (penicillin V) prophylaxis from the age of one month, at a dose of: 125 mg twice a day for infants and children up to five years of age. 250 mg twice a day for children from six to 12 years of age. 500 mg twice a day for adults and children older than 12 years of age. Erythromycin is recommended for people who are allergic to penicillin, at a dose of: 125 mg twice a day for infants and children up to two years of age. 250 mg twice a day for adults and children older than two years of age.)	Antibiotic prophylaxis with phenoxyethylpenicillin (penicillin V) from age one month until five years old for children with sickle-cell anaemia at a dose of: 125 mg twice a day for infants and children up to five years of age. 250 mg twice a day for children from six to 12 years of age. 500 mg twice a day for adults and children older than 12 years of age. Or Erythromycin for children who are allergic to penicillin, at a dose of: 125 mg twice a day for infants and children up to two years of age. 250 mg twice a day for children older than two years of age.
Oral rehydration solution. (Nausea, vomiting, or gastroesophageal reflux)	NICE guidance CG84: http://www.nice.org.uk/guidance/cg84/chapter/1-Guidance#fluid-management (Offer ORS solution as supplemental fluid to children at risk of dehydration or use in dehydrated children unless IV fluid is indicated.)	Amend: Oral rehydration solution for dehydrated children unless IV fluid therapy is indicated (shock, red flag symptoms despite ORS, persist vomiting of ORS).
Oral rehydration solution. (Diarrhoea)	NICE guidance CG84: http://www.nice.org.uk/guidance/cg84/chapter/1-Guidance#fluid-management (Offer ORS solution as supplemental fluid to children at risk of dehydration or use in dehydrated children unless IV fluid is indicated.)	Amend: Oral rehydration solution for dehydrated children unless IV fluid therapy is indicated (shock, red flag symptoms despite ORS, persistent vomiting of ORS).
Failure to propose a whooping cough booster vaccine for adults who are likely to become parents in the coming months or years (only applicable if the previous vaccination was more than 10 years ago). This booster vaccination should also be proposed to the family and entourage of expectant parents (parents, grandparents, nannies/child minders). (Cough).	NICE CKS Antenatal care of uncomplicated pregnancy: http://cks.nice.org.uk/antenatal-care-uncomplicated-pregnancy#!scenario (28 weeks gestation: Offer vaccination against pertussis.)	Amend: Failure to propose a whooping cough vaccine for pregnant women.

Palivizumab in the following cases: (1) babies born both at less than 35 weeks of gestation and less than six months prior to the onset of a seasonal RSV epidemic; (2) children less than two years old who have received treatment for bronchopulmonary dysplasia in the past six months; (3) children less than two years old suffering from congenital heart disease with hemodynamic abnormalities. (Bronchiolitis in infants).	SIGN guidance 91 (Bronchiolitis in children): http://www.sign.ac.uk/guidelines/fulltext/91/index.html (… recommends use of palivizumab in high risk groups, as defined by the committee (children under two years of age with chronic lung disease, on home oxygen or who have had prolonged use of oxygen; infants less than six months of age who have left to right shunt haemodynamically significant congenital heart disease and/or pulmonary hypertension; children under two years of age with severe congenital immuno-deficiency).)	Amend: Palivizumab in high-risk cases, defined as: children <2 years with chronic lung disease on home oxygen or who have prolonged use of oxygen; infants <6 months with left-to-right shunt haemodynamically significant congenital heart disease and/or pulmonary hypertension; children <2 years with severe congenital immunodeficiency.)
Asthma inhaler appropriate for the child's age. (Asthma)	NICE guidance TA10: https://www.nice.org.uk/guidance/ta10 (NICE has recommended that for children under the age of five years who have chronic stable asthma: both corticosteroids and bronchodilator therapy should routinely be delivered by Pressurised Metered Dose Inhaler (pMDI) and spacer system, with a facemask where necessary. Where this combination is not clinically effective for the child, and depending on the child's condition, nebulised therapy may be considered and in the case of children aged 3–5 years, a dry powder inhaler (DPI) may also be considered. The choice of which pMDI device and spacer to use should be determined by the specific needs of the child and how well it works for them. Once these factors have been taken into account the choice should be made on the basis of reducing costs.)	Amend: Asthma inhaler appropriate for the child's age (aged <5 years, either Metered Dose Inhaler with spacer system or nebuliser; age 3–5 years Dry Powder Inhaler may be appropriate).
Contraception (provided with a logbook/diary) for menstruating girls taking isotretinoin. (Acne vulgaris)	Children's BNF: https://www.evidence.nhs.uk/formulary/bnf/current/13-skin/136-acne-and-rosacea/1362-oral-preparations-for-acne/oral-retinoid-for-acne/isotretinoin (Effective contraception must be used.)	Amend: Contraception for menstruating girls taking isotretinoin.
A second dose of ivermectin two weeks after the first. (Scabies)	Children's BNF: https://bnfc.nice.org.uk/treatment-summary/skin-infections.html (Ivermectin only available by special order, unlicensed for scabies.) https://bnfc.nice.org.uk/drug/permethrin.html https://bnfc.nice.org.uk/drug/malathion.html (Apply once weekly for two doses.)	Amend: A second application of permethrin or malathion one week after the first.
Decontamination of household linen and clothes and treatment for other family members. (Scabies)	NICE Clinical Knowledge Summary: http://cks.nice.org.uk/scabies#!scenario (Decontamination of household linen and clothes and same day treatment of all members of the household.)	Amend: Decontamination of household linen and clothes and same day treatment of all members of the household.

The resulting modified POPI criteria therefore comprise 80 propositions assessing rational prescribing for children in accordance with up-to-date UK guidelines (see Table 6).

Table 6. The modified POPI (UK) tool.

DIVERSE ILLNESSES
PAIN AND FEVER
Inappropriate prescriptions. Prescription of two alternating antipyretics as a first-line treatment. Prescription of a medication other than paracetamol or ibuprofen as a first-line treatment for pain (except in the case of a migraine). The combined use of two NSAIDs. Doses of ibuprofen administered in more than three doses per day or exceeding maximum dose of 30 mg/kg daily in three doses per day. Opiates to treat migraine attacks. Omissions. Failure to give an osmotic laxative to patients being treated with morphine for a period of more than 48 h.
URINARY INFECTIONS
Inappropriate prescriptions. Antibiotic prophylaxis following an initial infection without complications (except in the case of uropathy). Antibiotic prophylaxis in the case of asymptomatic bacterial infection (except in the case of uropathy).
VITAMIN SUPPLEMENTS AND ANTIBIOTIC PROPHYLAXIS
Omissions. Healthy Start vitamins for infants and children 0.5–5 years or having less than 500 mL infant formula per day. Antibiotic prophylaxis with phenoxyethylpenicillin (penicillin V) from age one month until five years for children with sickle-cell anaemia at a dose of: • 125 mg twice a day for infants and children up to five years of age. • 250 mg twice a day for children from six to 12 years of age. • 500 mg twice a day for adults and children older than 12 years of age. Or Erythromycin for children who are allergic to penicillin, at a dose of: • 125 mg twice a day for infants and children up to two years of age. • 250 mg twice a day for children older than two years of age.
DIGESTIVE PROBLEMS
NAUSEA, VOMITING, OR GASTROESOPHAGEAL REFLUX
Inappropriate prescriptions. Metoclopramide. Domperidone. Oral administration of an intravenous proton pump inhibitor (notably by nasogastric tube). Acid-suppressing drugs to treat overt regurgitation in the absence of feeding difficulties, distress, or faltering growth. The combined use of proton pump inhibitors and NSAIDs, for a short period of time, in patients without risk factors. The use of H2 receptor antagonists for more than four weeks. Erythromycin. Omissions. Oral rehydration solution (ORS) for dehydrated children unless IV fluid therapy is indicated (shock, red flag symptoms despite ORS, persist vomiting of ORS).
DIARRHOEA
Inappropriate prescriptions. Loperamide before four years of age. Loperamide in the case of invasive diarrhoea. Omissions. Oral rehydration solution (ORS) for dehydrated children unless IV fluid therapy is indicated (shock, red flag symptoms despite ORS, persist vomiting of ORS).
ENT-PULMONARY PROBLEMS
COUGH
Inappropriate prescriptions. Pholcodine. Omissions. Failure to propose a whooping cough vaccine for pregnant women.
BRONCHIOLITIS IN INFANTS

Inappropriate prescriptions. Antibiotics, Beta2 agonists or corticosteroids to treat bronchiolitis. H1-antagonists, cough suppressants, mucolytic drugs, or ribavirin to treat bronchiolitis. Omissions. Palivizumab in high-risk cases, defined as: • Children <2 years with chronic lung disease on home oxygen or who have prolonged use of oxygen; • Infants <6 months with left-to-right shunt haemodynamically significant congenital heart disease and/or pulmonary hypertension; • Children <2 years with severe congenital immunodeficiency.
ENT INFECTIONS
Inappropriate prescriptions. An antibiotic for <4 days symptoms of acute upper respiratory tract infection (except: • Bilateral acute otitis media in children younger than two years; • Acute otitis media in children with otorrhoea; • Acute sore throat/acute pharyngitis/acute tonsillitis when three or more Centor criteria are present.) Antibiotic treatment for a sore throat except in severe cases (anticipated to be no more than 20% of cases). Antibiotics to treat otitis media with effusion in the first 6–12 weeks. Corticosteroids to treat acute suppurative otitis media, nasopharyngitis, or strep throat. Nasal or oral decongestant (oxymetazoline (Aturgyl), pseudoephedrine (Sudafed), naphazoline (Derinox), ephedrine (Rhinamide), tuaminoheptane (Rhinofluimicil), phenylephrine (Humoxal)). Sedating antihistamines (pheniramine, chlorpheniramine) before two years (except for anaphylaxis). Eardrops in the case of acute otitis media. Omissions. Doses in mg for drinkable (solutions of) amoxicillin or josamycin. Paracetamol combined with antibiotic treatment for ear infections to relieve pain.
ASTHMA
Inappropriate prescriptions. Ketotifen and other antihistamines. Cough suppressants. Omissions. Asthma inhaler appropriate for the child's age (aged <5 years, either Metered Dose Inhaler with spacer system or nebuliser; age 3–5 years Dry Powder Inhaler may be appropriate). Preventative treatment (inhaled corticosteroids) in the case of persistent asthma.
DERMATOLOGICAL PROBLEMS
ACNE VULGARIS
Inappropriate prescriptions. Minocycline. The combined use of an oral and a local antibiotic. Oral or local antibiotics as a monotherapy (not in combination with another drug). Cyproterone + ethinylestradiol (Diane 35) as a contraceptive to allow isotretinoin per os. Omissions. Contraception for menstruating girls taking isotretinoin. Topical treatment (benzoyl peroxide, retinoids, or both) in combination with antibiotic therapy.
SCABIES
Inappropriate prescriptions. Benzyl benzoate. Omissions. A second application of permethrin or malathion one week after the first. Decontamination of household linen and clothes and same day treatment of all members of the household.
LICE
Inappropriate prescriptions. The use of aerosols for infants, children with asthma, or children showing asthma-like symptoms such as dyspnea.
RINGWORM
Inappropriate prescriptions. Oral treatment other than griseofulvin. Omissions. Topical treatment combined with an orally administered treatment. Griseofulvin taken during a meal containing a moderate amount of fat.

IMPETIGO
Inappropriate prescriptions.
The combination of a locally applied and orally administered antibiotic.
Fewer than two applications per day for topical antibiotics.
Any antibiotic other than fusidic acid as a first-line treatment (except in cases of hypersensitivity to fusidic acid).
HERPES SIMPLEX
Inappropriate prescriptions.
Topical agents containing corticosteroids.
Topical agents containing aciclovir before six years of age.
Omissions.
Paracetamol during an outbreak of herpes.
Orally administered aciclovir to treat severe herpetic gingivostomatitis.
ATOPIC ECZEMA
Inappropriate prescriptions.
A potent topical corticosteroid applied to the face, or for >14 days applied to the axilla or groin.
More than one application per day of a dermocorticoid, except in cases of severe lichenification.
Prescription of antihistamines except as a trial for severe itching or where sleep disturbance has a significant impact on the child or carers.
Topically applied 0.03% tacrolimus before two years of age.
Topically applied 0.1% tacrolimus before 16 years of age.
Oral corticosteroids to treat outbreaks.
NEUROPSYCHIATRIC DISORDERS
EPILEPSY
Inappropriate prescriptions.
Carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine, or vigabatrin in the case of myoclonic epilepsy.
Carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine, or vigabatrin in the case of epilepsy with absence seizures (especially for childhood absence epilepsy or juvenile absence epilepsy).
Levetiracetam, oxcarbamazepine in mL or in mg without systematically writing XX mg per Y mL.
DEPRESSION
Inappropriate prescriptions.
An SSRI antidepressant other than fluoxetine as a first-line treatment (in the case of pharmacotherapy).
Tricyclic antidepressants to treat depression.
NOCTURNAL ENURESIS
Inappropriate prescriptions.
Desmopressin administered by a nasal spray.
Desmopressin in the case of d`aytime symptoms.
An anticholinergic agent used as a monotherapy in the absence of daytime symptoms.
Tricyclic agents in combination with anticholinergic agents.
Tricyclic agents as a first-line treatment.
ANOREXIA
Inappropriate prescriptions.
Prescription of medications as a sole or primary treatment for anorexia nervosa.
ATTENTION DEFICIT DISORDER WITH HYPERACTIVITY
Inappropriate prescriptions.
Pharmacological treatment before age six (before school), except in severe cases.
Antipsychotic drugs to treat attention deficit hyperactivity disorder.
Modified release methylphenidate as two doses per day, rather than only one dose.
Omissions.
Recording a growth chart (height and weight) if the patient is taking methylphenidate.

4. Discussion

The POPI criteria were modified to develop a list of potentially inappropriate prescriptions and omissions for children in the UK.

Over half of the propositions of the POPI criteria were altered. The majority of those changes were subtle modifications to bring the wording of propositions more closely in line with the specific

wording of UK clinical guidelines. In other cases, the propositions were directly in contradiction of relevant guidelines and were amended accordingly. In order for this tool to be useful in appraising rational prescribing in the UK, it is important that prescribers are being measured against the specific standards they are striving for, and this would also facilitate straightforward interventions using UK guidelines for education and service improvement.

For 22 propositions, there were no relevant UK clinical guidelines. Absence from guidelines does not necessarily invalidate the recommendations of those propositions but the propositions were omitted, as they appeared to relate to the irrational use of medicines that do not appear to be prevalent in the UK. In some cases, the propositions related to medications not available in the UK. For instance, in the case of diosmectite for diarrhoea, there is some emerging evidence supporting its use [11] but this is not reflected in the availability of the product in the UK.

In other cases, differing national practices may explain the absence if the type of irrational prescribing described is already rare in UK practise. This explanation likely underlies guidance about rectally administered drugs including paracetamol per rectum for pain and suppositories for cough. The cultural difference that may give rise to this variance in clinical practice was recognised in the European Medicines Agency Guideline on pharmaceutical development of medicines for paediatric use [12] when discussing medication acceptability in different countries, giving the example that "the rectal route of administration is not generally favoured in the UK".

Two of the omitted propositions, in relation to sucrose for painful procedures in infants and nitrofurantoin as prophylaxis for urinary infection, may be absent from national UK guidelines because these are areas where there is not a national consensus of best practice. In reviewing these topics, local guidelines were found to differ, including some recommending nitrofurantoin for that purpose [13,14] and some preferring breast or bottle-feeding over sucrose, recommending contraindications and qualifying the guideline according to gestation and the age of the infant [15,16]. In the absence of a unifying national guideline on these topics, they were therefore not considered to be good candidates for screening prescribing practice nationally.

Four propositions were omitted due to the existence of UK clinical guidelines that were in direct conflict with the original proposition (see Table 2).

Three of these appear to have been included as potentially inappropriate prescriptions in the original French tool due to the risk of interactions or side effects. One related to nitrofurantoin for the treatment of urinary infections. According to the report describing the development of the original POPI tool, this proposition was derived from a statement issued by AFSSAPS (the French Agency for the Safety of Health Products, Agence Française de Sécurité Sanitaire des Produits de Santé) in 2011, warning of cases of severe hepatic and pulmonary complications following long-term treatment with nitrofurantoin [17].

The cBNF does recommend monitoring liver function and for pulmonary symptoms if prescribing nitrofurantoin long-term, but it is licensed and indicated in acute uncomplicated urinary tract infections for children aged three months and older [9] and is second-line for children aged three months and older in the most recent NICE guideline NG109 [7].

The second related to isotretinoin and tetracycline antibiotics. This appears to be derived from a Good Practice Recommendation from AFSSAP describing isotretinoin as contraindicated with tetracyclines due to the reported occurrence of benign intracranial hyptertension with this combination [18]. This risk is recorded in the cBNF as a possible interaction, rated as "serious" with an anecdotal evidence base [9]. The combination is not recorded as a contraindication and combined topical retinoids and oral tetracyclines and recommended in the NICE Clinical Knowledge Summary.

The third related to fluoride supplements before age six months. The related French guideline, an AFSAPPS statement in 2008, recommended that fluoride containing supplements such as toothpaste, commence when teeth erupt, on average at age six months [19]. This statement, like the relevant UK guidelines, discusses the risk of dental fluorosis with excess fluoride consumption during tooth development and recommends lower dose fluoride in toothpaste for young children. Both the NICE and SIGN guidelines quoted in Table 2 acknowledge the risk of dental fluorosis and

state that the benefit of reduced caries favours starting fluoride supplementation as soon as teeth erupt with no definitive lower age limit of benefit to the child.

These all appear to reflect differing risk tolerance between the French and UK guidelines. In order that the modified tool reflects what is considered nationally to be good practice, the propositions were therefore omitted from the modified tool.

The fourth omitted proposition listed, "The use of setrons (5-HT3 antagonists) for chemotherapy-associated nausea and vomiting", as a potentially inappropriate prescription. It was not clear what evidence was used to develop this proposition as none of the references in the report describing the development of the original tool related to chemotherapy-associated nausea and vomiting. One reference from the American Centers for Disease Control and Prevention recommended ondansetron as an anti-emetic for children [20]. It is possible that the inclusion of this criterion in the original tool constitutes a typographical error, and that it was intended to read as an inappropriate omission, given the importance of treating chemotherapy-associated nausea. It was therefore felt not to accurately reflect rational prescribing and was omitted from the modified tool.

Following the described amendments, the modified POPI(UK) tool comprises eighty criteria describing potentially inappropriate prescriptions or omissions. This tool is intended to evaluate the quality of prescribing for children in both hospital and outpatient settings, and is not limited to a specific group of prescribers. Similar tools for evaluating rational prescribing for older adults have facilitated a broad range of research, including research into quality of prescribing across different settings [21], studies into healthcare outcomes associated with irrational prescribing [22], and to predict adverse health outcomes in patient groups [23]. The tool is not intended for routine use by individual prescribers, as it requires experience to use.

5. Conclusions

The modified POPI (UK) criteria comprise the first screening tool available to assess rational prescribing for children in UK hospitals and outpatient settings. Clinical validation and reliability studies are needed and planned by the authors in order to evaluate the usability and reliability of this tool, which it is hoped will be used to study the rational use of medicines in children in the UK.

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References

1. WHO. *The Rational Use of Drugs. Report of the Conference of Experts*; World Health Organization: Geneva, Switzerland, 1985.
2. Choonara, I. Rational prescribing is important in all settings. *Arch. Dis. Child*. **2013**, *98*, 720.
3. Rieder, M. Do we prescribe medicines rationally? *Arch. Dis. Child.* **2015**, *100*, 958–959.
4. Kaufmann, C.P.; Tremp, R.; Hersberger, K.E.; Lampert, M.L. Inappropriate prescribing: A systematic overview of published assessment tools. *Eur. J. Clin. Pharmacol.* **2014**, *70*, 1–11.
5. Weil, T.; Angoulvant, F.; Boulkedid, R.; Alberti, C.; Brion, F.; Bourdon, O.; Prot-Labarthe, S. POPI: A tool to identify inappropriate prescribing in pediatrics. Consensus validation. *Int. J. Clin. Pharm.* **2013**, *35*, 1264.
6. Barry, E.; O'Brien, K.; Moriarty, F.; Cooper, J.; Redmond, P.; Hughes, C.M.; Bennett, K.; Fahey, T.; Smith, S.M. PIPc study: Development of indicators of potentially inappropriate prescribing in children (PIPc) in primary care using a modified Delphi technique. *BMJ Open* **2016**, *6*, e012079.

7. The National Institute for Health and Care Excellence. Available online: https://www.nice.org.uk/ (accessed on 12 December 2018).
8. The Scottish Intercollegiate Guideline Network. Available online: https://www.sign.ac.uk/ (accessed on 12 December 2018).
9. The British National Formulary for Children. Available online: https://bnfc.nice.org.uk/ (accessed on 12 December 2018).
10. The European Medicines Agency. Available online: http://www.ema.europa.eu/ (accessed on 12 December 2018).
11. Das, R.R.; Sankar, J.; Naik, S.S. Efficacy and safety of diosmectite in acute childhood diarrhoea: A meta-analysis. *Arch. Dis. Child.* **2015**, *100*, 704–712.
12. European Medicines Agency. Guideline on Pharmaceutical Development of Medicines for Paediatric Use. 2013. Available online: http://www.ema.europa.eu/docs/ (accessed on 24 October 2013).
13. Nottingham University Hospitals. Guideline: The Investigation and Management of Urinary Tract Infection in Children. Available online: http://www.nuh.nhs.uk/ (accessed on 24 October 2013).
14. East Cheshire NHS Trust. Paediatric Antibiotic Policy for Children 1 Month–18 Years. Available online: http://www.eastcheshire.nhs.uk/About-The-Trust/policies/A/Antibiotic Policy-Paediatric ECT2037.pdf (accessed on 24 October 2013).
15. Calderdale and Huddersfield NHS Trust. Protocol for the Administration of Sucrose 2014. Available online: http://www.formulary.cht.nhs.uk/pdf,_doc_files_etc/MMC/055_Sucrose.076.pdf (accessed on 24 October 2015).
16. Nottingham University Hospitals. Guideline: Oral Sucrose for the Management of Procedural Pain. Available online: http://www.nuh.nhs.uk/ (accessed on 24 October 2013).
17. AFSSAPS. *Nitrofurantoïne et Risque de Survenue d'Effets Indésirables Hépatiques et Pulmonaires lors de Traitements Prolongés*; Agence Française de Sécurité Sanitaire des Produits de Santé: Paris, France, 2011.
18. AFSAPPS. *Recommandations de Bonne Pratique*; Agence Française de Sécurité Sanitaire des Produits de Santé: Paris, France, 2007.
19. AFSAPPS. *Utilisation du Fluor dans la Prévention de la Carie Dentaire Avant l'Âge de 18 Ans*; Agence Française de Sécurité Sanitaire des Produits de Santé: Paris, France, 2008.
20. Centers for Disease Control and Prevention. Managing acute gastroenteritis among children: Oral rehydration, maintenance, and nutritional therapy. *Pediatrics* **2004**, *114*, 507–507.
21. Aparasu, R.R.; Mort, J.R. Inappropriate prescribing for the elderly: Beers criteria-based review. *Ann. Pharmacother.* **2000**, *34*, 338–346.
22. Jano, E.; Aparasu, R.R. Healthcare outcomes associated with beers' criteria: A systematic review. *Ann. Pharmacother.* **2007**, *41*, 438–448.
23. Chang, C.M.; Liu, P.Y.Y.; Yang, Y.H.K.; Yang, Y.C.; Wu, C.F.; Lu, F.H. Use of the Beers criteria to predict adverse drug reactions among first-visit elderly outpatients. *Pharmacother. J. Hum. Pharmacol. Drug Ther.* **2005**, *25*, 831–838.

Appendix 3:
Corrick F, Smith C, Choonara I, Sammons HM. Developing paediatric rational prescribing criteria: a pilot study. Midlands Academy of Medical Sciences Research Festival; 2017

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Assessment Tools of Rational Prescribing in Children

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Background and Aims

Rational prescribing seeks to ensure that patients receive optimal medicines appropriate to their clinical need and at the lowest cost, both to them and their community. Irrational prescribing can lead to suboptimal treatment for patients, increased rates of adverse events or drug interactions, and waste of organisational resources that could be spent on health needs. The situation in paediatric prescribing has been described as an "evidence-based desert"[1] with high rates of use of off-label and unlicensed drugs. The aim of this study was to review the current research literature on rational prescribing in paediatrics and to conduct a systematic literature search for screening tools designed for use in this field.

Methods

We conducted a review of the research into rational prescribing in paediatrics and performed a systematic literature search in Embase and Medline for screening tools for the assessment of rational prescribing in paediatrics (patients<18 years).

Results

Antibiotic prescriptions were the most common topic of studies of rational prescribing for children. In particular, studies looking at rational use of antibiotics have demonstrated inappropriately high rates of antibiotic prescribing for conditions with low probability of clinical benefit:

- Risk et al[2] evaluated prescribing for children <5 years in 20 centres in The Gambia and found that approximately half of children presenting with diarrhoea or uncomplicated upper respiratory tract infection were prescribed antibiotics
- One review found that children in Italy are almost fourfold more likely to be prescribed antibiotics than in the UK

Only 1 screening tool was identified with the systematic search: the POPI (Pediatrics: Omissions of Prescriptions and Inappropriate Prescriptions) criteria[3], developed in France in 2015 (see Table 1). This contains region-specific guidance based on French, British and American clinical guidelines and has yet to be validated clinically.

Table 1- An excerpt of the POPI criteria

ENT-PULMONARY PROBLEMS	COUGH
	Inappropriate prescriptions
	Pholcodine
	Mucolytic drugs, mucokinetic drugs, or helicidine before two years of age
	Alimemazine (Theralene), oxomemazine (Toplexil), promethazine (Phenergan, and other types)
	Terpene-based suppositories
	Omissions
	Failure to propose a whooping cough booster vaccine for adults who are likely to become parents in the coming months or years (only applicable if the previous vaccination was more than 10 years ago). This booster vaccination should also be proposed to the family and entourage of expectant parents (parents, grand-parents, nannies/child minders)
	BRONCHIOLITIS IN INFANTS
	Inappropriate prescriptions
	Beta2 agonists, corticosteroids to treat an infant's first case of bronchiolitis
	H1-antagonists, cough suppressants, mucolytic drugs, or ribavirin to treat bronchiolitis
	Antibiotics in the absence of signs indicating a bacterial infection (acute otitis media, fever, etc.)
	Omissions
	0.9% NaCl to relieve nasal congestion (not applicable if nasal congestion is already being treated with 3% NaCl delivered by a nebulizer)
	Palivizumab in the following cases: (1) babies born both at less than 35 weeks of gestation and less than six months prior to the onset of a seasonal RSV epidemic; (2) children less than two years old who have received treatment for bronchopulmonary dysplasia in the past six months; (3) children less than two years old suffering from congenital heart disease with hemodynamic abnormalities
	ENT INFECTIONS
	Inappropriate prescriptions
	An antibiotic other than amoxicillin as a first-line treatment for acute otitis media, strep throat, or sinusitis (provided that the patient is not allergic to amoxicillin). An effective dose of amoxicillin for an pneumoncoccal infection is 80–90 mg/kg/day and an effective dose for a streptococcal infection is 50 mg/kg/day
	Antibiotic treatment for a sore throat, without a positive rapid diagnostic test result, in children less than three years old
	Antibiotics for nasopharyngitis, congestive otitis, sore throat before three years of age, or laryngitis; antibiotics as a first-line treatment for acute otitis media showing few symptoms, before two years of age
	Antibiotics to treat otitis media with effusion (OME), except in the case of hearing loss or if OME lasts for more than three months
	Corticosteroids to treat acute suppurative otitis media, nasopharyngitis, or strep throat
	Nasal or oral decongestant (oxymetazoline (Aturgyl), pseudoephedrine (Sudafed), naphazoline (Derinox), ephedrine (Rhinamide), tuaminoheptane (Rhinofluimicil), phenylephrine (Humoxal))
	H1-antagonists with sedative or atropine-like effects (pheniramine, chlorpheniramine), or camphor; inhalers, nasal sprays, or suppositories containing menthol (or any terpene derivatives) before 30 months of age
	Ethanolamine tenoate (Rhinotrophyl) and other nasal antiseptics
	Ear drops in the case of acute otitis media
	Omissions
	Doses in mg for drinkable (solutions of) amoxicillin or josamycin
	Paracetamol combined with antibiotic treatment for ear infections to relieve pain

Conclusions

Although rational prescribing for children appears to be an area of increasing research activity, only 1 screening tool was identified by a systematic search of the literature: the POPI criteria. There is evidence that prescribing practices vary greatly between regions but a paucity of validated assessment tools to compare prescribing practice at different times or in different areas.

References:
1) Sutcliffe, A.G. & Wong, I.C.K., 2006. Rational prescribing for children. *BMJ (Clinical research ed.)*, 332(7556), pp.1464–5.
2) Risk, R. et al., 2013. Rational prescribing in paediatrics in a resource-limited setting. *Archives of disease in childhood*, 98(7), pp.503–9.
3) Prot-Labarthe, S. et al., 2014. POPI (Pediatrics: Omission of Prescriptions and Inappropriate Prescriptions): Development of a tool to identify inappropriate prescribing. *PLoS ONE*, 9(6).

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Appendix 4:
Corrick FJ, Conroy S, Choonara I, Sammons H. Developing paediatric rational prescribing criteria. Archives of Disease in Childhood. 2017;102 (Supplement 1):A84.

G212 **DEVELOPING PAEDIATRIC RATIONAL PRESCRIBING CRITERIA**

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Aims Rational prescribing is the *therapeutically sound and cost-effective use of drugs* (World Health Organisation, 2008). Criteria lists are well-established as research tools in rational prescribing for adults but only one tool has been developed for paediatric practice. The French 'POPI' criteria comprise 105 inappropriate prescriptions or omissions. Having revised these to align with UK clinical guidelines, our aim was to assess the usefulness of the modified POPI criteria by evaluating their relevance to UK paediatric patients.

Methods This study was a single centre prospective observational study of 400 paediatric patients (0–18 years) in a children's emergency department and two paediatric wards. The only exclusion criterion was lack of parent/carer consent. Diagnoses, symptoms and prescriptions were recorded and checked against the modified POPI tool.

Results Patient age ranged from 3 days to 17 years. The median number of prescriptions per patient was 2.5 (range 0–26). 343 patients attended with at least one clinical indication in the tool. 255 were in the category of Pain or Fever; the next most frequent were Nausea, Vomiting or Gastro-oesophageal Reflux (n=123), Cough (n=77) and Diarrhoea (n=36). 29 cases had one or more inappropriate prescriptions or omissions; these related to Pain or Fever (n=25), Bronchiolitis (n=3), Nausea, Vomiting or Gastro-oesophageal Reflux (n=1), and Asthma (n=1) and comprised 20 omissions and 12 inappropriate prescriptions.

Conclusions The modified POPI criteria detected 32 inappropriate prescriptions or omissions. However, 7/21 clinical categories were not relevant to any patients in the study. Furthermore, a number of frequent presentations are absent from the criteria, including sepsis (n=36), viral-induced wheeze (n=35) and lower respiratory tract infections (n=26). In 27 cases, it was not possible to determine objectively whether or not an inappropriate prescription had occurred, highlighting complexity and subjectivity within the criteria. This study demonstrates the potential for a criteria list to act as a useful tool in studying rational prescribing for children. However, it also highlighted a number of limitations that must be resolved in order to develop an effective paediatric rational prescribing tool.

Appendix 5:
Corrick F, Smith C, Choonara I, Sammons HM. Rational Prescribing for Children: Evaluating the modified POPI criteria. RCPCH Annual QI Conference; 2016

Rational Prescribing for Children: Evaluating the modified POPI criteria

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What are the POPI criteria?

A set of 105 statements of inappropriate prescriptions or inappropriate omissions published in France in 2014 for use in paediatrics[1]. They were designed by Delphi consensus.

Aims

Having modified the criteria to match UK guidelines, we aimed to assess the usefulness of the modified POPI criteria by evaluating the proportion of patients and prescriptions that fall within the criteria.

Methods

A single centre cross-sectional observation study of prescribing for paediatric (0-18 years) inpatients. The only exclusion criterion was lack of parent/carer consent. Diagnoses, symptoms and prescriptions were recorded for 100 patients and checked against the modified POPI tool.

Results

Patient age ranged from 3 days to 17 years. The mean number of prescriptions per patient was 4.3 (range 0-20), 86% of patients were admitted for at least 1 clinical indication included in the criteria, the most common being pain and fever (see figure 1). The most commonly detected errors or omissions also related to pain and fever (see figure 2).

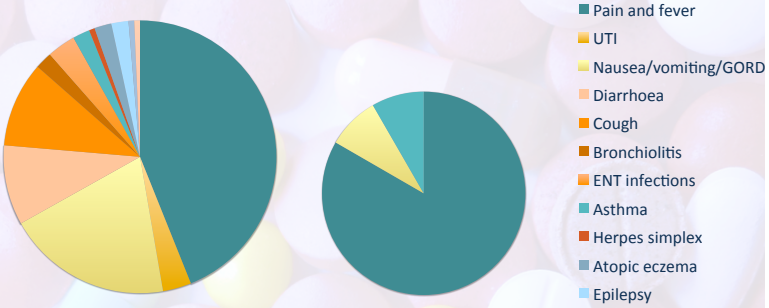


Figure 1: Cases with diagnoses or symptoms within criteria

Figure 2: Categories in which errors/omissions detected

Discussion points

Although the majority of patients had at least one diagnosis or symptom within the criteria, the study highlighted a number of significant limitations in the tool.

Do the criteria cover the right conditions?

- 8 of 21 categories in the tool were relevant to no patients
- Several frequent indications are missing from the tool:
  - Sepsis (16 cases)
  - Lower respiratory tract infections (10)
  - Wheeze (9)

Are the criteria reliable?

- Several criteria are subjective; was the patient "distressed"? What is a "short period of time"?
- Clearer exemptions are needed in some criteria; e.g. laxatives for all patients on morphine for >48hrs, but several cases described ongoing diarrhoea

Future development

- Extend testing to emergency department
- Inter- and intra-observer reliability testing
- Delphi consensus on categories & criteria

1) Prot-Labarthe, S. et al., 2014. POPI (Pediatrics: Omission of Prescriptions and Inappropriate Prescriptions): Development of a tool to identify inappropriate prescribing. *PLoS ONE*, 9(6).

www.nottingham.ac.uk

Appendix 6:

Corrick F, Sammons HM. Assessment Tools of Rational Prescribing in Children. Trent Paediatric Society Meeting; 2017.

Derby Teaching Hospitals NHS
NHS Foundation Trust

Rational prescribing for children

Dr FJ Corrick, Department of Child Health

University of Nottingham
UK | CHINA | MALAYSIA

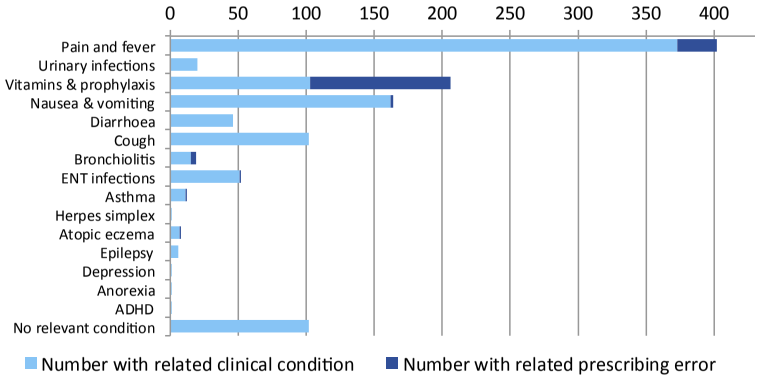
The project:

Rational prescribing criteria can be used to evaluate quality of prescribing. Only one tool (the "POPI" tool) has ever been published for prescribing in paediatrics. This project aims to develop validated criteria for use in quality improvement and research in paediatrics. There are five phases to the project:

Systematic review of the literature → Modify POPI to fit UK guidelines → Clinical evaluation → Reliability study → Refine tool

Preliminary results:

- Systematic review confirmed only one criteria list published as a research tool. Heterogeneous approaches to evaluating prescribing for children limits comparability and collaboration between studies, over time or between clinical settings.
- The modified criteria comprise 21 categories of clinical problems with related potentially inappropriate prescriptions or omissions.
- Initial evaluation of the modified criteria involved assessing its coverage of paediatric problems seen in 600 patients in Derbyshire Children's Hospital.



Impact:

Children
Avoided side effects
Right first line treatment

Families
Shorter hospital stays
Getting the right advice

Communities
Antibiotic resistance
Herd immunity

Short-term
Avoided prescriptions
Cost-effective treatments

Long-term
Can test interventions for quality improvement (QI) in optimal prescribing

Researchers
Facilitate collaboration
Tool to quantify quality of prescribing

Hospitals
Compare and collaborate
QI / audit

Families
Engage children and parents
Educate about research

Acknowledgements: Thanks to Dr Helen Sammons, Prof Imti Choonara, Dr Sharon Conroy and the staff and patients of Derbyshire Children's Hospital.

Appendix 7:

The original POPI criteria

DIVERSE ILLNESSES
PAIN AND FEVER
Inappropriate prescriptions
Prescription of two alternating antipyretics as a first-line treatment
Prescription of a medication other than paracetamol as a first line treatment (except in the case of migraine)
Rectal administration of paracetamol as a first-line treatment
The combined use of two NSAIDs
Oral solutions of ibuprofen administered in more than three doses per day using a graduated pipette of 10mg/kg (other than Advil)
Opiates to treat migraine attacks
Omissions
Failure to give sugar solution to new-born babies and infants under four months old two minutes prior to venepuncture
Failure to give an osmotic laxative to patients being treated with morphine for a period of more than 48 hours
URINARY INFECTIONS
Inappropriate prescriptions
Nitrofurantoin used as a prophylactic
Nitrofurantoin used as a curative agent in children under six years of age, or indeed any other antibiotic if avoidable
Antibiotic prophylaxis following an initial infection without complications (except in the case of uropathy)
Antibiotic prophylaxis in the case of asymptomatic bacterial infection (except in the case of uropathy)
VITAMIN SUPPLEMENTS AND ANTIBIOTIC PROPHYLAXIS
Inappropriate prescriptions
Fluoride supplements prior to six months of age
Omissions
Insufficient intake of vitamin D. Minimum vitamin D intake: Breastfed baby = 1 000 to 1 200 IU/day; Infant ,18 months of age (milk enriched in vitamin D) = 600 to 800 IU/day; Child aged between 18 months and five years, and adolescents aged between 10 and 18 years: two quarterly loading doses of 80 000 to 100 000 IU/day in winter (adolescents can take this dose in one go)
Antibiotic prophylaxis with phenoxymethylpenicillin (Oracilline) starting from two months of age and lasting until five years of age for children with sickle-cell anemia: 100 000 IU/kg /day (in two doses) for children weighing 10kg or less and 50 000 IU/kg/day for children weighing over 10kg (also in two doses)
MOSQUITOS
Inappropriate prescriptions
The use of skin repellents in infants less than six months old and picardin in children less than 24 months old
Citronella (lemon grass) oil (essential oil)
Anti-insect bracelets to protect against mosquitos and ticks
Ultrasonic pest control devices, vitamin B1, homeopathy, electric bug zappers, sticky tapes without insecticide
Omissions
DEET: ‘‘30%’’ (max) before 12 years old; ‘‘50%’’ (max) after 12 years old
IR3535: ‘‘20%’’ (max) before 24 months old; ‘‘35%’’ (max) after 24 months old

Mosquito nets and clothes treated with pyrethroids
DIGESTIVE PROBLEMS
NAUSEA, VOMITING, OR GASTROESOPHAGEAL REFLUX
Inappropriate prescriptions
Metoclopramide
Domperidone
Oral administration of an intravenous proton pump inhibitor (notably by nasogastric tube)
Gastric antisecretory drugs to treat gastroesophageal reflux, dyspepsia, the crying of new-born babies (in the absence of any other signs or symptoms), as well as faintness in infants
The combined use of proton pump inhibitors and NSAIDs, for a short period of time, in patients without risk factors
The use of type H2 antihistamines for long periods of treatment
Erythromycin as a prokinetic agent
The use of setrons (5-HT3 antagonists) for chemotherapy-associated nausea and vomiting
Omissions
Oral rehydration solution
DIARRHOEA
Inappropriate prescriptions
Loperamide before 3 years of age
Loperamide in the case of invasive diarrhea
The use of Diosmectite (Smecta) in combination with another medication
The use of Saccharomyces boulardii (Ultralevure) in powder form, or in a capsule that has to be opened prior to ingestion, to treat patients with a central venous catheter or an immunodeficiency
Intestinal antiseptics
Omissions
Oral rehydration solution
ENT-PULMONARY PROBLEMS
COUGH
Inappropriate prescriptions
Pholcodine
Mucolytic drugs, mucokinetic drugs, or helicidine before two years of age
Alimemazine (Theralene), oxomemazine (Toplexil), promethazine (Phenergan, and other types)
Terpene-based suppositories
Omissions
Failure to propose a whooping cough booster vaccine for adults who are likely to become parents in the coming months or years (only applicable if the previous vaccination was more than 10 years ago). This booster vaccination should also be proposed to the family and entourage of expectant parents (parents, grand-parents, nannies/child minders)
BRONCHIOLITIS IN INFANTS
Inappropriate prescriptions
Beta2 agonists, corticosteroids to treat an infant's first case of bronchiolitis
H1-antagonists, cough suppressants, mucolytic drugs, or ribavirin to treat bronchiolitis
Antibiotics in the absence of signs indicating a bacterial infection (acute otitis media, fever, etc.)
Omissions

0.9% NaCl to relieve nasal congestion (not applicable if nasal congestion is already being treated with 3% NaCl delivered by a nebulizer)
Palivizumab in the following cases: (1) babies born both at less than 35 weeks of gestation and less than six months prior to the onset of a seasonal RSV epidemic; (2) children less than two years old who have received treatment for bronchopulmonary dysplasia in the past six months; (3) children less than two years old suffering from congenital heart disease with hemodynamic abnormalities
ENT infections
Inappropriate prescriptions
An antibiotic other than amoxicillin as a first-line treatment for acute otitis media, strep throat, or sinusitis (provided that the patient is not allergic to amoxicillin). An effective dose of amoxicillin for an pneumoncoccal infection is 80–90 mg/kg/day and an effective dose for a streptococcal infection is 50 mg/kg/day
Antibiotic treatment for a sore throat, without a positive rapid diagnostic test result, in children less than three years old
Antibiotics for nasopharyngitis, congestive otitis, sore throat before three years of age, or laryngitis; antibiotics as a first-line treatment for acute otitis media showing few symptoms, before two years of age
Antibiotics to treat otitis media with effusion (OME), except in the case of hearing loss or if OME lasts for more than three months
Corticosteroids to treat acute suppurative otitis media, nasopharyngitis, or strep throat
Nasal or oral decongestant (oxymetazoline (Aturgyl), pseudoephedrine (Sudafed), naphazoline (Derinox), ephedrine (Rhinamide), tuaminoheptane (Rhinofluimicil), phenylephrine (Humoxal))
H1-antagonists with sedative or atropine-like effects (pheniramine, chlorpheniramine), or camphor; inhalers, nasal sprays, or suppositories containing menthol (or any terpene derivatives) before 30 months of age
Ethanolamine tenoate (Rhinotrophyl) and other nasal antiseptics
Ear drops in the case of acute otitis media
Omissions
Doses in mg for drinkable (solutions of) amoxicillin or josamycin
Paracetamol combined with antibiotic treatment for ear infections to relieve pain
ASTHMA
Inappropriate prescriptions
Ketotifen and other H1-antagonists, sodium cromoglycate
Cough suppressants
Omissions
Asthma inhaler appropriate for the child's age
Preventative treatment (inhaled corticosteroids) in the case of persistent asthma
DERMATOLOGICAL PROBLEMS
ACNE VULGARIS
Inappropriate prescriptions
Minocycline
Isotretinoin in combination with a member of the tetracycline family of antibiotics
The combined use of an oral and a local antibiotic
Oral or local antibiotics as a monotherapy (not in combination with another drug)
Cyproterone+ethinylestradiol (Diane 35) as a contraceptive to allow isotretinoin per os

Androgenic progestins (levonorgestrel, norgestrel, norethisterone, lynestrenol, dienogest, contraceptive implants or vaginal rings)
Omissions
Contraception (provided with a logbook/diary) for menstruating girls taking isotretinoin
Topical treatment (benzoyl peroxide, retinoids, or both) in combination with antibiotic therapy
SCABIES
Inappropriate prescriptions
The application of benzyl benzoate (Ascabiol) for periods longer than eight hours for infants and 12 hours for children or for pregnant girls
Omissions
A second dose of ivermectin two weeks after the first
Decontamination of household linen and clothes and treatment for other family members
LICE
Inappropriate prescriptions
The use of aerosols for infants, children with asthma, or children showing asthma-like symptoms such as dyspnoea
RINGWORM
Inappropriate prescriptions
Treatment other than griseofulvin for Microsporum
Omissions
Topical treatment combined with an orally-administered treatment
Griseofulvin taken during a meal containing a moderate amount of fat
IMPETIGO
Inappropriate prescriptions
The combination of locally applied and orally administered antibiotic
Fewer than two applications per day for topical antibiotics
Any antibiotic other than mupirocin as a first-line treatment (except in cases of hypersensitivity to mupirocin)
HERPES SIMPLEX
Inappropriate prescriptions
Topical agents containing corticosteroids
Topical agents containing acyclovir before six years of age
Omissions
Paracetamol during an outbreak of herpes
Orally administered acyclovir to treat primary herpetic gingivostomatitis
ATOPIC ECZEMA
Inappropriate prescriptions
A strong dermocorticoid (clobetasol propionate 0.05% Dermoval, betamethasone dipropionate Diprosone) applied to the face, the armpits or groin, and the backside of babies or young children
More than one application per day of a dermocorticoid, except in cases of severe lichenification
Local or systemic antihistamine during the treatment of outbreaks
Topically applied 0.03% tacrolimus before two years of age
Topically applied 0.1% tacrolimus before 16 years of age
Oral corticosteroids to treat outbreaks
NEUROPSYCHIATRIC DISORDERS

EPILEPSY
Inappropriate prescriptions
Carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine, or vigabatrin in the case of myoclonic epilepsy
Carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabaline, tiagabine, or vigabatrin in the case of epilepsy with absence seizures (especially for childhood absence epilepsy or juvenile absence epilepsy)
Levetiracetam, oxcarbamazepine in mL or in mg without systematically writing XX mg per Y mL
DEPRESSION
Inappropriate prescriptions
An SSRI antidepressant other than fluoxetine as a first-line treatment (in the case of pharmacotherapy)
Tricyclic antidepressants to treat depression
NOCTURNAL ENURESIS
Inappropriate prescriptions
Desmopressin administered by a nasal spray
Desmopressin in the case of daytime symptoms
An anticholinergic agent used as a monotherapy in the absence of daytime symptoms
Tricyclic agents in combination with anticholinergic agents
Tricyclic agents as a first-line treatment
ANOREXIA
Inappropriate prescriptions
Cyproheptadine (Perlactin), clonidine
ATTENTION DEFICIT DISORDER WITH OR WITHOUT HYPERACTIVITY
Inappropriate prescriptions
Pharmacological treatment before age six (before school), except in severe cases
Antipsychotic drugs to treat attention deficit disorder without hyperactivity
Slow release methylphenidate as two doses per day, rather than only one dose
Omissions
Recording a growth chart (height and weight) if the patient is taking methylphenidate

Appendix 8:
The POPI UK criteria

Code	DIVERSE ILLNESSES
A	**PAIN AND FEVER**
	Inappropriate prescriptions
1	Prescription of two alternating antipyretics as a first-line treatment
2	Prescription of a medication other than paracetamol or ibuprofen as a first-line treatment for pain (except in the case of migraine)
3	The combined use of two NSAIDs
4	Doses of ibuprofen administered in more than three doses per day or exceeding maximum dose of 30mg/kg over three doses per day
5	Opiates to treat migraine attacks
	Omissions
6	Failure to give an osmotic laxative to patients being treated with morphine for a period of more than 48 hours
B	**URINARY INFECTIONS**
	Inappropriate prescriptions
1	Antibiotic prophylaxis following an initial infection without complications (except in the case of uropathy)
2	Antibiotic prophylaxis in the case of asymptomatic bacterial infection (except in the case of uropathy)
C	**VITAMIN SUPPLEMENTS AND ANTIBIOTIC PROPHYLAXIS**
	Omissions
1	Healthy Start vitamins for infants and children 6 months- 5 years or having less than 500mL infant formula per day
2	Antibiotic prophylaxis with phenoxyethylpenicillin (penicillin V) from age 1 month until 5 years for children with sickle-cell anaemia at a dose of: • 125 mg twice a day for infants and children up to 5 years of age. • 250 mg twice a day for children from 6 to 12 years of age. • 500 mg twice a day for adults and children older than 12 years of age. OR Erythromycin for children who are allergic to penicillin, at a dose of: • 125 mg twice a day for infants and children up to 2 years of age. • 250 mg twice a day for children older than 2 years of age.

	DIGESTIVE PROBLEMS
D	**NAUSEA, VOMITING, OR GASTROESOPHAGEAL REFLUX**
	Inappropriate prescriptions
1	Metoclopramide
2	Domperidone
3	Oral administration of an intravenous proton pump inhibitor (notably by nasogastric tube)
4	Acid-suppressing drugs to treat overt regurgitation in the absence of feeding difficulties, distress, or faltering growth
5	The combined use of proton pump inhibitors and NSAIDs, for a short period of time, in patients without risk factors
6	The use of H_2 receptor antagonists for more than 4 weeks
7	Erythromycin
	Omissions
8	Oral rehydration solution (ORS) for dehydrated children unless IV fluid therapy is indicated (shock, red flag symptoms despite ORS, persist vomiting of ORS)
E	**DIARRHOEA**
	Inappropriate prescriptions
1	Loperamide before 4 years of age
2	Loperamide in the case of invasive diarrhoea
	Omissions
3	Oral rehydration solution (ORS) for dehydrated children unless IV fluid therapy is indicated (shock, red flag symptoms despite ORS, persist vomiting of ORS)
	ENT-PULMONARY PROBLEMS
F	**COUGH**
	Inappropriate prescriptions
1	Pholcodine
2	Mucolytic drugs, mucokinetic drugs, or helicidine before two years of age
3	Alimemazine (Theralene), oxomemazine (Toplexil), promethazine (Phenergan, and other types)
	Omissions
4	Failure to propose a whooping cough vaccine for pregnant women.
G	**BRONCHIOLITIS IN INFANTS**
	Inappropriate prescriptions
1	Antibiotics, ß2 agonists or corticosteroids to treat bronchiolitis

2	H_1-antagonists, cough suppressants, mucolytic drugs, or ribavirin to treat bronchiolitis
	Omissions
3	Palivizumab in high-risk cases, defined as: 1) children < 2 years with chronic lung disease on home oxygen or who have prolonged use of oxygen 2) infants < 6 months with left-to-right shunt haemodynamically significant congenital heart disease and/or pulmonary hypertension 3) children < 2 years with severe congenital immunodeficiency
H	**ENT INFECTIONS**
	Inappropriate prescriptions
1	An antibiotic for < 4 days symptoms of acute upper respiratory tract infection (except : • bilateral acute otitis media in children younger than 2 years • acute otitis media in children with otorrhoea • acute sore throat/acute pharyngitis/acute tonsillitis when three or more Centor criteria are present.
2	Antibiotic treatment for a sore throat except in severe cases (anticipated to be no more than 20% of cases)
3	Antibiotics to treat otitis media with effusion in the first 6-12 weeks
4	Corticosteroids to treat acute suppurative otitis media, nasopharyngitis, or strep throat
5	Nasal or oral decongestant (oxymetazoline (Aturgyl), pseudoephedrine (Sudafed), naphazoline (Derinox), ephedrine (Rhinamide), tuaminoheptane (Rhinofluimicil), phenylephrine (Humoxal))
6	Sedating antihistamines (pheniramine, chlorpheniramine) before 2 years (except for anaphylaxis)
7	Ear drops in the case of acute otitis media
	Omissions
8	Doses in mg for drinkable (solutions of) amoxicillin or josamycin
9	Paracetamol combined with antibiotic treatment for ear infections to relieve pain
I	**ASTHMA**
	Inappropriate prescriptions
1	Ketotifen and other antihistamines
2	Cough suppressants
	Omissions

3	Asthma inhaler appropriate for the child's age (aged < 5 years, either Metered Dose Inhaler with spacer system or nebuliser; age 3-5 years Dry Powder Inhaler may be appropriate)
4	Preventative treatment (inhaled corticosteroids) in the case of persistent asthma
	DERMATOLOGICAL PROBLEMS
J	**ACNE VULGARIS**
	Inappropriate prescriptions
1	Minocycline
2	The combined use of an oral and a local antibiotic
3	Oral or local antibiotics as a monotherapy (not in combination with another drug)
4	Cyproterone+ethinylestradiol (Diane 35) as a contraceptive to allow isotretinoin per os
	Omissions
5	Contraception for menstruating girls taking isotretinoin
6	Topical treatment (benzoyl peroxide, retinoids, or both) in combination with antibiotic therapy
K	**SCABIES**
	Inappropriate prescriptions
1	Benzyl benzoate
	Omissions
2	A second application of permethrin or malathion one week after the first
3	Decontamination of household linen and clothes and same day treatment of all members of the household
L	**LICE**
	Inappropriate prescriptions
1	The use of aerosols for infants, children with asthma, or children showing asthma-like symptoms such as dyspnoea
M	**RINGWORM**
	Inappropriate prescriptions
1	Oral treatment other than griseofulvin
	Omissions
2	Topical treatment combined with an orally-administered treatment
3	Griseofulvin taken during a meal containing a moderate amount of fat
N	**IMPETIGO**
	Inappropriate prescriptions
1	The combination of locally applied and orally administered antibiotic

2	Fewer than two applications per day for topical antibiotics
3	Any antibiotic other than fusidic acid as a first-line treatment (except in cases of hypersensitivity to fusidic acid)
O	**HERPES SIMPLEX**
	Inappropriate prescriptions
1	Topical agents containing corticosteroids
2	Topical agents containing aciclovir before six years of age
	Omissions
3	Paracetamol during an outbreak of herpes
4	Orally administered aciclovir to treat severe herpetic gingivostomatitis
P	**ATOPIC ECZEMA**
	Inappropriate prescriptions
1	A potent topical corticosteroid applied to the face, or for > 14 days applied to the axilla or groin
2	More than one application per day of a dermocorticoid, except in cases of severe lichenification
3	Prescription of antihistamines except as a trial for severe itching or where sleep disturbance has a significant impact on the child or carers
4	Topically applied 0.03% tacrolimus before 2 years of age
5	Topically applied 0.1% tacrolimus before 16 years of age
6	Oral corticosteroids to treat outbreaks
	NEUROPSYCHIATRIC DISORDERS
Q	**EPILEPSY**
	Inappropriate prescriptions
1	Carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine, or vigabatrin in the case of myoclonic epilepsy
2	Carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabaline, tiagabine, or vigabatrin in the case of epilepsy with absence seizures (especially for childhood absence epilepsy or juvenile absence epilepsy)
3	Levetiracetam, oxcarbamazepine in mL or in mg without systematically writing XX mg per Y mL
R	**DEPRESSION**
	Inappropriate prescriptions

1	An SSRI antidepressant other than fluoxetine as a first-line treatment (in the case of pharmacotherapy)
2	Tricyclic antidepressants to treat depression
S	**NOCTURNAL ENURESIS**
	Inappropriate prescriptions
1	Desmopressin administered by a nasal spray
2	Desmopressin in the case of daytime symptoms
3	An anticholinergic agent used as a monotherapy in the absence of daytime symptoms
4	Tricyclic agents in combination with anticholinergic agents
5	Tricyclic agents as a first-line treatment
T	**ANOREXIA**
	Inappropriate prescriptions
1	Prescription of medications as a sole or primary treatment for anorexia nervosa
U	**ATTENTION DEFICIT DISORDER WITH HYPERACTIVITY**
	Inappropriate prescriptions
1	Pharmacological treatment before age 6 (before school), except in severe cases
2	Antipsychotic drugs to treat attention deficit hyperactivity disorder
3	Modified release methylphenidate as two doses per day, rather than only one dose
	Omissions
4	Recording a growth chart (height and weight) if the patient is taking methylphenidate

Appendix 9:

Parent/carer information sheet, Kincaid reading grade 8.8

Rational Prescribing

Parent/Carer Information Sheet

The University of Nottingham

UNITED KINGDOM • CHINA • MALAYSIA

Please read the attached Participant Information Sheet with your child.

This page includes some more information. If you have any questions, you will have an opportunity to speak to one of our researchers about it before deciding.

What is the study?

The main purpose of the study is educational. It is a part of Dr Ella Corrick's Master's degree.

The study is testing a new checklist, called "POPI" (Paediatric Omissions of Prescriptions and Inappropriate Prescriptions), which will be used to check that medicines are being prescribed for children in line with the most up-to-date guidelines and scientific evidence.

This is the first time POPI has been used in the UK so our main question will be:

1) Is POPI useful in the UK?

We will also use POPI to see if there are any ways in which our prescribing could be improved, so we are also testing:

2) Does POPI identify any missed or inappropriate prescriptions?

We are testing POPI in 600 children in Derby Children's Hospital.

Do you have to take part?

The study is completely voluntary. If you agree for your child to be included, we will ask you to sign a consent form then give you a copy of this leaflet and your signed form to keep.

What does it involve?

One of our team will talk to you for 10 minutes and ask if you want to be included.

If you are happy for your child's information to be used, we will record your child's prescriptions (list of medicines) and symptoms or diagnosed illness from their medical notes. Your child won't need to do anything.

This study will not help your child directly but the information we get might help improve prescribing in future. If any missed or inappropriate prescriptions were to be identified, it would be brought to the attention of both you and your child's doctors.

Confidential Information

We will follow ethical and legal practice and all information will be handled in confidence.

If you join the study, some parts of your child's medical records and the data collected for the study may be looked at by authorised persons from the University of Nottingham who are organising the research. They may also be looked at by authorised people to check that the study is being carried out correctly. All will have a duty of confidentiality to your child as a research participant.

All information which is collected about your child during the course of the research will be kept strictly confidential, stored in a secure and locked office, and on a password protected database. Any information about your child which leaves the hospital will have their name and address removed (anonymised) and a unique code will be used so that your child cannot be recognised from it.

Version 2.0 - 30.12.15

The University of Nottingham
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Some examples from the POPI checklist:

Are all children who are in pain being prescribed paracetamol or ibuprofen as the first choice painkiller?

Are children who are having morphine receiving the right laxative to prevent constipation?

Are children with diarrhoea and vomiting being given Oral Rehydration Solution (Dioralyte)?

Are we avoiding unnecessary medicines, including steroids, in babies with bronchiolitis (a viral chest infection)?

Are we avoiding antibiotics for viral ear and throat infections?

Are we giving children with asthma age-appropriate inhalers?

Are we giving antibiotic cream for impetigo at least twice a day?

Are we avoiding giving strong steroid cream for eczema for too long on sensitive areas like the face and groin?

Are we keeping a growth chart up-to-date for children on medicines for ADHD?

Who is organising and funding the research

The researchers are based at Derby Children's Hospital and associated with the University of Nottingham.

Who is funding the research?

This study has not received any external funding.

Who has reviewed the study?

This study has been reviewed and given favourable opinion by the Brighton and Sussex Research Ethics Committee.

What will happen to the results?

The anonymised results will be published in Dr Corrick's thesis and may be published in academic journals or presented at conferences.

Contact details

If you have any questions, concerns or wish to make a complaint, please contact Dr Helen Sammons, the Chief Investigator of the study.

Dr Helen Sammons
Consultant Paediatrician
helen.sammons@nottingham.ac.uk

If you wish to hear about the results after the study is completed in August 2017, information will be available on our website:
https://nottingham.ac.uk/research/groups/paediatricmedicines/index.aspx

Version 2.0 - 30.12.15

Appendix 10:

Participant information sheet ages 6-13 years, Kincaid reading grade 4.1

Rational Prescribing

A project to check if the right medicines are being given to children

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

Participant Information Sheet
Ages 6-13
To be shown and read with parent/carer

What is the project?

What is research?

Research is a project that is done to answer an important question.

What is the project for?

"Rational prescribing" means making sure the best medicines are being given to children. It means checking you really need all your medicines and checking your medicines work. It also means making sure no medicines are missed out.

Why have you been invited to take part?

We want to test a new list of questions called POPI. It checks if a child is getting the right medicines. We are asking 600 children altogether and we'd love your help.

How does it work?

We are asking if you would join in a project to test a new checklist, called POPI. The checklist is to help researchers find out if children are getting all the right medicines.

Before you decide if you want to join in, we want you to know why we are doing the project and what it means for you. Please think about this leaflet carefully. Talk to your family, friends, doctor or nurse if you want to.

Version 1.0 - 4.11.15

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What happens?

What will happen if you take part?

One of our team will talk to you for 10 minutes. They will ask if you want to join in.

If you are happy to take part, this is what will happen:

We will read your prescriptions (list of medicines) and doctors' notes. Then we will write down the medicines you have been given and why you needed to come to hospital. You won't need to do anything else.

We can't promise the study will help you but it might help us make sure children are given better medicines in the future.

Will anyone else know you are in the project?

We will keep your information private. This means we will only tell people who already have a need or right to know. If we let other people read the project, it will be made anonymous. That means no one will be able to tell who it is about.

Do you have to take part?

No! It is up to you. We will ask you and your parents if you want to take part. If you say yes we will ask your parents to sign a form. We will give you a copy of this leaflet and your form to keep. It will only take 10 minutes but you can stop any time if you want. If you decide to stop, this will not change the care you get in hospital.

Dr Ella Corrick

People in the project

Dr Ella Corrick will talk to you about it and go through the form with your parent or carer
Dr Helen Sammons is in charge of the project. If you are worried and want to ask any questions or complain about a problem, you or your parent or carer can ask your nurse or doctor or just contact Dr Sammons.

We will collect all the information in the project and see if it helps make sure children are given the right medicines. After the project finishes next summer, if you want to find out what happened you will be able to read about it on our website:
https://nottingham.ac.uk/research/groups/paediatricmedicines/index.aspx

Version 1.0 - 4.11.15

Appendix 11:
Participant information sheet for participants aged 13-15 years with a Kincaid reading grade of 8.4

Rational Prescribing

A project to check if the right medicines are being given to children

The University of Nottingham
UNITED KINGDOM • CHINA • MALAYSIA

Participant Information Sheet
Ages 13-15

To be shown and read with parent/carer

What is the study?

The main purpose of the study is educational. It is a part of Dr Ella Corrick's degree.

The study is testing a new checklist, called "POPI" (Paediatric Omissions of Prescriptions and Inappropriate Prescriptions), which will be used to check that the right medicines are being given to children using the best scientific evidence.

The project is asking 2 questions about this new checklist.

1) Is POPI useful in the UK?
2) Does POPI pick up any missed or inappropriate prescriptions?

We are testing POPI in 600 children in Derby Children's Hospital.

If the researchers were to find any problems with your prescriptions, both you and your doctors would be informed.

The study is being organised by the University of Nottingham and is not being paid for by anyone. All research in the NHS 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 Brighton and Sussex Research Ethics Committee.

Before you decide if you are happy to be included, it's important to understand why the project is being done and what it will involve for you. So please think about this leaflet carefully. Talk to your family, friends, doctor or nurse if you want to.

Do you have to say yes?

No! Being in the study is completely up to you. If you and your family agree to be included, we will ask you to sign your agreement and your parent/carer to sign their consent. We will give you a copy of this leaflet and your signed form to keep.

Will anyone else know you are in the study?

Authorised researchers from the University of Nottingham may have access to some of your medical records for the research and to check that the study is being carried out correctly. We will keep your information private. This means we will only tell people who already have a need or right to know, for example the nurse and doctor looking after you.

Your information will be stored securely in password protected databases and locked offices. Any information that leaves the hospital will not have your name or address on it.

When we publish the results of the study, your information will be made anonymous, which means no one will be able to tell who it is about.

How your information is stored

We will keep information including your name for up to a year after the study finishes. After that, only anonymous information will be kept, stored for up to 7 years then disposed of securely. All steps will be taken to keep it secure and confidential.

Version 2.0 - 30.12.15

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

Some examples from the POPI checklist:

Are all children who are in pain being prescribed paracetamol or ibuprofen as the first choice painkiller?

Are children who are having morphine receiving the right laxative to prevent constipation?

Are children with diarrhoea and vomiting being given Oral Rehydration Solution (Dioralyte)?

Are we avoiding unnecessary medicines, including steroids, in babies with bronchiolitis (a viral chest infection)?

Are we avoiding antibiotics for viral ear and throat infections?

Are we giving children with asthma age-appropriate inhalers?

Are we giving antibiotic cream for impetigo at least twice a day?

Are we avoiding giving strong steroid cream for eczema for too long on sensitive areas like the face and groin?

Are we keeping a growth chart up-to-date for children on medicines for ADHD?

What do you have to do?

One of our team will talk to you and ask if you want to be included.

If you are happy for your information to be used we will record your prescriptions (list of medicines) and reason for being in hospital from your medical notes. You won't need to do anything.

The study won't help you directly but the information we get might help children in the future.

Dr Ella Corrick

People in the project

Dr Ella Corrick will talk to you about it and go through the form with your parent or carer **Dr Helen Sammons** is in charge of the project. If you are worried and want to ask any questions or complain about a problem, you or your parent or carer can ask your nurse or doctor or just contact Dr Sammons.

We will collect all the information in the project and see if it helps make sure children are given the right medicines. After the project finishes in August 2017, if you want to find out what happened you will be able to read about it on our website:
https://nottingham.ac.uk/research/groups/paediatricmedicines/index.aspx

Version 2.0 - 30.12.15

Appendix 12:
Participant information sheet for participants aged 16-18 years with Kincaid reading grade 8.4

Rational Prescribing

A project to check if the right medicines are being given to children

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

Participant Information Sheet
Ages 16-18

What is the study?

The main purpose of the study is educational. It is a part of Dr Ella Corrick's degree.

The study is testing a new checklist, called "POPI" (Paediatric Omissions of Prescriptions and Inappropriate Prescriptions), which will be used to check that the right medicines are being given to children using the best scientific evidence.

The project is asking 2 questions about this new checklist.

1) Is POPI useful in the UK?

2) Does POPI pick up any missed or inappropriate prescriptions?

We are testing POPI in 600 children in Derby Children's Hospital.

If the researchers were to find any problems with your prescriptions, both you and your doctors would be informed.

The study is being organised by the University of Nottingham and is not being paid for by anyone. All research in the NHS 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 Brighton and Sussex Research Ethics Committee.

Before you decide if you want to be included, it's important to understand why the project is being done and what it will involve for you. So please think about this leaflet carefully. Talk to your family, friends, doctor or nurse if you want to.

Do you have to say yes?

No! Being in the study is completely up to you. If you and your family agree to be included, we will ask you to sign you a consent form. We will give you a copy of this leaflet and your signed form to keep.

Will anyone else know you are in the study?

Authorised researchers from the University of Nottingham may have access to some of your medical records for the research and to check that the study is being carried out correctly. We will keep your information private. This means we will only tell people who already have a need or right to know, for example the nurse and doctor looking after you.

Your information will be stored securely in password protected databases and locked offices. Any information that leaves the hospital will not have your name or address on it.

When we publish the results of the study, your information will be made anonymous, which means no one will be able to tell who it is about.

How your information is stored

We will keep information including your name for up to a year after the study finishes. After that, only anonymous information will be kept, stored for up to 7 years then disposed of securely. All steps will be taken to keep it secure and confidential.

Version 2.0 - 30.12.15

Some examples from the POPI checklist:

Are all children who are in pain being prescribed paracetamol or ibuprofen as the first choice painkiller?

Are children who are having morphine receiving the right laxative to prevent constipation?

Are children with diarrhoea and vomiting being given Oral Rehydration Solution (Dioralyte)?

Are we avoiding unnecessary medicines, including steroids, in babies with bronchiolitis (a viral chest infection)?

Are we avoiding antibiotics for viral ear and throat infections?

Are we giving children with asthma age-appropriate inhalers?

Are we giving antibiotic cream for impetigo at least twice a day?

Are we avoiding giving strong steroid cream for eczema for too long on sensitive areas like the face and groin?

Are we keeping a growth chart up-to-date for children on medicines for ADHD?

What do you have to do?

One of our team will talk to you and ask if you want to be included.

If you are happy for your information to be used we will record your prescriptions (list of medicines) and reason for being in hospital from your medical notes. You won't need to do anything.

The study will not directly help you but the information we get might help children in the future.

Dr Ella Corrick

People in the project

Dr Ella Corrick will talk to you about it and go through the form with your parent or carer **Dr Helen Sammons** is in charge of the project. If you are worried and want to ask any questions or complain about a problem, you or your parent or carer can ask your nurse or doctor or just contact Dr Sammons.

We will collect all the information in the project and see if it helps make sure children are given the right medicines. After the project finishes in August 2017, if you want to find out what happened you will be able to read about it on our website:

https://nottingham.ac.uk/research/groups/paediatricmedicines/index.aspx

Version 2.0 - 30.12.15

Appendix 13:
Updated parental and participant information sheets using mandatory language with a Kincaid reading grade of 9.5

Title of Study: Rational Prescribing for Children

Name of Researcher(s): Dr Ella Corrick, Dr Helen Sammons

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?

The study is testing a new checklist, called "POPI" (Paediatric Omissions of Prescriptions and Inappropriate Prescriptions), which will be used to check that medicines are being prescribed for children in line with the most up-to-date guidelines and scientific evidence.
This is the first time POPI has been used in the UK so our main question will be:
1) Is POPI useful in the UK?
We will also use POPI to see if there are any ways in which our prescribing could be improved, so we are also testing:
2) Does POPI identify any missed or inappropriate prescriptions according to the checklist?
It only involves looking at prescriptions that have already been written and includes looking at children who did not have any medicines prescribed.

Why have we been invited?

You are being invited to take part because your child is attending Royal Derby Hospital. We are inviting 600 participants like you to take part

Do we have to take part?

It is up to you to decide whether or not to take part. 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 your child is aged 6-15 years we would like them to also be involved in the decision-making process and will ask them to sign their agreement ("assent") if they would like to take part. 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 legal rights.

What will happen to my child if we take part?

One of our team will talk to you and ask if you want to join in.
If you are happy to take part, we will record your prescriptions (list of medicines) and reason for being in hospital from your medical notes. You won't need to do anything else.
It will only take 10 minutes but you can stop at any time. If you decide to stop, this will not affect the care you receive, simply let one of your child's medical team or one of the researchers know.
It will not be possible for any information that has already been collected to be deleted or removed from the study.

Expenses and payments

Participants will not be paid to participate in the study.

What are the possible disadvantages and risks of taking part?

There are no risks or disadvantages that have been identified.

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 us study the use of medicines in children in the future.

What happens when the research study stops?

After the project finishes next summer, if you want to find out what happened you will be able to read about it on our website:
https://nottingham.ac.uk/research/groups/paediatricmedicines/index.aspx

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 & Liaison Service (PALS)

- Freephone: 0800 783 7691
- Office: 01332 785156
- Email: dhft.contactpals@nhs.net
- Text: 07799 337500

Will our 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, some parts of your child's medical records and the data collected for the study will be looked at by authorised persons from the University of Nottingham who are organising the research. They may also be looked at by authorised people to check that the study is being carried out correctly. All will have a duty of confidentiality to your child as a research participant and we will do our best to meet this duty.

All information which is collected about your child during the course of the research will be kept **strictly confidential**, stored in a secure and locked office, and on a password protected database. Any information about your child which leaves the hospital will have his/her name and address

removed (anonymised) and a unique code will be used so that he/she cannot be recognised from it.

Your child's personal data (address, telephone number) will be kept for up to 3 months after the end of the study so that we are able to contact you about the findings of the study and possible follow-up studies (unless you advise us that you do not wish to be contacted). All other data (research data) will be kept securely for 7 years. After this time your child's data will be disposed of securely. During this time all precautions will be taken by all those involved to maintain your child's confidentiality, only members of the research team will have access to your child's personal data.

If a missed prescription or possible inappropriate prescription were to be identified according to the checklist, the consultant doctor looking after your child would be informed at the time.

What will happen if we 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 then the information collected so far cannot be erased and this information may still be used in the project analysis.

Involvement of the General Practitioner/Family doctor (GP)

Your GP will not be involved in this study.

What will happen to the results of the research study?

The results may be published in academic journals or presented at conferences. They will also be included in an academic dissertation about the project. All data will be anonymised. These publications will be publicised on our website:
https://nottingham.ac.uk/research/groups/paediatricmedicines/index.aspx

Who is organising and funding the research?

This research is being organised by the University of Nottingham and has no external funding.

Who has reviewed the study?

All research in the NHS 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 [*complete when allocated*] Research Ethics Committee.

Further information and contact details

Chief investigator: Dr Helen Sammons
Associate Professor in Child Health
Division of Medical Sciences & Graduate
Entry Medicine
School of Medicine
Faculty of Medicine & Health Sciences
University of Nottingham
Royal Derby Hospital Centre
Uttoxeter Road, Derby, DE22 3DT
Tel: 01332 724691
helen.sammons@nottingham.ac.uk

Researcher: Dr Fenella Corrick
Postgraduate student (MRes)
Division of Medical Sciences & Graduate Entry Medicine
School of Medicine
Faculty of Medicine & Health Sciences
University of Nottingham
Royal Derby Hospital Centre
Uttoxeter Road, Derby, DE22 3DT
stxfc2@nottingham.ac.uk

Appendix 14:
Ethics approval from the Brighton & Sussex Research Ethics Committee (REC reference 15/LO/2191)

NHS
Health Research Authority
South East Coast – Brighton & Sussex Research Ethics Committee
Research Ethics Committee (REC) London Centre
Ground Floor, Skipton House
80 London Road
London
SE1 6LH

19 January 2016

Dr. Fenella Corrick
Division of Medical Sciences & Graduate Entry Medicine
School of Medicine, University of Nottingham
Royal Derby Hospital Centre
DE22 3DT

Dear Dr. Corrick,

Study title:	**A Study into the Validity and Usefulness of the Pediatrics: Omission of Prescriptions and Inappropriate Prescriptions (POPI) Criteria to Assess Rational Prescribing for Children**
REC reference:	**15/LO/2191**
Protocol number:	**15097**
IRAS project ID:	**191321**

Thank you for your letter of 14 January 2016, responding to the Proportionate Review Sub-Committee's request for changes to the documentation for the above study.

The revised documentation has been reviewed and approved by the sub-committee.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager Mr. Ian Braddick, NRESCommittee.SECoast-BrightonandSussex@nhs.net. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of

the study.

You should notify the REC once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. Revised documents should be submitted to the REC electronically from IRAS. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which you can make available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA Approval (England)/ NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" above).

Approved documents

The documents reviewed and approved by the Committee are:

Document	*Version*	*Date*
Copies of advertisement materials for research participants [INFO POSTER Rational prescribing for children v1.0 date 24.11.15]	v1.0	24 November 2015
Covering letter on headed paper [COVERING LETTER Rational prescribing for children date 2.12.15]	1.0	02 December 2015
Covering letter on headed paper [COVERING LETTER Rational Prescribing for Children 6.1.16]	2	06 January 2016
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Evidence of Sponsor insurance]		21 July 2015
IRAS Checklist XML [Checklist_18012016]		18 January 2016
Letter from sponsor [Sponsor letter Rational Prescribing for Children date 4.12.15]		04 December 2015
Other [PIS LEAFLETS AGES 13-15 YEARS Rational Prescribing for Children v2.0 date 6.1.16]	2	06 January 2016
Other [PIS LEAFLETS AGES 6-13 YEARS Rational prescribing for Children v 3.0 date 17.1.16]	3	17 January 2016
Other [CONSENT FORM 16-18 YEARS Rational prescribing for Children v 3.0 date 17.1.16]	3	17 January 2016
Participant consent form [CONSENT FORM PARENTAL Rational prescribing for Children v 3.0 date 17.1.16]	3	17 January 2016
Participant information sheet (PIS) [PIS PARENT Rational prescribing for Children v 3.0 date 17.1.16]	3	17 January 2016
Participant information sheet (PIS) [PIS 16-18 YEARS Rational prescribing for Children v 3.0 date 17.1.16]	3	17 January 2016
REC Application Form [REC_Form_09122015]		09 December 2015
Research protocol or project proposal [PROTOCOL Rational prescribing for children v1.0 date 24.11.15]	1.0	24 November 2015
Summary CV for Chief Investigator (CI) [CV for CI Helen Sammons Rational Prescribing for Children]	1.0	30 November 2015
Summary CV for student [CV for student Fenella Corrick Rational Prescribing for Children]	1.0	30 November 2015
Summary CV for supervisor (student research) [CV for Supervisor Helen Sammons Rational Prescribing for Children]	1.0	30 November 2015

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

15/LO/2191	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely,

P·P·

Dr. John Bull
Vice-Chair

Email: NRESCommittee.SECoast-BrightonandSussex@nhs.net

Enclosures: *"After ethical review – guidance for researchers"*

Copy to: *Ms. Angela Shone*
Dr. Helen Sammons
Dr. Teresa Grieve, Derby Hospitals NHS Foundation Trust

Appendix 15:
University of Nottingham Research & Development department sponsorship letter

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

Our reference: RGS 15097
IRAS Project ID: 191321

0115 9515679
Sponsor@nottingham.ac.uk

NHS Research Ethics Committee
Health Research Authority

Research and Graduate Services
University of Nottingham
King's Meadow Campus
Lenton Lane Nottingham
NG7 2NR

Dr Helen Sammons
Division of Medical Sciences & GEM
School of Medicine
Faculty of Medicine & Health Sciences
University of Nottingham
Royal Derby Hospital Centre
Uttoxeter Road, Derby, DE22 3DT

04 December 2015

Dear Chair of the Ethics Committee,

Sponsorship Statement

Re: A Study into the Validity and Usefulness of the modified Pediatrics: Omission of Prescriptions and Inappropriate Prescriptions (POPI) Tool to Assess Rational Prescribing in Children

I can confirm that this research proposal has been discussed with the Chief Investigator and agreement to sponsor the research is in place.
An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.*

Any necessary indemnity or insurance arrangements will be in place before this research starts. Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.

Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.

The duties of sponsors set out in the NHS Research Governance Framework for Health and Social Care will be undertaken in relation to this research.**

* Not applicable to student research (except doctoral research).
** Not applicable to research outside the scope of the Research Governance Framework.

Yours faithfully

Angela Shone
Head of Research Governance
University of Nottingham

world-changing research
from the University of Nottingham

Appendix 16:
Derby Hospitals NHS Foundation Trust approval letter

DHFT Research & Development Dept. Issued 29 FEB 2016

Derby Hospitals NHS
NHS Foundation Trust

Royal Derby Hospital
Uttoxeter Road
Derby
DE22 3NE

Tel: 01332 340131
Minicom: 01332 785566
www.derbyhospitals.nhs.uk
Follow us on Twitter @DerbyHospitals

Research and Development Office

TRUST APPROVAL LETTER

Dr Helen Sammons
Clinical Associate Professor
Division of Medical Sciences & Graduate Entry Medicine
School of Medicine, University of Nottingham
Royal Derby Hospital
Uttoxeter Road
Derby DE22 3DT

Dear Dr Helen Sammons

Re: A Study into the Validity and Usefulness of the Pediatrics: Omission of Prescriptions and Inappropriate Prescriptions (POPI) Criteria to Assess Rational Prescribing for Children

R&D Reference: DHRD/2016/013

The agreed Recruitment Target for this Study is: 600

Further to the Research Ethics Committee approval for the above study, I am pleased to confirm Trust management approval for you to proceed in accordance with the agreed protocol, the Trust's financial procedures for research and development and the Research Governance Framework (which includes the Data Protection Act 1998 and the Health & Safety at Work Act 1974).

Please supply the following information at the appropriate time points to Dr Teresa Grieve, Assistant Director of R&D via (dhft.randdadmin@nhs.net):

- The date of your first patient recruited to the study
- A report every six months if the study duration is greater than six months
- Notification of any SUSARS, amendments, urgent safety measures or if the trial is abandoned.
- Notification of end of the study and an end of study report.
- Details of any publications arising from this research project.

Please note that approval for this study is dependent on full compliance with all of the above conditions.

The 70 day Target Date for Recruiting the First Patient is 26th April 2016

The Government's Plan for Growth (March 2011) announced the transformation of incentives at local level for efficiency in initiation and delivery of research. As a result the NIHR have introduced research performance benchmarks: ***studies must recruit to time and target, and first patient must be recruited onto the study within 70 days of submission of local***

Derby Hospitals NHS
NHS Foundation Trust

Royal Derby Hospital
Uttoxeter Road
Derby
DE22 3NE

Tel: 01332 340131
Minicom: 01332 785566
www.derbyhospitals.nhs.uk
Follow us on Twitter @DerbyHospitals

application. Trusts will be fined, otherwise penalised and funding withheld if these metrics are not met. Please ensure you work towards recruiting the first patient by the above date, and inform us if you envisage any problems as we will endeavour to help you meet this target.

I would like to take this opportunity to wish you every success with this study.

Yours sincerely

pp **Prof. Fran Game FRCP**
Director of Research & Development

Short Study Title: Rational Prescribing for Children (POPI)
R&D Ref: DHRD/2016/013

In accordance with your application and subsequent R&D approval dated 29th February 2016 the following documentation was reviewed and may therefore be used on the above study with Trust approval.

List of reviewed Documents:

Document	*Version*	*Date*
INFO POSTER Rational prescribing for children	v1.0	24.11.15
COVERING LETTER Rational prescribing for children date	v1.0	2.12.15
COVERING LETTER Rational Prescribing for Children	v2.0	6.1.16
Evidence of Sponsor insurance		21.07.2015
Sponsor letter		04.12.2015
PIS LEAFLETS AGES 13-15 YEARS Rational Prescribing for Children	v2.0	6.1.2015
PIS LEAFLETS AGES 6-13 YEARS Rational prescribing for Children	v3.0	17.1.2016
CONSENT FORM 16-18 YEARS Rational prescribing for Children	v3.0	17.1.2016
CONSENT FORM PARENTAL Rational prescribing for Children	v3.0	17.1.2016
PIS PARENT Rational prescribing for Children	v3.0	17.1.2016
[PROTOCOL Rational prescribing for children	V1.0	24.11.2015
Cv PI, CI, student		
REC approval		19.1.2016
IRAS R&D Form		6.12.2015