

## The PIPc study: Development and validation of indicators of potentially inappropriate prescribing in children (PIPc) in primary care

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**The PIPc study: Development and validation of indicators of potentially inappropriate prescribing in children (PIPc) in primary care.**

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A thesis submitted to the School of Postgraduate Studies, Faculty of Medicine and Health Sciences, Royal College of Surgeons in Ireland, in fulfilment of the Degree of Master of Science (MSc)

1 Volume

Supervisors: Professor Susan Smith and Dr Kirsty O'Brien

April 2016

Declaration: I declare that this thesis which I submit to RCSI for examination in consideration of the award of degree of Master of Science is my own personal effort. Where any of the content presented is the result of input or data from a related collaborative research programme this is duly acknowledged in the text such that it is possible to ascertain how much of the work is my own. I have not already obtained a degree in RCSI or elsewhere on the basis of this work. Furthermore, I took reasonable care to ensure that the work is original and to the best of my knowledge does not breach copyright law and has not been taken from other sources except where such work has been cited and acknowledged within the text.

Signed\_\_\_\_\_

Student number\_\_\_\_\_

Date\_\_\_\_\_

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## **List of abbreviations**

AAP American Academy of Paediatrics

ADE Adverse Drug Event

ADR Adverse Drug Reaction

AE Accident and Emergency department

ATC Anatomical Classification System

BMJ British Medical Journal

BNFc British National Formulary for Children

BTS British Thoracic Society

CHMP Committee for Medicinal Products for Human Use

DDD Daily Defined Doses

DME Drug Metabolizing Enzyme

FDA Food and Drugs Authority

EMA European Medicines Authority

ESPGHAN European Society for Gastroenterology, Hepatology and Nutrition

ESAC European Surveillance of Antimicrobial Consumption

EU European Union

GINA Global Initiative for Asthma

GMS General Medical Services

GP General Practitioner

GRADE Grading of Recommendations Assessment Development and Evaluation

HRB Health Research Board

HSE Health Service Executive

HTD High Tech Drugs

ICS Inhaled Corticosteroid

IMB Irish Medicines Board

IMF Irish Medicines Formulary

IQR Interquartile Range

LABA Long Acting Beta 2 Agonist

LTI Long Term Illness

LTRA Leukotriene Receptor Antagonist

MA Marketing Authorisation

MAI Medication Appropriateness Index

MHRA Medicines and Health Regulatory Authority

MeSH Medical Subject Heading

NGT Nominal Group Technique

NHS National Health Service

NI Northern Ireland

NICE National Institute for Clinical Excellence

NMIC National Medicines Information Centre

OECD Organisation for Economic Cooperation and Development

PCRS Primary Care Reimbursement Service

PIL Patient Information Leaflet

PIP Potentially Inappropriate Prescribing

PIPC Potentially Inappropriate Prescribing in children

pMDI pressurised Metered Dose Inhaler

POPI Paediatrics: Omissions of prescriptions and inappropriate prescriptions

PROMPT Prescribing Optimally in Middle Aged Peoples Treatments

QOF Quality Outcomes Framework

QUB Queens University Belfast

RAND Research and Development Corporation

RCPCH Royal Colleges of Paediatrics and Child Health

RCSI Royal College of Surgeons in Ireland

SABA Short Acting Beta 2 Agonist

SIGN Scottish Intercollegiate Guidelines Network

SPC Summary of Product Specification

START Screening Tool to Alert Doctors to the Right Treatment

STOPP Screening Tool of Older Person's Prescriptions

UK United Kingdom

US United States

VAT Value Added Tax

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## Summary

**Background:** There is limited evidence regarding the quality of prescribing for children in primary care. Several prescribing criteria (indicators) have been developed to assess the appropriateness of prescribing in older and middle aged adults but few are relevant to children. This thesis outlines the development of a set of prescribing indicators to be applied to the Primary Care Reimbursement Database (PCRS) to determine the prevalence of potentially inappropriate prescribing (PIP) in children in primary care settings.

**Methods:** Two round Delphi consensus method: A literature search was conducted to identify published indicators for children (< 16 years). A Project Steering Group reviewed the suitability of the indicators. These criteria underwent a two round Delphi process using an expert panel consisting of general practitioners, pharmacists, paediatricians and clinical pharmacologists from the Republic of Ireland and the United Kingdom. Using a web based questionnaire, 15 panellists were asked to indicate their level of agreement with each indicator via a five point Likert scale to assess applicability to children in the absence of clinical information. Criteria were accepted or rejected or revised based on the panel's level of agreement using the median response/interquartile range and additional comments. The final set of indicators was applied to the PCRS database for 2014 to determine the prevalence of PIP in children. The association of PIPc and gender were examined. Costs of PIP were calculated

**Results:** The final list consisted of 12 indicators categorized by respiratory system (n=6), gastrointestinal system (n=2), neurological system (n=2) and dermatological system (n=2). The most common commission of PIPc was the prescribing of carbocysteine to children (32.7/1000 GMS children). The most common omission of appropriate prescribing was the failure to prescribe a spacer device at least annually for children < 12 years who used a pressurised metered dose inhaler (70% of eligible children). The relative risk of PIPc in males compared to females was statistically significant by indicators of omission (RR 1.3; 95% CI 1.02-1.66) but not by indicators of commission (RR 1.03; 95% CI 0.65-1.62). The costs not incurred or saved due to omissions of appropriate prescribing (€678,816.30) far exceeded the costs incurred by commissions of PIPc in 2014. (€129,255.04)

**Conclusions:** The PIPc indicators are the first set of prescribing criteria developed for use in children in primary care. The prevalence of PIP in GMS eligible children was found to be low.



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# **Chapter 1 Introduction to the thesis**

## **1.1 Introduction**

This thesis documents the design and conduct of a cross sectional observational study to investigate potentially inappropriate prescribing in children in Irish primary care. This chapter briefly outlines why the quality of prescribing in children was chosen as the area of study. Section 1.2 details the evidence and contextual background to this research. Section 1.3 provides a brief overview of the Irish healthcare system and child health in the Irish healthcare setting. Section 1.4 presents the aims and objectives of the research while section 1.5 presents an outline of the thesis structure. Section 1.6 outlines the ethical approval required for the study.

## **1.2 Background**

### *1.2.1 Prescribing*

Prescribing medication is one of the most useful tools a general practitioner has in the prevention and treatment of disease. (1) However, when not used appropriately or effectively, prescribing of medication can lead to harm (medication related adverse events) as well as unnecessary expense.

Medicines are generally considered appropriate in an adult population when they have a clear evidence based indication, are well tolerated in the majority of patients and are cost effective. (2) Medicines or prescribing patterns that do not fit this description can be considered inappropriate or potentially inappropriate. (2) Potentially inappropriate prescribing (PIP) is generally understood to include mis- prescribing, over prescribing and under prescribing. This encompasses the use of medications at a higher frequency and for longer than clinically indicated, the use of medicines that have recognized drug- drug interactions, and the underuse of clinically relevant medications. (3)

Prescribing to children is complicated by the age associated physiological and developmental differences between children and adults. (4) Many drugs have altered pharmacodynamic and pharmacokinetic properties in children compared to adults, and therefore extrapolation of appropriateness and dose based on adult data can lead to unforeseen adverse drug reactions e.g. aspirin can lead to Reyes syndrome in children but not in adults.

In recent years there has been concern over the quality of care that children receive and the lack of studies in this area. (5) The rational use of medicines in children is an area of research that has been inadequately studied. (6) PIP in older adults has been shown to lead to increased morbidity, adverse drug events and hospitalisations. (7, 8) In Ireland 36% of those aged 70years or over received at least one potentially inappropriate prescription in 2007, with an associated expenditure of over €45 million (9). No comparable data is available on potentially inappropriate prescribing in children (PIPc) in Ireland.

### *1.2.2 Indicators of prescribing*

The evaluation of whether medicines are prescribed rationally or appropriately is difficult. There has been insufficient research on developing validated tools to assess prescribing especially in children. (6) Indicators or prescribing indicators are a method of assessing medication use that has been used extensively in adult prescribing for example the Screening Tool of Older Persons Prescriptions (STOPP)/ Screening Tool to Alert Doctors to the Right Treatment (START) criteria, developed in the UK and Ireland to identify potentially inappropriate prescribing in adults. (64) Prescribing indicators can be defined as a measurable element of prescribing for which there is evidence or consensus that it can be used to assess quality, and hence change in the quality of treatment provided. (10) They also provide a means for comparing the prescribing practices of countries or if an intervention, aimed at improving quality, has been effective. (11)

Ideally an indicator would be based on a thorough review of patient records with access to the full clinical and treatment history of the patient (11, 12), but this would be time consuming and could be extremely complex. A more realistic option is the development of prescribing quality indicators that can be

applied to automated databases containing information on dispensed drugs. These databases are available in most developed countries; they generally lack detailed information about the patient or indication for the prescription but they allow process based prescribing indicators to be applied and to assess aspects of prescribing patterns, safety and cost effectiveness. (11)

Although a number of indicator lists exist to assess appropriateness of prescribing, they are mostly aimed at the general population (13), or they only consider prescribing in older age groups, mostly the 65+ years age group. (14, 15) A number of indicator lists are relevant to children but are limited to particular medical conditions, for example asthma (4) or diabetes (16) or relate to medication use in secondary care e.g. in the emergency department. (17) Recently a set of indicators have been developed in France which are designed to assess quality of prescribing in children (91). In the UK a set of indicators have been designed to be used in auditing the quality of care in children in primary care. These indicators cover broad areas of care and include a number of prescribing indicators. (20)

### *1.2.3 The Delphi technique*

The Delphi technique is a consensus methodology used to generate agreement on topics that do not yet have empirical evidence to support future decisions or actions. (18) The technique was originally developed by the US military at the Research and Development (RAND) Corporation and has been frequently used in the validation of prescribing indicators in older people (19) and more recently in the development of prescribing indicators in children. (20)

## **1.3 Child health in Ireland and the Irish health care setting**

### *1.3.1 Child health*

Census figures for 2014 show that there were 1,072,222 children under 16 years in Ireland. Ireland has the highest proportion (22%) of young people

(aged under 15years) of all countries in the European Union. (21) The Growing up in Ireland study is a national longitudinal study of children commenced in 2007 and provides an overview of child health in Ireland. (22) The study took place over seven years and followed the progress of two groups of children: 8,000 9-year-olds and 10,000 9-month-olds. (22) Most children in each cohort were reported to be in good health in the study (98%). At birth and nine months, eczema or related skin allergies, followed by respiratory diseases and digestive allergies were the most commonly reported conditions. The most common health problem requiring contact with a medical professional was the common cold (47%), followed by chest infections (32%) and ear infections (17%). (23)

In the three year old cohort, just under 16% of children were reported as having at least one longstanding illness, condition or disability, in line with international research which shows between 10% and 20% of children will be affected by a long-term health condition. In the Irish cohort of three years olds asthma was the most commonly reported illness (5.8%) followed by eczema (3.9%) and digestive/food allergies (1.2%). Two-thirds of three-year-olds had received at least one course of antibiotics in the 12 months preceding the study interview. (24) In the nine year old cohort, 11% of children had a chronic illness or disability, of which respiratory conditions were the most common (46%) followed by mental and behavioural conditions (19%) and skin conditions (4%). Boys were more commonly affected by health problems than girls in each cohort. A socio-economic gradient in health was evident at three years. One in four children were reported as being overweight or obese at nine years old. (25)

### *1.3.2 Irish health care system*

Ireland has a mixed health care system, financed by public taxation and private expenditure. Public taxation contributes approximately 75% of total health care resources. (26) Private expenditure is comprised of direct out of pocket payments by patients and private health insurance companies. There are two broad categories of entitlement to public health services in Ireland; full or limited eligibility. Eligibility is based on means testing. Individuals who earn an income below a certain threshold receive a full

medical card under the General Medical Services (GMS) scheme. A full medical card entitles an individual and their dependents to free inpatient care, outpatient care including emergency department services and GP care. However a prescription charge of €2.50/item to a maximum of €25 per month applies. Approximately 38% of the overall population were entitled to a medical card with 34% of children eligible in 2014. (27, 28)

The remaining two thirds of the population have limited eligibility to public health services. Some individuals who do not qualify for a full medical card may be entitled to a free GP visit card, based on means, which entitles patients to free GP visits only. Childhood immunisations and maternity care are free for all citizens. Following the recent implementation of government policy, all children under 6 years, irrespective of means, are entitled to free GP care from 2015. For all individuals who do not hold a medical card, a €75/day hospital charge applies (to a maximum of €750/year) and a €100 charge for AE visits without a GP referral letter. For all individuals who do not hold a medical card, a number of schemes exist to limit medication charges. All citizens are eligible for the drugs payment scheme, which limits the cost of prescription medications to €144/month per family. Under the long term illness scheme (LTI) and high tech drugs (HTD) scheme some medications are free for individuals suffering from eligible conditions.

Private health insurance companies insure against the cost of inpatient treatment in public hospitals and private hospitals depending on the level of insurance cover purchased. In general, medication charges are not included, with only very limited cover for GP visits.

### *1.3.3 General Practitioners in Ireland*

General Practitioners (GPs) are self- employed and contracted by the state through the Health Services Executive (HSE) to provide primary care to individuals who hold medical cards or GP visit cards. Individuals including children who are not eligible for these services pay for GP care directly at approximately €45 to €60 per visit. Although there is no complete national register of GPs it is thought that there are approximately 2,954 GPs in Ireland (29) which at one GP for every 1,600 people is slightly lower than the OECD average of one GP per 1,200 people. (30)

#### *1.3.4 Paediatrics in General Practice*

There is considerable variation in Europe on what type of professional provides the first point of care for children. (31) In Ireland, this service is provided by GPs with a small number of directly accessible private paediatricians available in the community. It is estimated that young children consult their GP on average three times per year, with up to six additional visits in the first 18 months of life for immunisations. (32) Twenty percent of the consultations seen in general practice are paediatric with a wide variety of acute and chronic conditions managed. (33) Only 5% of paediatric consultations in general practice result in referral to secondary care; mainly for diagnostics (5%) and to the emergency department (15%). (33)

#### *1.3.5 Prescribing in General Practice*

GP's have considerable discretion in prescribing and can prescribe any medication once it has been licensed by the Irish Medicines Board (IMB). There is no routine auditing of GP prescribing practices, unlike in countries such as the UK. However, GPs can access administrative information on their prescribing to GMS patients through the HSE Primary Care Reimbursement Service (HSE PCRS) website and do receive feedback on their prescribing of some drugs e.g. benzodiazepines. (34) The Medicines Management Programme was developed in 2013 by the HSE to promote safe, effective and cost effective prescribing. A small number of preferred drugs have been identified which GPs are encouraged to prescribe under this programme. (35) To date, none of the preferred drugs are relevant to paediatric prescribing however the HSE's National Service Plan for 2015 aims to further develop the programme. (36)

#### *1.3.6 The PCRS database*

The PCRS is an administrative arm of the HSE which is responsible for reimbursing primary care providers including GPs and community pharmacists for the provision of health services under the GMS scheme. The PCRS database stores data on prescriptions and other health services,

originating in both primary and secondary care for all children who are eligible for free medical services. Eligibility for free medical care is established via means testing and therefore the data collected by the PCRS is not fully representative of the entire population of Ireland. Children who receive a prescription from a hospital specialist will have their prescription transcribed to a GMS prescription by their GP in order to avail of free medication. The PCRS does not record data on whether a prescription has originated in primary or secondary care.



## **1.4 Aims and Objectives**

The aim of this thesis is to develop explicit indicators of potentially inappropriate prescribing in children in primary care and to determine the prevalence of potentially inappropriate prescribing in children in Ireland.

- 1) To develop and validate a list of explicit prescribing indicators of potentially inappropriate prescribing in children in primary care using best available evidence and the Delphi consensus technique.
- 2) To apply these indicators to a national dispensing database in 2014 to determine the prevalence of potentially inappropriate prescribing in children. Secondary objectives will be to determine the cost of PIP in children and to explore the association between potentially inappropriate prescribing and gender.

## **1.5 Thesis outline**

This thesis is presented in five chapters. Chapter two outlines the current literature in relation to PIP and medication use in children in addition to methods of measuring PIP and the clinical impact of PIP providing a background to subsequent chapters. Chapter 3 describes the process of development of indicators of PIP. Chapter 4 details the application of the indicators to a dispensing database. Chapter 5 summarises the findings of the thesis and explores the implications for future research.

## **1.6 Ethical considerations**

Ethical approval for this research project was granted by the RCSI Research Ethics Committee in July 2014. (REC reference 000926). Written consent was required from all members of the Delphi panel to participate in the development of the indicators. Consent forms were stored securely in a locked filing cabinet in line with RCSI policy. All data will be destroyed in 5 years according to Data Protection Act 2008.

Individual patient consent was not required by the Research Ethics Committee as all patient data was anonymised and the research team did not have access to any patient identifiable information. Permission to access the PCRS database and data extraction was provided by the data controller Prof Kathleen Bennett, who supported this part of the study.

## **Chapter 2 Literature Review**

### **2.1 Introduction**

This chapter examines the relevant current literature in relation to potentially inappropriate prescribing in children in order to put this research project in context. Section 2.2 describes the literature search strategy. Section 2.3 provides a definition of PIP and discusses medication error versus PIP. Section 2.4 explores the clinical background to prescribing in children and examines off label and unlicensed prescribing. Section 2.5 discusses methods of measuring PIP. Section 2.6 reports the prevalence of PIP, section 2.7 explores the health of PIP and finally section 2.8 provides a conclusion to this chapter.

### **2.2 Literature search**

The aim of this literature search was to retrieve articles relating to PIP in children in primary care and to identify previously developed indicators of PIP.

#### *2.2.1 Information source and search strategy*

The search was conducted using PubMed and the Cochrane Database of Systematic Reviews. A combination of the following search terms were used using keywords and MeSH terms: appropriate; inappropriate; ineffective; unnecessary; optimal; suboptimal; medication; prescribing; prescribing indicator; quality indicator; guideline adherence; prescribing tool. ( Appendix 1) Records were kept of databases searched, terms used and results obtained. The reference lists of retrieved articles were manually searched for relevant articles where appropriate. The British National Formulary for Children (BNFc 2015) (37) and Irish Medical Formulary (IMF 2013) (38) provided dosing instructions, licensing information and clinical guidance. The websites of international regulatory authorities; Medicines and Health Regulatory Authority (MHRA) (39), Food

and Drugs Administration (FDA) (40) and European Medicines Agency (EMA) (41) were accessed as part of the initial search and as needed throughout the duration of the project. Tertiary sources of evidence were used to identify clinical guidelines including National Medicines Information Centre (NMIC) (42), BMJ Clinical Evidence (43) and BMJ Best Practice (44), in addition to the National Institute for Clinical Excellence (NICE) (45) and specialist groups such as British Thoracic Society (BTS) (46) and European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN). (47) Appendix 2 provides a summary of sources searched.

### *2.2.2 Study Selection*

Any studies, observational or interventional that focused on PIP in children were included. No time period or language limitations were applied. A PubMed search was performed in April 2014 and an updated search was performed in August 2014 and September 2015. Clinical guideline searches were under constant review. Studies were identified through the RCSI Library and retrieved using ENDNOTE software. Title and abstract were reviewed in terms of relevancy. Articles that were not deemed relevant and duplicate articles were deleted.

## **2.3. Potentially Inappropriate Prescribing (PIP)**

### *2.3.1 Definitions PIP*

Medicines are generally considered appropriate in an adult population when they have a clear evidence based indication, are well tolerated in the majority of patients and are cost effective. (2) Medicines or prescribing patterns that do not fit this description can be considered inappropriate. Inappropriate prescribing can also include mis-prescribing, under-prescribing and over-prescribing.(48) Mis-prescribing refers to the prescriptions of medication that significantly increases the risk of an adverse drug event (ADE). It includes prescribing that involves incorrect dose, duration, frequency or modality of administration. It also refers to the

prescribing of medications that are likely to result in clinically significant drug- drug or drug disease interactions. Under-prescribing refers to the omission of beneficial medication that are clinically indicated for treatment or prevention of disease. Over- prescribing describes prescribing medication for which no clear clinical indication exists. (48) For example, the use of cough and cold medications which contain carbocysteine in treatment of viral upper respiratory tract infections. (49) The term potentially inappropriate prescribing acknowledges the reality of prescribing in clinical practice, whereby the prescription of an inappropriate medication may be justified by the individual needs of a particular patient. (50) For example, sedating antihistamines may be considered inappropriate for young children, however they may in some instances, be useful in the treatment of insomnia relating to itch caused by eczema.

### *2.3.2 Rational prescribing*

Various definitions of appropriate prescribing exist in the literature, some of which link the construct of appropriateness to that of rationality. In 1985 a conference of experts on the rational use of drugs, convened by the World Health Organization (WHO) in Nairobi in 1985 defined that: “rational use of drugs requires that patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements for an adequate period of time”. (51) The term rational prescribing is more frequently used in the literature in the context of cost effectiveness and efficacy of health care. However, prescribing can be rational and yet inappropriate for example when correct reasoning leads to a poor outcome because of informational deficits or differences in perceptions or cognitive styles of the doctor and patient. Conversely, it has been found that irrational prescribing can be appropriate when flawed reasoning can lead fortuitously to an appropriate medication choice, for example an appropriate antibiotic choice may be made by a clinician despite flawed reasoning relating to susceptibility of an organism. (52) The concept of rational prescribing is also limited by the fact that it does not necessarily include patient’s views, experience and preferences which can influence prescribing. Inappropriate prescribing may also be influenced by factors

that transcend logic such as feelings, values, and intuition and prior outcomes. (53)

### *2.3.2 Beyond pharmacology*

A further understanding of appropriate prescribing beyond pharmacological rationality has been described in the literature in recent years. It has been argued that “good” or appropriate prescribing is a balance of the technical qualities of the medicine (its scientific and pharmacological properties-dose, formulation, evidence base etc), the patient’s wants and the greater good. (54) The correct balance will depend on the specific circumstances surrounding the prescribing act. Appropriate prescribing is seen as a decision making process rather than an outcome, as the outcome of a prescribing act is often subject to significant uncertainty that a prescriber cannot influence. (55) In this view, appropriate prescribing starts with a whole view of the patient (which includes his/her expressed wants, values, personal biography, social circumstances, symptoms and disease state), and involves the choice of a medicine (including the choice not to have one), based on a knowledge of its properties and likely effects on the patient, while also taking into account the likely effects, directly and indirectly on others. (55) In the 1990s, researchers strove to broaden the definition of appropriateness to encompass patient factors and arrived at a definition of appropriateness as “the outcome of a process of decision making that maximises net individual health gains within society’s available resources”. (53) Although not as often used in paediatric prescribing potentially inappropriate prescribing and potentially inappropriate medications are the terms that are frequently used in adult prescribing

### *2.3.3 Medication error*

Much of the current literature relating to prescribing in children discusses medication error rather than potentially inappropriate prescribing, although there is significant overlap between the concepts. The National Coordinating Council for Medication Error Reporting and Prevention in the US provide a broad definition of medication error as: “A medication error is

any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient or consumer. Such events may be related to professional practice, health care products, procedures and systems, including prescribing; order communication; product labelling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.” (56) Potentially inappropriate prescribing could be considered to be included within this definition of medication error.

## **2.4 Issues associated with prescribing in children**

This section provides detail on the pharmacological and pharmacokinetic factors which influence prescribing in children, in addition to some general practical considerations. The issue of off label and unlicensed use of medication is examined with a summary of the issues relating to paediatric medicines research.

### ***2.4.1 General considerations***

Prescribing in children offers specific challenges, which are different to those encountered with adult patients. The primary difference between adult and paediatric prescribing relates to the physiological changes occurring in the first 15 to 20 years of life which far outstrip those in the next 3-4 decades. (57) The effect of the physiological changes on the pharmacology and pharmacokinetics will be discussed in more detail in the subsequent section.

Another important factor which influences prescribing in children is the significant difference in the range of diseases of childhood compared to those of adulthood. In primary care the commonest type of childhood illness are disorders of respiratory system, followed by skin conditions, infectious diseases, gastrointestinal disorders and problems with the eyes and ears. (58)

A third important consideration when prescribing for children is that of drug formulation. Liquid formulations are required for children under 7 years and sometimes older due to difficulties with swallowing tablets. Altering the formulation of a medicine may affect the licencing status of a medication and lead to off label or off licence use. Some formulations have an unpleasant taste and should not be mixed with food or in a bottle. Crushing tablets or opening capsules alters the formulation of a medicine. Most formulations contain excipients such as alcohol, aspartame, gluten, sulphites, tartrazine, arachis oil and sesame oil, which may cause allergic reactions in some children. (59)

#### 2.4.2 Pharmacology and pharmacokinetics

Children are not just “small adults”, more physiological changes occur in the first 2 years of life and during puberty than in any other period of life. (57) This results in different child populations, ranging from premature babies, born as early as 24 weeks gestation, to 18-year old adolescents, all of which have specific prescribing requirements. The European Medicines Agency (EMA) classification of children is presented in Table 2.1.

Table 2.1 Paediatric populations and age ranges.

Definition of paediatric population	Age range
Preterm newborn	<37 weeks gestation
Term newborn	0-27 days
Infant and toddlers	28 days-23 months
Children	2-11 years
Adolescents	12-16/18 years.(16 years in the USA, 18 years in the EU)

The European Committee for Medicinal Products for Human Use (CHMP) further subdivides the age group “children” (2–11 years) into “preschool children” (2–5 years), and “school children” (6–11 years) to



more precisely reflect the children's ability to accept and use different dosage forms. However, the classification of the paediatric population into age categories is to some extent arbitrary because children of the same chronologic age may still develop at different rates. (60) Table 2.2 on the following page details the different considerations that are important in drug metabolism in children. (59)

Table 2.2 Summary of developmental-dependent changes in drug handling

System	Age-related trends	Pharmacokinetic implications	Clinical implications
<b>Gastrointestinal</b>	<p><b>Neonates and young infants:</b> reduced/irregular peristalsis with ↑gastric emptying time.</p> <p><b>Neonates:</b> ↑ intragastric pH (&gt;4) relative to infants.</p> <p><b>Infants:</b> enhanced lower GI motility</p>	<p><b>Neonates and young infants:</b> potential↓ rate of drug absorption</p> <p><b>Neonates:</b> potential↓ or ↑absorption of certain medicines</p> <p><b>Infants:</b> potential↓ retention of suppository formulations</p>	<p><b>Neonates and young infants:</b> potential delay in onset of drug action following oral admin.</p> <p><b>Neonates:</b> ↑absorption of acid labile medicines e.g. penicillin &amp; ↓absorption of weak acids e.g. phenobarbitone</p> <p><b>Infants:</b> potential↓ absorption from rectally administered medicines</p>
<b>Skin &amp; Mucosa</b>	<p><b>Neonates and young infants:</b> greater cutaneous perfusion, enhanced hydration and larger ratio of total body surface area to body mass</p>	<p><b>Neonates and young infants:</b> potential↑ percutaneous drug absorption. ↑relative exposure of topically applied medicines compared to adults</p>	<p><b>Neonates and young infants:</b> ↑bioavailability and potential toxicity from systemic absorption of topical medicines. Need to ↓ amount of medicines applied topically e.g. corticosteroids</p>
<b>Body Compartments</b>	<p><b>Neonates and infants:</b> ↓fat, ↓muscle mass, ↑extracellular and total body water spaces</p>	<p><b>Neonates and infants:</b> ↑apparent vol. of distribution for medicines distributed to body water spaces, and ↓ apparent vol. of distribution for medicines that bind to muscle and or fat</p>	<p><b>Neonates and infants:</b> medicines with high vol. of distribution can accumulate in the body and cause toxicity. In general, the vol. of distribution of medicines tends to be↑ in infants, which ↓to adult levels during childhood e.g. gentamicin.</p>
<b>Plasma protein binding</b>	<p><b>Neonates:</b> ↓concentrations of albumin and α1-acid glycoprotein with ↓binding affinity for albumin</p>	<p><b>Neonates:</b> ↑unbound concentrations of highly protein-bound medicines and potential ↑level of free drug in the body</p>	<p><b>Neonates:</b> Potential for toxicity in neonates e.g. phenytoin</p>

Table 2.2 Summary of developmental-dependent changes in drug handling contd.

System	Age-related trends	Pharmacokinetic implications	Clinical implications
<b>Drug metabolizing enzyme (DME) activity</b>	<b>Neonates and young infants:</b> immature and discordant patterns of DME development	<b>Neonates and young infants:</b> ↓plasma drug clearance early in life with in apparent↑ half-life ( $t_{1/2}$ )	<b>Neonates and young infants:</b> ↑drug dosing intervals and/or ↓maintenance doses e.g. theophylline, morphine
	<b>Children 1-6 years:</b> apparent ↑activity for selected DMEs over adult normal values	<b>Children 1-6 years:</b> ↑plasma drug clearance (i.e. reduced elimination $t_{1/2}$ ) for specific pharmacological substrates of DME	<b>Children 1-6 years:</b> for selected medicines may need to↑ dose and/or ↓interval in comparison to usual adult dose e.g. carbamazepine, phenytoin,
<b>Renal Drug excretion</b>	<b>Neonates and young infants:</b> ↓glomerular filtration rates (first 6 months) and active tubular secretion (first 12 months) with adult values attained by 24 months	<b>Neonates and young infants:</b> accumulation of renally excreted medicines and/or active metabolites with ↓plasma clearance and ↑elimination $t_{1/2}$ , greatest during first 3 months of life	<b>Neonates and young infants:</b> ↑drug dosing intervals and/or ↓maintenance doses during the first 3 months of life e.g. ibuprofen, penicillin

### *2.4.3 Off label and unlicensed prescribing*

A significant consideration in prescribing for children is the lack of scientific evidence on the safety and efficacy of pharmaceuticals in paediatric populations on which to base prescribing decisions. Off label prescribing is defined as prescribing outside the specifications of the “Summary of Product Specification” (SPC). (61) Off label prescribing can be defined according to nine categories, including

- ◁ prescribing a drug withdrawn from the market
- ◁ contraindications
- ◁ different indications
- ◁ age
- ◁ different dose of administration
- ◁ higher or lower dose than recommended
- ◁ inadvisable co-prescribing

Unlicensed drugs are those with no valid marketing authorisation (MA). (61) This can therefore mean the use of a medicine or dosage form of a medicine that has not been approved for use in a particular country, although it may be licensed in another jurisdiction. (62) Confusingly, “unlicensed use of medicine” can include the use of a medicine that has a valid marketing authorisation but is prescribed or administered outside the terms of the authorisation. It is important to note that exact definitions vary between authors. (63)

Only one-third of all medicines approved by the EMA over the period of 1995 to 2005 were licensed for use in children. (60) In the EU it is estimated that 50% of the medicines used in children have only been studied in adults, and not necessarily for the same indication (41) A large recently published prospective survey on paediatric prescribing in 46 general practices in France found that 37.6% of children who were prescribed a medication were exposed to  $\geq 1$  off label medication and 6.7% were exposed to  $\geq 1$  unlicensed medication. (61) Studies looking at off label prescribing using prescription databases revealed higher levels of off label prescribing ranging from 13.5% to 62%, with some of the heterogeneity of these results explained by differences in definitions of off label prescribing. (61) A review of studies of off label and unlicensed prescribing in children showed that ranged from 3.3.% to 56% of prescriptions in the

community; studies in hospital settings show higher levels of off label prescribing with some in neonatal units demonstrating levels of up to 100%. (63) The types of drugs most commonly used off label in children up to 18 years in a community setting were identified in a large cohort study of three European countries to be topical, inhaled and systemic corticosteroids, oral contraceptives, and topical or systemic antifungal drugs. (64)

#### *2.4.4 Off label and unlicensed prescribing and adverse drug events*

Off label prescribing has been widely observed in children, and the administration of a drug outside the clinical conditions assessed during clinical trials may result in adverse drug reactions (ADR) or adverse drug events (ADE).(61) It has been argued that children could be considered unknowing participants in informal and uncontrolled experiments when they are prescribed unlicensed and off label medications. (65) A high rate of unlicensed medication use has implications in terms of the prediction, avoidance, detection and treatment of ADRs. Safety data for an approved medicine that is being used off label may not always be applicable or relevant because it relates only to the use of medicine as specified by the manufacturer. Unlicensed medication may not have any safety data detailed in the marketing authorisation. (63)

Only 1.5% of patients with off label prescriptions suffered an ADE compared to 1.0% in other patients, which did not reach statistical significance in a large French prospective study. (61) This result is in contrast with a previous similar study in France performed in the early 2000s which found that off label prescribing was highly prevalent (42%), and significantly associated with ADE occurrence.(RR 3.44; 95% CI 1.26-9.38). (66) The authors note that many of the ADEs in the earlier study related to antibiotics and vaccines which were prescribed less frequently in the more recent study. (61)

The relationship between ADE and the use of off label and unlicensed medications in primary care remains conflicted. A recent UK prospective cohort study which examined the unplanned admissions to a paediatric hospital, found that off-label and unlicensed medicines were more likely to be implicated in an ADR than authorized medicines (relative risk 1.67, 95% CI 1.38, 2.02, P<0.001).

However, the results were no longer statistically significant when oncology patients were excluded from the study. (67) A much older prospective study in Canada found an ADE incidence of 11.1% in the study population and an increased relative risk of probable or definite ADE's in patients receiving a total daily dose of medicine above that recommended by the manufacturer.( 7% vs 4.3%;RR 1.63; CI 1.23-2.16; p<0.001). (68)

Studies in the inpatient paediatric setting tend to demonstrate higher levels of ADEs associated with unlicensed medication use. In one large UK based case control study the records of a total of 10,699 medicine courses administered to 1,388 patients were examined. The odds ratio (OR) of an off label or unlicensed use medicine being implicated in an ADR compared with an authorized medicine was 2.25 (95% confidence interval (CI) 1.95 to 2.59). (69) Nevertheless, the authors of a narrative review of the literature on the relationship between off label and unlicensed medicine use in children conclude that there is still a lack of clarity in the association due to the fact that studies to date have been small with varying methodologies and inexact definitions. (63)

Despite concerns about ADEs and fear of litigation by practitioners, off label or unlicensed prescribing is legal, can be used when necessary and may occasionally constitute best practice. (70) (71) For example the use of salbutamol metered dose inhalers with spacers at doses of 2 to 10 puffs for acute asthma attacks is in keeping with best practice (37) although the SPC and patient information leaflet (PIL) state 100 or 200 micrograms (one or two puffs) is the therapeutic dose and on demand use should not exceed four hourly. (72) Indeed, the American Academy of Paediatrics (AAP) explicitly states that "labelling is not intended to preclude practitioners from using their own judgement including current evidence in choosing to prescribe off label", (71) a view echoed by the Royal College of Paediatrics and Child Health (RCPCH) who acknowledge that the informed use of some unlicensed medicines or licensed medicines for unlicensed applications is necessary in paediatric practice. (73)

#### *2.4.5. Reasons for off label prescribing*

There are a number of reasons including technical, ethical and financial, identified in the literature that are thought to contribute to the difficulties in doing research in children which lead to the current situation of high levels of off label and unlicensed medication use.

Children, foremost the youngest, are often excluded from premarketing clinical trials unless the medicine is specifically developed for this population, limiting access to age specific information on dose recommendations, efficacy and risks. It is difficult to recruit sufficient numbers of relatively homogenous children at relevant age groups. (57) Formulations suitable for children have been difficult to develop. (59) Ethical concerns are often raised as a barrier to conducting trials in children with risks perceived by parents to include side effects of new treatments, being randomised to a less effective treatment and inconveniences such as additional blood tests, visits to hospital and extra time. (65) Moreover, the relatively small market for paediatric drugs conspires against adequate investment in children's medicines by the pharmaceutical industry. (57)

Changes to the way medicines are developed mean that since 2007, when the Paediatric Regulation was enforced; every new medicine under development in Europe must have a paediatric investigation plan. (41) The objective of the EU regulation is to improve the health of children in Europe by:

- ◁ Facilitating the development and availability of medicines for children aged 0 to 17 years
- ◁ Ensuring that medicines for use in children are of high quality, ethically researched, and authorised appropriately
- ◁ Improving the availability of information on the use of medicines in children, all without subjecting children to unnecessary trials or delaying the authorisation of medicines for use in adults

In addition to these measures, the regulation aims to improve communication and transparency of paediatric information by including in the prescribing information data from all completed paediatric studies (including negative studies). (74) Similar regulations have previously been instituted in the US namely the Best Pharmaceuticals for Children Act and The Paediatric Research Equity Act. (75)

#### *2.4.6 Specialist prescribing*

Occasionally the marketing authorisation or licensing conditions of a medication may demand that the prescribing clinician is experienced in the treatment of the indicated condition and the side effects of the medication for example roaccutane. The BNFC cautions that roaccutane should be prescribed “under expert supervision”. (37) In Ireland, it is estimated that up to 38% of public prescriptions issued across all ages are initiated by specialists in secondary care. (76) When primary care reimbursement or dispensing data is used to calculate off-label or unlicensed use of medication it is not possible to determine whether a specialist or primary care physician has initiated the prescription and therefore, medications may incorrectly be framed as off licence or inappropriate.

### **2.5 Measurement of PIP**

This section discusses the advantages and limitations of various methods of measuring PIP in general, so as to inform measurement of PIP in children.

#### *2.5.1 Overview of methods of measurement*

Ideally assessment of prescribing would be based on a thorough review of patient records with access to the full clinical and treatment history of the patient (11, 12) but this can be time consuming and extremely complex. A more realistic option is the use of explicit indicators that can be applied to databases containing information on dispensed drugs. These prescribing databases are available in most developed countries; they generally lack detailed information about the patient or indication for the prescription but they allow process-based prescribing indicators to be applied, allowing for assessment of aspects of safety, cost-effectiveness and variation in prescribing. (11) Of note, such indicators applied to a prescribing database do not take in to consideration the patient’s views or experience.

Many different tools to assess appropriateness of prescribing have been developed in recent years mainly based on prescribing in adult populations. Despite showing some differences in structure and content, these tools can be



grouped into three categories; implicit (judgement-based) and explicit (criterion-based) tools and those which show a combination of both approaches. (77) A recent systematic review of published prescribing indicator tools in adults found 46 different tools (28 were explicit, 8 were implicit and 10 were mixed) to assess inappropriate prescribing. (77) The tools were developed using a wide variety of methodologies and clinical validation.

### *2.5.2 Explicit Indicators*

Explicit indicators are specific statements of appropriateness of prescribing that are generally drug or diseases orientated and commonly focus on drugs to avoid. (8) “Drugs to avoid” lists include medications that should be avoided in any circumstance, doses that should not be exceeded, and drugs that should be avoided in patients with specific conditions or disorders. These criterion based tools can be applied to large prescription or dispensing databases with little or no clinical information available regarding diagnosis or investigations.

Explicit tools including the Screening Tool of Older Person's Prescriptions (STOPP) and Screening Tool to Alert doctors to Right Treatment (START) (78) and the Beers criteria (50) are usually developed from published reviews, expert opinion and consensus techniques such as the RAND appropriateness method, the Delphi technique and the Nominal Group Technique (NGT). Explicit criteria are limited in that they do not address individual differences among patients or the complexity or appropriateness of entire medication regimens. (79)

Furthermore they need to be regularly updated in line with evidence and country specific adaptation are necessary where countries differ in their guidelines, standards and approved medications. The advantages of explicit tools are lower cost of application and a high degree of fairness. (80)

The Beers criteria are the most commonly used criteria for measuring PIP (81) They were originally developed in the US in 1991 for use in nursing home patients and consist of 19 medications or medication classes to avoid generally in the elderly and 11 criteria describing doses, frequencies or durations that should not be exceeded. Updates in 1997 and 2003 extended the relevant population to include all adults aged 65 and older, regardless of healthcare setting. (15) The list was updated in 2012 and again in 2015 and now lists 34

medications/medication classes to be avoided in the elderly in general, 14 medications to be avoided in certain conditions and 5 medications to be used with caution in older adults. (82) The Beers Liste and the Maio Criteria are country specific adaptations for Germany and Italy respectively. (83, 84)

Many explicit tools used to assess appropriateness of prescribing do not include under-prescribing which represents an important aspect of inappropriate prescribing. (77) One of the few criteria which do consider omissions of prescribing or under- prescribing are the START criteria, developed in Ireland in 2007 which consist of a list of 22 prescribing indicators to identify prescribing omissions in elderly people. (78) The START criteria can be combined with the STOPP criteria, a list of 65 criteria of potentially inappropriate prescribing in the elderly. A comparative review of explicit criteria for measuring PIP concluded that STOPP/START criteria appear to be the most universal criteria and are advantageous in terms of being up to date with clinical evidence, easy to use and flexible across continents. (81)

### *2.5.3 Implicit indicators*

In contrast to explicit tools, implicit tools are based on clinical judgement and are not specific to particular diseases or drugs. To apply these criteria, a clinician uses patient specific information in the context of published literature to make a judgement about the appropriateness of medication. (8) Implicit tools are therefore judgement based and patient specific and can often depend on the user's knowledge, experience and attitude. They also take into account patient preferences however they can be time consuming and have low reliability and are used less frequently than explicit criteria. (8) The Medication Appropriateness Index (MAI) is an example of an implicit tool. (85) The MAI developed in the USA in 1992 is one of the most commonly used implicit criteria. It consists of ten questions used to assess medication appropriateness which are answered using a three point Likert scale. Clinical judgement is required to assess the criteria but definitions and explicit instructions are available to standardise the process. The MAI is mainly used in hospitalised older people and has found to be associated with improved medication appropriateness over the duration of a hospital stay however its reliability has found to be lower when

assessed by researchers other than the initial authors. (86) Table 2.3 summaries the differences between implicit and explicit indicators.

Table 2.3 Summary of characteristics; explicit versus implicit criteria.

Criteria	Advantages	Disadvantages
<b>Explicit</b>	Based on literature and expert opinion	Need to be updated regularly
	Reliable and reproducible	Not generalisable to other countries
	Can be applied to large samples	Do not include co- morbidities
	Can be applied without clinical knowledge	Delphi technique means important items may be omitted if consensus not reached
<b>Implicit</b>	Incorporate clinical judgement	Clinical knowledge needed to apply
	Generalisable internationally	Subjectivity may lower reliability
	Sensitive to differences between patients	Time consuming to apply

#### 2.5.4 Validity of indicators

To fulfil their purpose indicators should be valid i.e. they measure what they claim to measure. Four aspects of validity should be considered. (11)

- < Face validity
- < Content validity
- < Concurrent validity
- < Construct validity

Face validity is related to the indicator's relevance, credibility and acceptability. It can be assessed using different consensus methods. (87) Delphi studies and the RAND appropriateness method have been used for this purpose in addition to the Nominal Group technique (NGT).(88) (13) It is recommended that face validity is assessed in the target groups who are going to use the indicators in

practice, including both those who measure quality and those who have their performance measured.(11)

Content validity implies that indicators should be evidence- based, in accordance with updated recommendations and current guidelines. The content validity is related to the initial steps of developing indicators, often involving discussion and consensus among experts. The link between indicators and the relevant evidence should be documented and explicit. This is particularly important when process indicators are used as substitutes for outcome indicators to ensure that meeting the indicator can be expected in reality to improve patients' health. (89)

Concurrent validity is established by comparing a proposed indicator to other quality measurements. Preferably this should be a “gold standard”, a reference measurement widely accepted as the best available. It is sometimes possible to create such a standard by assessing detailed clinical data. (90)

Construct validity relates to the need for indicators to relate to theoretical concepts or constructs of quality such as treatment appropriateness, rational therapy and cost effectiveness. (11)

#### *2.5.5 Existing explicit indicators in children*

A small number of explicit indicators relating to the care of children in the community were found during the literature search and are summarised in Table 2.4. The Paediatrics: Omission of prescriptions and inappropriate prescriptions (POPI) tool developed in France in 2014 provides a list of 104 explicit criteria for both hospital and community prescribing in children. (91) In a two round Delphi process, a panel of 16 experts were asked to agree with statements on prescribing using a 9 point Likert scale. The authors selected health problems requiring either drug intervention, or no pharmacological intervention whatsoever (i.e. treatment in such cases would be considered as inappropriate). This is the first list or tool of explicit prescribing indicators to include omissions of prescriptions (25 indicators) in addition to inappropriate prescriptions (79 indicators). However, the prescribing criteria were developed by hospital based

pharmacists and paediatricians without the input of general practitioners. Clinical information such as diagnosis would be required to implement these indicators.

Primary care quality indicators for children have also recently been developed by a research group in the UK in response to the lack of Quality Outcomes Framework (QOF) incentives relating to the assessment of the quality of care to children.(20) QOF is a financial incentives scheme which rewards high quality clinical practice. A multi-step development process including the nominal group technique to identify relevant areas of care, a systematic review of UK guidelines to identify recommendations and a two round Delphi process using a 10 member panel was used to develop indicators of quality of care for children in primary care. General practitioners were the only stakeholders involved in the process of development. The indicators covered broad areas of care including routine acute care, recognition and management of chronic illnesses and child protection and developmental assessment. Six of thirty five indicators developed in this study relate to prescribing to children in primary care. These indicators were developed with the aim of applying them to computerised general practice systems for the purposes of audit. Detailed clinical information would be required to implement many of these indicators.

Researchers in the Netherlands have examined the quality of out of hours care provided in general practice to both adults and children using an explicit list of indicators for prescribing and referring to secondary care. Of this set of 24 indicators, 3 indicators related specifically to prescribing in children based on the availability of clinical information. (92)

Some prescribing indicator lists although developed for use in adults in primary care include some indicators which are relevant to prescribing in children. For example the indicator “prescription of a long acting beta agonist inhaler to a patient with asthma who is not also prescribed and inhaled corticosteroid” is relevant in the management of asthma in both children and adults. (93) A UK based research group developed a list 35 prescribing indicators in 2011 for use in primary care, which was updated to 56 indicators in 2014. This list includes 4 indicators which are relevant to prescribing in both adults and children.(13, 94)

One of the earliest studies identified in the literature search described the development of 17 explicit indicators of prescribing in children in primary care. (95) These indicators were based on drug choices that were likely to be known as contraindicated in children and many of the indicators are still relevant today. 167 indicators of quality of care were developed in one of the most comprehensive studies of care of children in ambulatory setting in the USA in 2007. (5) Although the vast majority of these indicators related to process of care, 35 related to medication use, approximately 10 of which could be described as explicit prescribing indicators and applicable to a prescribing or dispensing database without clinical information.

Indicators have also been developed for use in high acuity conditions seen in the paediatric emergency department such as meningitis, anaphylaxis and diabetic ketoacidosis. (17) These indicators focused on emergency department processes and outcomes rather than specific prescribing practices. Another recently published study has focused on the development of criteria for prescribing medicines safely in children. These indicators relate to the process of prescribing in children, e.g. the inclusion of patient age and weight on all prescriptions. (96) Other indicator lists have been developed relating to the care of particular conditions in children e.g. diabetes (16) and mental health. (97) The indicators in these studies focus on structures of health care and outcomes of care, neither of these indicator lists included any specific prescribing indicators.

Table 2.4. Existing explicit indicators in children

Study	Country	No. of criteria	Target group	Setting	Method of development	Description	Aspect of prescribing appropriateness
POPI 2014	France	79	Children	Primary and secondary care	2 round Delphi process	79 prescribing indicators to detect omission of prescriptions or inappropriate prescriptions in the treatment of various diseases /conditions	Under-prescribing, Over-prescribing, drug choice, dosage, duration of treatment, drug- drug interactions, drug- food interactions
Gill 2014	UK	35	Children	Primary care	Nominal Group Technique, systematic review of guidelines and RAND consensus method	35 indicators of which 7 were prescribing indicators. Divided into 3 subgroups of routine care chronic illness and child protection and development	Drug choice, under-prescribing, over-prescribing, drug monitoring, drug-disease interactions
Giesen 2007	The Netherlands	24	Adults and children	Out of hours primary care	Guideline based and expert opinion	24 Indicators of choice of antibiotic in different types of infection.	Drug choice
Spencer 2014 (update of Avery 2011)	UK	56(34)	Not specified	Primary care	Systematic review, RAND consensus method and eDelphi method	56 prescribing indicators of hazardous prescribing for a range of indications, hazardous drug-drug combinations and inadequate laboratory test monitoring. 4 indicators relevant to children and adults.	Drug choice, drug- drug interactions, drug monitoring.
Mangione-Smith 2007	USA		Children	Ambulatory care	Guideline review and modified Delphi method	175 indicators for the continuum of care functions incl. screening, diagnosis, treatment, and follow up. 35 indicators relate to medication use approx 10 are explicit prescribing indicators.	Drug choice, drug interactions, under and over prescribing, duration of treatment, drug monitoring,
Catford 1980	UK	17	Children	Primary care	Literature search	17 drug groups or drug combinations categorized as hazardous or undesirable	Drug choice

## **2.6 Prevalence and incidence of PIP**

Prevalence and incidence of PIP are discussed in the following section with reference to PIP in adults and children where available in the literature.

### *2.6.1 Definitions*

Prevalence studies provide evidence on the number of people with a specified outcome at a given time point, and can be used to determine if a particular problem exists within a healthcare setting. Incidence studies concern the rate at which new instances of an outcome occur and may provide evidence as to why new instances occur. (98)

### *2.6.2 PIP in adults in the community*

PIP in adult populations has been well studied in the US and Europe. Rates vary widely depending on the instrument of measurement used and the healthcare setting in which it is measured. In Ireland, PIP has been examined in a number of population groups using explicit prescribing indicators. PIP as measured using the STOPP criteria in older adults in a community setting in Ireland was found to be 36%. (9) Using the Prescribing Optimally in Middle Aged People's Treatment (PROMPT) criteria, PIP in middle aged adults in Ireland was found to be 42.9%. (99) A recently published study on prescribing in >65year olds in primary care in Ireland found that the prevalence of PIP using the STOPP criteria rose from 32.6% in 1997 to 37.3% in 2012. (100) Globally the WHO estimates that half of all medications are inappropriately prescribed or purchased to adults and children and that more than 50% of all countries do not implement basic policies to promote rational use of medications. (101)

### *2.6.3 PIP in children in the community*

The WHO has long recognised the importance of the provision of essential medicines in primary health care. (101) In 1978, the WHO Alma Ata conference identified the availability, quality and rational use of essential medicines as one of the components of primary health care. This led to the development of the highly successful Model of Essential Medicines List; however it was not until 2007 that the first Model List of Essential Medicines for Children was made



available. (102) However, rational prescribing however has been inadequately studied in paediatric populations to date in both low and high income countries. (6) Only two of the studies presented in Table.2.3 have been applied clinically to determine prevalence of PIP. “Inappropriate prescribing” only became a MeSH term in 2011, but there has been an interest in measuring the quality of care provided to children in general practice since the early 1980’s. The authors of one of the earliest studies on this topic, found that only 1% of prescriptions could be called into question while 42% of the doctors used drugs that were considered harmful or hazardous. (95) Deficits in the quality of ambulatory care delivered to children in the United States were highlighted in a large retrospective study that applied 175 quality indicators to the medical records of 1536 children. The indicators were categorized according to type of care (acute, chronic, preventative) function of care (screening, diagnosis, treatment, follow-up) mode of care (encounter, medication, physical examination, treatment, immunization, laboratory testing, radiography) and type of clinical area (e.g. acne). The authors found that children received only 46.5% of the indicated care. Of the 34 indicators which related to the use of medication, the authors found an adherence rate of 81% to these indicators.(5) A large retrospective survey of prescribing practices in children under 5 years of age (n=2,400 patient encounters) in the resource limited setting of The Gambia in West Africa found over-prescription of antibiotics (63.4% of patient encounters) and substantial usage of micronutrients (21.7% of patient encounters) despite a lack of evidence based guidelines. (103) The remaining indicator lists described in section 2.5.5 have not yet been applied to clinical databases

A large retrospective cohort study of drug use in over half a million children in primary care across three European countries (UK, Italy and the Netherlands) found the most commonly prescribed drugs to be anti-infectives, dermatological agents and respiratory drugs. The prevalence of the most commonly prescribed drugs was highest in children under 2 years. Although this study used population based data on primary care prescriptions and did not examine PIP, the authors found that topical inhaled and systemic steroids, oral contraceptives, and topical or systemic anti-fungals were most commonly used off label. (64) No studies were found in the literature that directly examine the prevalence of potentially

inappropriate prescribing in children in primary care. Given that the most commonly prescribed medications to children in Europe are anti-infectives, dermatologicals and respiratory drugs, I will now discuss these topics in more detail in the subsequent sections.

#### *2.6.4 Anti-infectives*

Antibiotics are the most commonly prescribed medication given to children. (104) In the UK there are around 6 million antibiotic prescriptions for children each year, the majority of which are for upper respiratory infections which are most likely viral in origin. (104) The European Surveillance of Antimicrobial Consumption (ESAC) collects comparable and reliable data on antibiotic consumption in the general population however surveillance of antimicrobial consumption in children is poor and not systematic. (105)

The majority of antibiotic prescribing takes place in primary care and it has been estimated that nearly 50% of antibiotic prescriptions for children given by primary care physicians are unnecessary. (106) Variation in the prescription of antibiotics within and between countries has been identified with children in Italy being four times more likely to receive antibiotics than children in the UK, Denmark and The Netherlands. (107) Similar results were reported in a review of published surveys of antibiotic prescribing in the outpatient paediatric population in Europe and the North America between 2002 and 2005. This study showed a seven fold difference between the lowest prescribing European country, the Netherlands (200-400 prescriptions/1000 children/year) and a high prescribing country such as Italy (900-1300 prescriptions/1000 children/year). (108) An update of this review in 2010 again showed that Italy and Canada had the highest prescription rates in contrast to The UK and the Netherlands. (107) In the UK, paediatric community antibiotic prescribing declined by over a third in the late 1990's and early 2000's following an international trend but has now increased again by almost 10% since 2003. (105)

Data on paediatric primary care antibiotic prescribing is lacking in Ireland. A multi-national cross sectional observational study using ESAC data showed that adult antibiotic prescribing in Ireland had decreased slowly since 2009 however, high seasonal variation is still apparent which, in other countries, is also

associated with high antibiotic consumption (France, Greece, Portugal and Italy). (109) A recent Irish study of antibiotic prescribing in primary care which looked at guideline adherence and unnecessary prescribing identified that respiratory illness accounted for 22.63% of consultations; the majority, 57.66% of these received an antibiotic prescription. Children aged 4–14 years had the highest consultation rate where a respiratory symptom/diagnosis was recorded (33.94%) but interestingly children aged from 0–14 years had the lowest percentage rate of antibiotic prescribing when presenting with respiratory symptoms (52.25%). (110)

#### *2.6.5 Respiratory drugs*

In the above mentioned cohort study of drug use in children across the UK, the Netherlands and Italy it was found that the prevalence rate for respiratory drugs among children under 2 years was 30%, decreasing to 21% in 2-11 year olds and reducing further to 10% in adolescents' age 12-18 years. (64)

The well-established and accepted British Thoracic Society (BTS) guidelines provide a step by step guide to the management of asthma in children under and over 5 years. (46) The ratio of corticosteroid to bronchodilator prescribing is used as a marker or indicator of the quality of asthma prescribing in general practice. (111) (93) It can be calculated for individual general practices rather than individual patients. The corticosteroid to bronchodilator ratio reflects the rate of preventative to reliever medication and a low ratio is considered to indicate “poorer” prescribing because less corticosteroid is prescribed relative to bronchodilator. (93) A large retrospective analysis of primary care prescribing data in the UK from 2001 to 2006 demonstrated, in line with other studies, a reduction in the proportion of children prescribed high and unlicensed dose inhaled corticosteroids (ICS) and a low rate of long- acting beta- agonist (LABA) monotherapy. (112) The authors concluded that prescribing practices reflected a growing awareness of and adherence to guideline recommendations. Nonetheless a small study in Northern Ireland published in 2014 reported that 67% of patients (age 5-35 years) who were prescribed a combination ICS/LABA did not receive an ICS in the previous six months contrary to current BTS guidelines. (113)

### *2.6.6 Dermatologicals*

Childhood eczema or atopic dermatitis is becoming increasingly common, affecting approximately 13.5% of school children in Ireland. (114) In the aforementioned study of drug in three European countries 30% of children under two years were prescribed dermatological drugs, reducing to 17% of children age 2-11 years. The therapeutic class with the highest prevalence of use among the dermatological drugs were topical corticosteroids, emollients and barrier creams. (64) The evidence base for many commonly used treatments for atopic eczema is poor but there is consensus that the mainstay of treatment is regular emollient use with short term topical corticosteroids for flare ups. (115) Children are susceptible to the effects of corticosteroids, potent topical corticosteroids should not be used in children under 12 months and very potent topical corticosteroids should be avoided in all children.(BNFc) A large community based study in Scotland of 25,484 children  $\leq 6$  years found that almost a quarter of all young children received topical corticosteroids over a 17month period, half of these children did not receive an emollient and a substantial number received potent topical corticosteroids. (116) A recognised limitation of this study was the possibility that all emollient use was not captured as emollients can be purchased over the counter without prescription. The authors note however that over the counter use of emollients is likely to be infrequent as prescriptions are free of charge.

## **2.7 Impact of PIP**

This section briefly discusses the health impact of PIP in children specifically examining the impact of overuse of antibiotics and the impact of poorly controlled asthma.

### *2.7.1 Impact of PIP and medication error*

Although no studies were found in the literature that directly examines the relationship between PIP and health or economic outcomes in children, there is a larger body of evidence in existence which examines the impact of medication

errors. Medication errors are common in paediatric patients; 5-27% of all paediatric medication orders result in a medication error depending on the location of care, inpatient or intensive care. (56) Paediatric medication incidents have been extensively explored in the hospital setting but less so in primary care. (117)

Children are at particularly high risk of medication errors and it is thought that medication errors are three times more likely in children than in adults and these errors are frequently harmful. (117) For children 1% of all medication errors carry significant potential for harm, with 0.24% of errors causing actual harm. (118) Many factors contribute to the risk of medication error, including weight-based dosing; the need for stock medicine dilution; decreased communication abilities of children; an inability to self-administer medications; and the high vulnerability of young, critically ill children to injury from medications, particularly those with immature renal and hepatic systems. (117) The need for weight based dosing creates many opportunities for error including 10-fold dosing errors resulting from misplaced decimal points.

An analysis of national family practice related paediatric safety incident reports based in the UK over the years 2003 to 2012 found that prescribing errors accounted for the majority of medication related incidents (53.8%) and that one third of medication related incidents resulted in harm. Moderate or severe harm was more likely to be due to prescribing or dispensing incidents with overdosing being a recurring theme. (119)

### *2.7.2 Impact of antibiotic overuse*

Antibiotic overuse is considered a major public health problem, one of the most important factors in the emergence of antibiotic resistance in the treatment of bacterial pathogens is selection pressure from microbial agents. (106) Antibiotic resistance is associated with high social costs for communities and severe consequences such as failure to respond to treatment, prolonged illness, increased length of hospitalisation and greater risk of complications and mortality. (120)

As antimicrobial resistance increases, the need for more specific and inevitably more expensive and sometimes more toxic antibiotics arises, placing a growing demand on healthcare. (103) Recent studies have suggested the individual child can host resistant pathogens after antibiotic use for up to 3 months, which is sufficient to sustain high levels of antibiotic resistance in the general population. (121) Centralised paediatric resistance data is not available but several studies have noted the strong relationship between antibiotic overuse and resistance. Southern and eastern European countries with antibiotic prescribing rates such as France Italy Hungary Turkey and Cyprus were associated with a high prevalence penicillin resistant streptococcus pneumonia (PNSP) and/or erythromycin resistant streptococcus pneumonia (ENSP). (107)

### *2.7.3 Impact of poorly controlled asthma*

Asthma control falls short of guideline recommendations in large proportions of children with asthma worldwide. Only a small percentage of children with asthma reach the goals of good asthma control set out by Global Initiative for Asthma (GINA). (122, 123) Studies report high frequencies of sleep disturbances, emergency visits, school absence and limitations of physical activity due to asthma. (112) There is evidence of underuse of inhaled corticosteroids even in children with moderate or severe persistent asthma and over-reliance on short-acting beta-agonist rescue medication. (124) Despite the wide dissemination of asthma management guidelines and recommendations for the appropriate use of inhaled corticosteroids to reduce morbidity and mortality, adherence to guideline recommendations is low. (112) Studies show that children with persistent asthma who are treated with inhaled anti-inflammatory drugs (e.g. inhaled corticosteroids) as compared with those who are not have fewer asthma symptoms and improved pulmonary function (125) are hospitalised less frequently and have lower asthma-related mortality.(126)

## **2.8 Conclusion**

Many criteria or indicators, both implicit and explicit have been developed to identify potentially inappropriate prescribing in adults. More recent interest in

paediatric prescribing has led to the development of a small number of explicit tools specifically for children. These tools have yet to be validated. PIP in adults is prevalent and associated with hospitalisations and less consistently, with ADEs. The prevalence of PIP in children is low in community settings but higher in hospitals particularly in intensive care units and is more common in younger age groups especially those under 2 years. Although paediatric prescribing has been found to be more prone to medication errors and ADE's, PIP in children is not consistently associated with ADEs or poor health outcomes. A lack of research into paediatric medicines has led to high levels of off label and unlicensed prescribing in children contributing to potentially inappropriate prescribing both in primary and secondary care.

## **Chapter 3 Development of PIPc Indicators**

### **3.1 Introduction**

The rationale for developing PIPc indicators has been outlined in chapter two. This chapter describes the methodology used to develop the indicators of PIP in children. Section 3.2 describes the study design and the formation of the steering group followed by the process of searching the literature for existing indicators and the development of new indicators. Section 3.3 describes the selection, recruitment and makeup of the Delphi panel. Section 3.4 explains the Delphi process used to develop and refine the list of indicators. Section 3.5 details the results of the Delphi process which are then discussed in section 3.6. Section 3.7 provides a summary to this chapter.

### **3.2 Study design**

This is an observational study that involved a two round Delphi consensus process. A project steering group was formed to oversee the process. The first step of the study involved the identification of a draft list of indicators of potentially inappropriate prescribing in children by literature search, followed by a two round Delphi process to achieve consensus on the chosen list of indicators for PIP in children. Children are defined as <16 years.

#### *3.2.1 Project Steering Group*

A Project Steering Group was formed to offer advice and expertise on the development of the draft indicator list and it included professionals who are likely to use the indicators in practice. The steering group was made up of four academic/clinical general practitioners, three academic/clinical pharmacists, a pharmacoepidemiologist/statistician and a postdoctoral researcher, all members of either the HRB Centre for Primary Care Research at the RCSI Dublin or the Department of Pharmacy at Queens University Belfast (QUB). A paediatric psychiatrist was involved in the steering group at the very early stages of the



process but resigned from the steering group when it became apparent that there were no indicators relating to psychiatric prescribing. Appendix 3 contains a detailed list of the members of the steering group and their areas of expertise.

### *3.2.2 Search Strategy*

To compile the indicator list a search strategy was devised for searching the published literature available in PubMed. Appendix 1 shows the search string used. As very few indicators from lists devised for adults or older adults are applicable to children, the search strategy was limited to include only those articles involving infants, children or adolescents. A preliminary search was performed in 2012 as a scoping exercise then formally updated in May 2014 and September 2015.

Clinical guidelines were searched for appropriate indicators in specific areas e.g. the SIGN/BTS British Guideline on the Management of Asthma. (46) UK and Irish guidelines were included as a first step; if no appropriate guidelines were available from the UK or Ireland, then European and US guidelines were consulted. In addition, the references of relevant papers were screened for relevant articles and previously validated indicator lists were searched to identify indicators that may be relevant to paediatric prescribing, e.g. Quality and outcomes framework (QOF), (127) START/STOPP criteria. (78) Additional web sources were also used to identify potential indicators including BMJ Clinical Evidence, (43) MHRA website (39) and NMIC bulletins. (42) A full list of the information sources used is found in Appendix 2

Inclusion criteria: potential indicators had to

- ◁ describe a pattern of prescribing that was potentially hazardous or known to be ineffective
- ◁ describe a pattern of prescribing that is not in keeping with best practice or current guidelines
- ◁ apply to the population of interest; children < 16 years.

## Exclusion criteria

- ◁ medications currently unavailable in the Republic of Ireland
- ◁ criteria which could not be applied in the absence of clinical information
- ◁ criteria containing medications with a low prevalence of use (to define uncommon use, a cut-off of less than 0.5% was agreed by the Project Steering Group)

The prevalence of individual drug use in children in 2011 was determined using dispensing data from the Health Service Executive- Primary Care Reimbursement Service (HSE-PCRS). As described in Chapter one, the PCRS is a national dispensing database, it stores information on all medications, and other health services, provided without charge to people eligible for free medical services in Ireland under the General Medical Scheme (GMS). Medications are coded using the Anatomical Therapeutic Chemical Classification System (ATC) on the PCRS database therefore an ATC code was assigned to each indicator to allow for extraction from the dispensing database. (128)

### *3.2.4 Refinement of the potential indicator list.*

A table was created using Microsoft Word® which detailed the indicator, a brief rationale for its inclusion, the prevalence of prescribing of the relevant medication from Jan to Dec 2011 and a hyperlink to the best evidence available to support its inclusion. An overview of the top 100 dispensed medication for girls and boys in those aged 0-15 years in the PCRS was also provided. This table of indicators was screened by all members of the Project Steering Group. The group met on multiple occasions over a two year period from 2014 to 2015 to discuss and refine this list. The group applied the exclusion criteria and examined the evidence supporting each indicator, removing those which did not fulfil the study requirements. For example, the indicator ‘Fluoxetine is the most appropriate antidepressant for children, other SSRI’s should not be prescribed’ was removed by the Steering Group during this screening stage as the indicator related specifically to patients with depression and could only be successfully applied to a dataset with clinical information. Some indicators identified from

literature were modified by the Steering Group to make them applicable to dispensing data for example “children with eczema should be prescribed an emollient” was altered to “children prescribed greater than one topical corticosteroid in a year should also be prescribed an emollient.” Many of the indicators were found to be from older articles or from different countries and included drugs that were unavailable or rarely used in the UK or Ireland. The online BNFc (37) and IMF 2013 (38) were used to decide if an indicator was out of date or irrelevant to clinical practice in the UK or Ireland. Appendix 4 details the indicators removed and the reasons for exclusion by the Steering group.

### **3.3 Delphi panel**

The Delphi method was used to develop these prescribing indicators. This technique allows an estimate of an overall group opinion to be reached by improving agreement between a panel of experts through rounds of questionnaires. (129) The Delphi process was used to ensure the face validity of the indicators, in other words to ensure the indicators relevance, credibility and acceptability. This technique is used in the development and validation of prescribing indicators as described in Chapter one and two.

#### ***3.3.1 Delphi Panel Selection***

The Delphi panel consisted of professionals who use the indicators in clinical practice, audit and research, including both those who measure quality of prescribing and those who have their prescribing practice measured. The panel therefore included academic and clinical GPs, pharmacists and paediatricians. A sample of experts identified as potential Delphi panel members were drawn from the extended professional contacts of the steering group members. Experts were required to have recent clinical experience of prescribing to children relevant to primary care in addition to a research or academic interest in paediatric care.

### *3.3.2 Delphi Panel Recruitment*

Email invitations to participate in the study were sent to approximately thirty experts in the fields of general practice, paediatrics and pharmacy from the Republic of Ireland, Northern Ireland and the United Kingdom in November 2014. Eighteen experts returned signed consent forms by post or electronic signature agreeing to participate in the Delphi panel.

### *3.3.3 Makeup of the Delphi panel*

The panel consisted of a broad and balanced sample of experts in paediatric medicine from across Ireland and the UK. There were three general practitioners, three general paediatricians, and three pharmacists from Ireland. From the UK, there were three GPs, three paediatricians and three pharmacists. All of the experts had recent clinical experience of prescribing to children and the paediatricians and pharmacists had an academic interest in paediatric prescribing. Appendix 5 lists the members of the Delphi Panel, their area of expertise and academic affiliations.

## **3.4 Delphi Process**

### *3.4.1 The questionnaire*

The consensus process involved two rounds of web based questionnaires. The software tool SurveyGizmo® was used to create an anonymous online survey. Each potential indicator was presented in the form of a factual statement followed by a brief rationale for its inclusion along with a hyperlink to evidence based guidelines. Within the survey the panel were asked to evaluate each statement or indicator using a Likert scale. The Likert scale allows the level of agreement by the participant to be shown using a five level point scale

Strongly disagree	1 Point
Disagree	2 Points
Uncertain	3 Points
Agree	4 Points
Strongly agree	5 Points

A free text comment box was also provided for each indicator. The questionnaire was piloted among the steering group and an additional two clinical lecturers in the Department of General Practice, RCSI. Minor adjustments relating to format and ease of use were made as a result of the piloting process.

#### *3.4.2 Round one of the Delphi process*

The members of the Delphi panel were emailed a hyperlink to the survey with details of how to complete it and a suggested time frame of 30 minutes for completion. The survey was anonymous and confidential, members of the Delphi panel were not aware of the responses of other members.

For each statement the median response and interquartile range (IQR) was calculated using Microsoft Excel®. Where the lower quartile was more or equal to 4, the statement was accepted as part of the explicit prescribing criteria. Where the upper quartile was less than or equal to 2 the indicator was rejected. If the IQR of a statement included 3, the indicator was reverted to the steering group.

Members of the steering group then had the option of revising, rewording or rejecting the indicator based on the opinion given by the Delphi panel and a review of the quality of the evidence supporting the indicator.

#### *3.4.3 Round two of the Delphi process*

Following review by the steering committee the revised set of remaining indicators were presented to the Delphi panel in the second round of the process. For any indicator where no consensus was reached after the second round, the prescribing indicator was removed. All indicators that were accepted based on consensus by the Delphi panel and the steering committee formed the final list of indicators of potentially inappropriate prescribing in children.

### 3.5 Results

Figure 3.1 summarises the development of the indicators. The literature search identified 47 potential indicators. Thirty one indicators were removed following the application of the inclusion and exclusion criteria along with a detailed examination of the evidence by the Steering Group. Sixteen indicators were presented to the Delphi panel in the first round. Fifteen of the 18 experts who consented to participate completed each round of the questionnaire. The remaining three experts did not complete either round. Consensus was reached for nine indicators in round one. No indicators were rejected; consensus was not reached on seven indicators. From these seven indicators, two were rejected by the Steering Group on the basis of the clinical comments of the Delphi panel.

Five indicators were then presented to the Delphi panel in round two. Consensus was reached on three indicators and none were rejected outright. Consensus was not reached on the remaining two indicators which were then removed by the Steering group following review of the comments of the Delphi panel.

Table 3.1 summarises the progression of the indicators through the Delphi process and Table 3.2 provides an example of some of the comments of the Delphi panel. Following a two round Delphi process the final list of indicators consisted of 12 indicators by system; respiratory n=6, gastrointestinal n=2, dermatological n=2, neurological n=2. Table 3.3 summarises the accepted indicators.

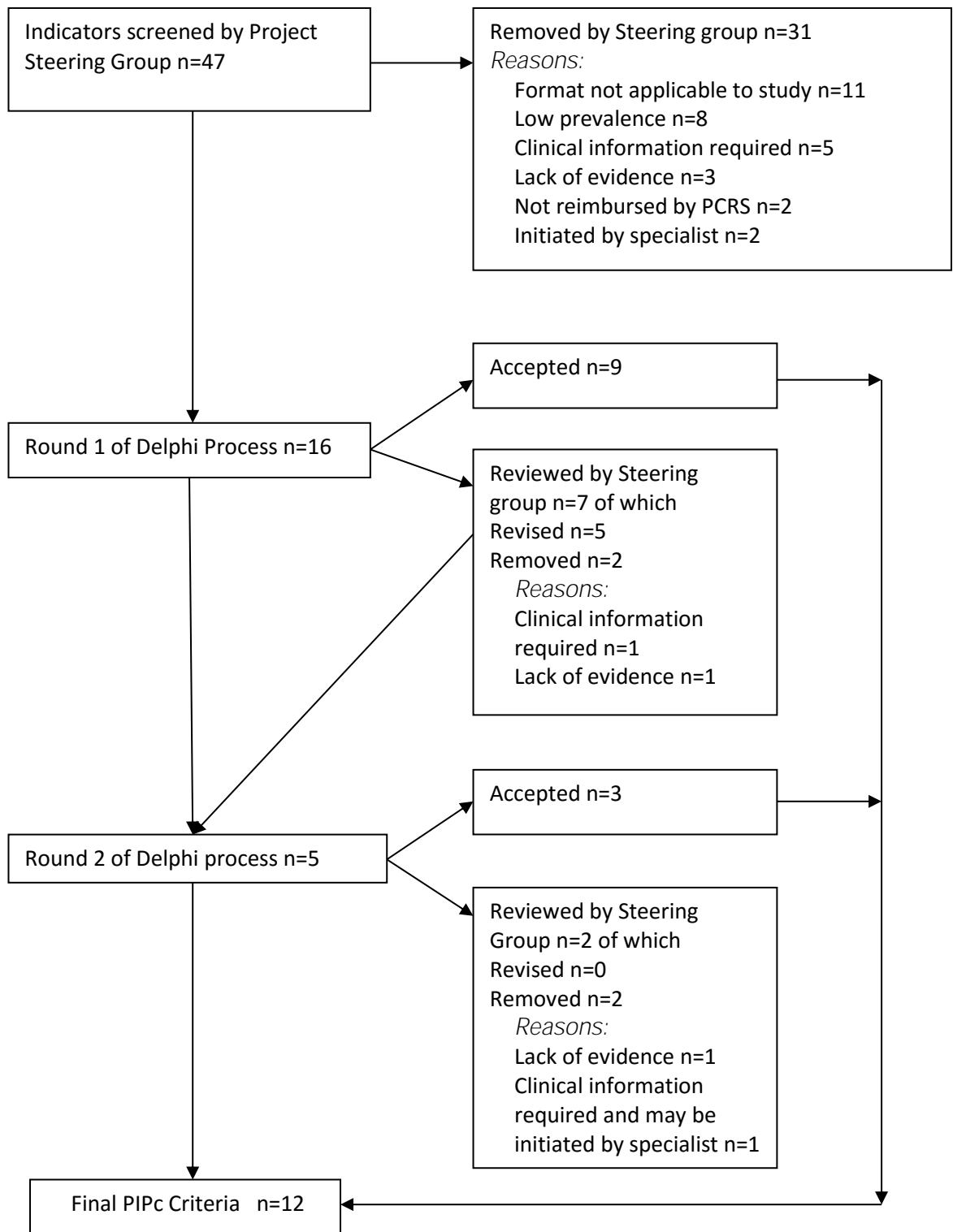


Figure 3.1 Flow of indicators through the Delphi Process

Table 3.1 Progression of indicators through the Delphi process

	Indicator	Round 1 Median IQR	Outcome	Revised indicator	Round 2 Median IQR	Outcome
1	Systemic antihistamines should not be prescribed to children under 1 year.	3 (2.5 to 4)	Revision required	<b>Sedating</b> anti histamines should not be prescribed to children under 2 years	4 (4 to 4)	Accepted
2	Intranasal beclometasone should not be prescribed to children under 6 years	4 (4 to 4)	Accepted	n/a	n/a	Accepted
3	Mucolytics should not be prescribed to children under 2 years	4 (3.5 to 5)	Revision required	<b>Carbocisteine</b> should not be prescribed to children	4 (4 to 5)	Accepted
4	An inhaled short acting beta-2 agonist (SABA) should be prescribed to all children who are prescribed two or more inhaled corticosteroids	5 (4 to 5)	Accepted	n/a	n/a	Accepted
5	An inhaled SABA should be prescribed to children under 5 years who are also taking a leukotriene receptor antagonist	5 (4 to 5)	Accepted	n/a	n/a	Accepted
6	An inhaled corticosteroid should be prescribed to children aged 5-15 years who are taking a long acting beta-2 agonist (LABA)	5 (4 to 5)	Accepted	n/a	n/a	Accepted
7	LABAs should not be prescribed to children under 5 years.	4 (3.5 to 4)	Revision required	LABA's ( <b>either in combination or on their own</b> ) should not be prescribed to children under 5 years. New evidence presented	4 (3.5 to 4)	Rejected lack of consensus of Delphi panel
8	Children under 12 years who are prescribed a pressurised metered-dose inhaler (pMDI) should also be prescribed a spacer device at least every 12 months.	4 (4 to 5)	Accepted	n/a	n/a	Accepted
9	Loperamide should not be used in the treatment of diarrhoea in children under 4 years.	4 (3.5 to 5)	Revision required	Loperamide should not be used in the treatment of diarrhoea in children under 4 years. New evidence presented.	4 (4 to 5)	Accepted



Table 3.1 Progression of indicators through the Delphi process (contd.)

	Indicator	Round 1 Median IQR	Outcome	Revised indicator	Round 2 Median IQR	Outcome
10	Domperidone should not be prescribed to children under 1 year and for children over 1 year, it should not be prescribed for greater than 7 days.	<1 year 5 (3.25 to 5)  <7 days 4.6 (3.25 to 5)	Revision required	Rejected by Steering group due to lack of evidence to support indicator	n/a	Rejected
11	Domperidone should not be prescribed concomitantly with erythromycin.	4 (4 to 5)	Accepted	n/a	n/a	Accepted
12	Codeine/Dihydrocodeine medications should not be prescribed to children under 12 years.	4 (4 to 5)	Accepted	n/a	n/a	Accepted
13	Systemic corticosteroids should not be prescribed to children aged 5-15years without evidence of asthma.	3 (2.5 to 4)	Revision required	<b>Other than in children with asthma,</b> systemic corticosteroids should not be prescribed to children aged 5-15years.	4 (2 to 4)	Rejected- lack of consensus of Delphi panel.
14	Children prescribed greater than one topical corticosteroid in a year should also be prescribed an emollient.	4 (4 to 5)	Accepted	n/a	n/a	Accepted
15	Very potent or potent topical corticosteroids e.g. Clobetasol propionate should not be prescribed to children under 1 year.	4 (3 to 4)	Revision required	Rejected by Steering group on the basis that clinical information is required	n/a	Rejected
16	Tetracyclines should not be prescribed to children under 12 years.	5 (4 to 5)	Accepted	n/a	n/a	Accepted

Table 3.2. Exemplar comments received from the Delphi panel on rejected indicators

<p><b>Rejected following Round 1</b></p> <p><b>Indicator</b></p> <p><b>Rationale</b></p>	<p><b>Comments</b></p>
<p><b>Domperidone should not be prescribed to children under one year and for children over 1 year it should not be prescribed for more than 7 days.</b></p> <p>Efficacy in GORD and gastroenteritis is uncertain in this age group. Extrapyrimal side effects occur in young children. Can be used for short term treatment of nausea and vomiting, max duration of use should not normally exceed 1 week.</p>	<p>“a [ { ] ^ ! ã á [ } ^ Á ã • Á } [ c Á ^ ç ã á ^ } &amp; ^ Á à æ • ^ á %o, [ ~   á Á } [ c Á ] ! ^ • &amp; ! ã à ^ Á È È È à ^ &amp; æ ~ • ^ Á [ %o @æç ^ Á his long term in many cases with no adverse effects But æ { Á æ, æ ! ^ Á [ ~ Á ! ^ &amp; ^ } c Á ~ ~ ^ • c ã [ } • + %o &amp; æ } q c Á • ^ ^ Á c @ ^ Á ^ ç ã á ^ } &amp; ^ Á ~ [ ! Á c @ ^ Á ~ %o ^ ~ ~ ã &amp; æ &amp; ^ Á [ ~ Á c @ ã • Á á ! ~ * Á ã • Á ~ } ] ! [ ç ^ or disease progression should never be prescribed for apparent * æ • c ! [ ^ } c ^ ! ã c ã • +</p>
<p><b>Very potent or potent topical corticosteroids should not be prescribed to children under 1 year</b></p> <p>Topical corticosteroids can cause adrenal suppression and Cushing’s syndrome.</p>	<p>%o [ &amp; &amp; æ • ã [ } æ   Á ~ if a child &amp; ^ æ q • c • Á æ   ^ ^ ] Á, [ } q c %o ç ^ ! ^ Á ! æ ! ^ Á • ã c ~ æ c ã [ } • Á c @ ã • Á { ã * @ c Á %o æ * ! ^ ^ Á ~ }   ^ • • Á ] ! ^ • &amp; ! ã à ^ á Á à ^ Á æ Á &amp; [ } %o ã ~ Á &amp; @ ã   á Á @ æ • Á • ^ ç ^ ! ^ Á ^ &amp; : ^ { æ Á c @ ^ ^ Á c ã { ^ + %o ] [ • • ã à   ^ Á ~ } á ^ ! Á á ^ ! { æ c [   [ * ^ Á * ~ ã á æ</p>

Table 3.2. Exemplar comments received from the Delphi panel on rejected indicators (contd)

**Rejected following Round 2**

**Indicator**  
**Rationale**

**Comments**

**Other than in children with asthma, systemic corticosteroids should not be prescribed to children aged 5-15years.**

Systemic corticosteroids can cause serious side effects including adrenal suppression, immunosuppression and mood disturbances. In the general paediatric population there are few indications for systemic corticosteroids apart from asthma and croup. Croup commonly affects children under 5 years

*"Agree unless there is a clinical indication such as flare of juvenile*

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*+ Á c @^ relative rare indications for systemic steroids in children-  
they would always be initiated by a specialist"*

**@c b [ ' U Wh ] b [ ' V Y h U ' U [ c b ] g  
not be prescribed to children under 5 years.**

Use of LABA's is associated with increased risk of asthma exacerbations, hospitalisations and asthma related deaths in children and adults. It is not known if combination use with inhaled corticosteroids reduces this risk.

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not significantly decrease exacerbations or hospitalisations as opposed  
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those on long acting bronchodilators"*

Table 3.3 Accepted indicators

Respiratory System	
1	Intranasal beclometasone should not be prescribed to children under 6 years.
2	Carbocisteine should not be prescribed to children
3	An inhaled short acting beta-2 agonist should be prescribed to all children who are prescribed two or more inhaled corticosteroids
4	An inhaled short acting beta-2 agonist should be prescribed to children under 5 years who are also taking a leukotriene receptor antagonist
5	An inhaled corticosteroid should be prescribed to children aged 5-15 years who are taking a long acting beta-2 agonist (LABA)
6	A spacer device should also be prescribed at least every 12 months to children under 12 years who are prescribed a pressurised metered-dose inhaler (pMDI)
Gastrointestinal System	
7	Loperamide should not be used in the treatment of diarrhoea in children under 4 years.
8	Domperidone should not be prescribed concomitantly with erythromycin.
Dermatological System	
9	An emollient should be prescribed to children prescribed greater than one topical corticosteroid in a year
10	Tetracyclines should not be prescribed to children under 12 years.
Neurological System	
11	Codeine/Dihydrocodeine medications should not be prescribed to children under 12 years.
12	Sedating antihistamines should not be prescribed to children under 2 years.

### 3.6 Discussion

This research project has led to the development a set of twelve indicators of potentially inappropriate prescribing for use in children in primary care through a consensus Delphi method. These twelve indicators can be applied to large prescribing or dispensing datasets in the absence of clinical information. The indicators developed in this study were not designed as an exhaustive list of PIP in children, but rather represent a list of commonly prescribed medications in Ireland and the UK, which may be used to explore the prevalence of PIP in children. The utility and validity of these indicators can be investigated in future studies using national prescription-based databases.

#### *3.6.1 Comparison with existing literature*

Mangione- Smith in 2007 highlighted concerns about the quality of care received by children in the USA in a study which examined the management of common medical conditions in primary care using 175 indicators applied to the medical records of 1536 children. (5) Although the majority of the indicators in that study related to processes of care, 35 related to medication use, approximately 10 of which could be applied to a database without clinical information. For example “Tetracycline should not be prescribed for adolescents less than 12 years of age”. Others could be used without clinical information if an acceptable proxy for diagnosis was available e.g. “All patients > 5 years of age with the diagnosis of asthma should have been prescribed a beta2-agonist inhaler for symptomatic relief of exacerbations”.

The POPI screening tool consisting of 104 explicit criteria for identifying the omission of prescriptions and inappropriate prescriptions in children has recently been developed in France using a Delphi process. (91) The authors of the POPI study took a disease based approach and developed indicators of both inappropriate prescriptions and omissions of prescription. As in the US study, many of the POPI indicators (85/104) require clinical information such as diagnosis and previous treatment history for implementation. Nonetheless there was some overlap

between the POPI indicators and the PIPc indicators developed in this study, for example “Loperamide is an inappropriate prescription in the treatment of diarrhoea in children under 3 years” and “Mucolytics are an inappropriate prescription in the management of cough in children under 2 years” in the POPI criteria are similar to “Loperamide should not be used in the treatment of diarrhoea in children under 4 years” and “Carbocisteine should not be prescribed to children” in this study.

Although intended for community and hospital settings, the POPI tool was developed without the input of general practitioners and has not yet been validated.

A set of 35 primary care quality indicators for children have been developed in the UK using a multi-step consensus methodology. (20) These indicators are based on routine and chronic care in addition to child development and child protection and include six prescribing indicators. There is an overlap between two of these previously identified prescribing indicators and the PIPc indicators. For example “Children with asthma should be prescribed a spacer” and “Children with atopic eczema should be prescribed emollients” are similar to the PIPc indicators “Children under 12 years who are prescribed a pMDI should also be prescribed a spacer device every 12 months” and “children prescribed greater than one topical corticosteroid in a year should also be prescribed an emollient”. The UK indicators were designed for auditing computerised primary care records and have yet to be validated.

An earlier UK study which developed prescribing safety indicators for primary care, although not specifically designed for use in the paediatric population was also found to have four indicators which could be relevant to children. (13, 130) For example “prescription of a long acting beta-2 agonist inhaler to a patient with asthma who is not also prescribed an inhaled corticosteroid” and “prescription of aspirin to a child under 16 years”. This aspirin indicator was removed from the current study at the screening stage because of low prevalence of use.

A US study from the 1980's developed a list of 17 indicators of undesirable or hazardous use of medications in children. (95) While some of the drugs identified such as barbituates and amphetamines as appetite suppressants are not relevant

today, it is interesting that there is a significant overlap between many of the drugs included in that study and the indicators developed in current study. For example the indicators “Loperamide in children under 4 year olds” and “Tetracyclines in children under 11 year olds” which feature in the current study were also identified as hazardous or undesirable use in 1980.

Finally, a cross sectional study performed in the Netherlands examined prescribing and referring in a single out of hours setting using 24 indicators developed by from national guidelines and a GP expert panel. These indicators focused on drug choice; primarily antibiotics in the management of infections, requiring diagnostic information and there was no overlap with the indicators developed in the current study. (92)

### *3.6.2 Strengths and limitations*

This study followed a well-defined process that has been refined by others in the development of similar criteria in populations other than children e.g. The START/STOPP criteria for detection of PIP in older adults and the PROMPT criteria for detection of PIP in middle aged adults. (78, 131) Potential PIPc criteria were constructed from two sources -literature search and the expertise of the Project Steering group, whose members had experience in both clinical medicine and in the development of quality indicators of prescribing in other population groups. A second strength was the broad and representative sample of medical professionals involved in paediatric prescribing on the Delphi panel. The panel members were evenly spread in academic and clinical experience across specialities of paediatrics, general practice and pharmacy providing a high level of (face) validity to the process and were representative of geographically diverse areas of Ireland and the UK. All members who participated in the panel completed both rounds of the process. The number of rounds and consensus method was decided in advance of questionnaire distribution with pre- defined limits for the acceptance, revision or rejection of indicators. Feedback was not provided to the panellists between rounds in order to remove any potential bias of panellists altering their

responses to fit those of the groups. The highest level of evidence available to support each indicator was provided to the panel in an easily accessible format to facilitate informed decision making. Some criteria were rejected by the panellists due to the difficulty in determining the appropriateness of a prescribed medication without knowledge of whether a treatment had been initiated by a specialist. Medications which were considered to be appropriate “under specialist supervision only” were therefore removed. Finally, to ensure relevance to clinical general practice each indicator was presented with a clear rationale that described either a lack of clinical effectiveness or the potential serious side effects of the relevant medication. The rationale for the indicator was supported by the highest level of evidence available, provided to the panel in an easily accessible format to facilitate informed decision making.

The main limitation of this study relates to use of the Delphi technique. The Delphi method has been criticised for its potential lack of proven reliability. 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. (19) In the current study, a panel size of 15 experts with clinical and academic expertise in prescribing to children was used to mitigate this limitation. This is thought to be sufficient when the experts have similar training and general understanding of the field of interest. (18) Ideally the level of expertise required to be a member of the Delphi panel would be clearly defined prior to the beginning of the study, (18) nonetheless significant efforts were made to ensure that the Delphi panel were heterogeneous in experience and setting to limit this potential bias. There may be variation in knowledge underpinning panel member’s views but the Delphi panel were provided with the best available evidence to mitigate this effect. It may have been useful to provide the panel with a more objective rating of the evidence e.g. using the GRADE system to further aid decision making, but this was beyond the scope of the current study. (132)

Finally the database used in this study is not fully representative of the entire population of children in Ireland. The PCRS database contains information on



prescriptions dispensed under the means tested GMS scheme for which approximately 40% of the population under 16 years were eligible in 2014.(27) Poorer health has been reported in socioeconomically deprived areas (133) with an increased prevalence of prescribing, therefore the use of this database would have inflated the prevalence of prescribing thus mitigating against the effects of this potential source of bias (134). Unfortunately dispensing data on non- eligible patients is not routinely collected in the Republic of Ireland.

### *3.6.3 Implications for research and practice*

The examination of individual clinical information to assess the appropriateness of prescribing can be time consuming and difficult. These indicators can be applied quickly and easily to large population based datasets in the absence of clinical information to identify PIP in children unexamined to date. The indicators can be used to examine the impact of changes in guidelines on prescribing patterns on a population level e.g. asthma care. Changes in prescribing patterns can be identified across time and geographical area. Researchers in other countries outside of Ireland and the UK could use these indicators with translation and some modifications based on country specific guidelines, clinical practices, drug availabilities and drug formularies. The indicators may be used as a screening tool at the level of individual clinical practices. Community pharmacists, who routinely dispense medications without clinical information, could also use these indicators as a prescribing resource.

Identification and quantification of PIP in older populations has led to the development of interventions that improve prescribing. For example a randomised controlled trial of a multi-faceted interventions which included pharmacist advice, web based pharmaceutical treatment algorithms and tailored patient information leaflets had positive results on PIP in older populations.(135) Integrating some of these PIPc indicators into clinical decision support systems may prove to be a practical method of improving PIP in children.

### **3.7 Conclusion**

This chapter details the Delphi consensus methodology used to develop a list of 12 evidence-based explicit prescribing indicators to identify PIP in children in primary care settings.

## **Chapter 4 Application of PIPc indicators to the PCRS database**

### **4.1 Introduction**

This chapter describes the application of the 12 PIPc prescribing indicators developed in chapter 3 to a population based dispensing database. Section 4.2 describes the methodology used in this part of the study. The results are presented in section 4.3 and discussed in section 4.4. Section 4.5 provides a conclusion to this chapter.

### **4.2 Methods**

#### *4.2.1 Study design and setting*

This is a cross sectional study using data from 2014 from the Health Services Executive Primary Care Reimbursement Service (HSE PCRS) database in the Republic of Ireland.

#### *4.2.2 HSE Primary Care Reimbursement Service Database*

As outlined in Chapter one, HSE-PCRS database records pharmacy claims for dispensed medicines that were prescribed to patients by their general practitioner or prescribed by a hospital specialist and transcribed by their GP. Drug information on strength, quantity dispensed, dosage form and defined daily doses (DDD) is also included. Limited patient demographic data are recorded including age, gender and region but there is no clinical information. Approximately 39% (414,856) of the total population (1,072,220) of children <16 years in the Republic of Ireland were eligible for the scheme in 2014. (27, 28) The population of GMS eligible patients is changeable as patients join and leave the scheme therefore the average population over a 12 month period was used in this study. Due to the eligibility criteria, the GMS scheme over-represents children from socio-economically deprived families.

#### *4.2.3 Study population*

The study population included all children under 16 years eligible for the HSE-PCRS GMS scheme, who were dispensed a prescription during the study period. The data was anonymised and access to patient identifiable information was not possible.

#### *4.2.4 Data extraction*

Data were extracted for the study period between 1st January 2014 and 31st December 2014. For some indicators, prescribing data from 1<sup>st</sup> January to 31<sup>st</sup> December 2013 was required to determine previous medication history for example, “Children under 12 years who are prescribed a pressurised metered-dose inhaler (pMDI) should also be prescribed a spacer device at least every 12 months”. Each medication was identified using World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) codes. (128) Population data is recorded in age bands in the PCRS database for example, 0-4 years, 5-11 years and 12-15 years. The age limits of some of the PIPc indicators crossed these age bands, therefore it was necessary to calculate an average of the number of children within certain age limits.

During the development of the 12 PIPc indicators by Delphi process described in Chapter 3, it was convenient to present the indicators by biological system. However, for the purposes of applying the indicators to the PCRS database for data extraction, analysis and presentation it was more logical to divide the indicators into two broad categories as follows:

- ◁ Indicators that described the commission of potentially inappropriate prescribing, for example, “Carbocisteine should not be prescribed to children”
- ◁ Indicators that described the omission of an appropriate prescribing, for example, “An emollient should be prescribed to children prescribed greater than one topical corticosteroid in a year”. The medication inappropriately omitted is an emollient.

Table 4.1 presents each of the 12 PIPc indicators. A description of the analytical approach used to apply the indicators is included in Appendices 6 and 7.

Table 4.1 List of indicators of PIP by commission and omission.

Indicators of commission of potentially inappropriate prescribing	
1	Carbocisteine should not be prescribed to children.
2	Intranasal beclometasone should not be prescribed to children under 6 years.
3	Loperamide should not be used in the treatment of diarrhoea in children under 4 years.
4	Domperidone should not be prescribed concomitantly with erythromycin.
5	Tetracyclines should not be prescribed to children under 12 years.
6	Codeine/Dihydrocodeine medications should not be prescribed to children under 12 years.
7	Sedating antihistamines should not be prescribed to children under 2 years.
Indicators of omission of appropriate prescribing	
8	An inhaled short acting beta-2 agonist (SABA) should be prescribed to all children who are prescribed two or more inhaled corticosteroids (ICS).
9	An inhaled SABA should be prescribed to children under 5 years who are also taking a leukotriene receptor antagonist (LTRA).
10	An inhaled corticosteroid should be prescribed to children aged 5-15 years who are taking a long acting beta-2 agonist (LABA).
11	A spacer device should be prescribed at least every 12 months to children under 12 years who are prescribed a pressurised metered-dose inhaler (pMDI).
12	An emollient should be prescribed to children prescribed greater than one topical corticosteroid in a year.

#### *4.2.5 Outcomes*

Children were categorized as having received, or not having received, any of the PIPc indicators. The primary outcomes were as follows:

- ◁ The overall prevalence of commission of PIPc, defined as the occurrence of any one of the indicators of commission
- ◁ The overall prevalence of omission of appropriate prescribing defined as the occurrence of any one of the indicators of omission.

The secondary outcomes were as follows:

- ◁ The prevalence of each individual PIPc indicator within the relevant age category.
- ◁ The association between the presence of any PIPc (binary variable) and gender (male/female).
- ◁ The cost of PIPc, including the omission and commission of PIPc.

#### *4.2.6 Gender and PIPc*

The Growing Up in Ireland Study, a longitudinal study over seven years which followed the progress of two groups of children: 8,000 9-year-olds and 10,000 9-month-olds found that boys were more likely to suffer from health problems than girls across all age cohorts. (22) Correspondingly studies of medication use in children in Europe have found that boys are more likely to be prescribed some medications such as respiratory drugs than girls up to adolescence (64) A large population based Canadian study of one million children found that boys were more likely than girls to receive prescription medication in the 0-12 age category.(145) Therefore it was decided to investigate if boys were more likely to be prescribed a potentially inappropriate prescription in the Irish context.

#### *4.2.7 Cost calculations*

The cost of PIP was defined as total cost of PIPc, including the cost of commission of PIP and the apparent savings gained by omission of appropriate prescribing.

Where an indicator described an omission of a prescription, an approximate calculation of the costs not incurred by the state was made. For example, “an inhaled corticosteroid should be prescribed to children aged 5-15 years who are taking a long term beta agonist”, the cost of inhaled corticosteroids which were omitted or not prescribed was calculated. Cost was calculated using HSE reimbursement information for ingredient cost, VAT and pharmacy fees. Ingredient cost was determined via the HSE PCRS website (136). The National Centre for Pharmacoeconomics (137) provide guidelines for inclusion of drug costs in pharmacoeconomic evaluations and advise that pharmacy fees are calculated at a rate of €5 per item and VAT is applied at a rate of 23% to non-oral medicines. Where the ingredient cost varied according to medication strength and pack size an average cost was determined. For example, the ingredient cost of an inhaled corticosteroid (ICS) varied from €5.36 for Beclomethasone 50mcg strength 200dose aerosol inhaler to €48.28 for Mometasone 400mcg strength, 60 dose twisthaler. The average ingredient cost of an ICS was therefore calculated taking into account all types of ICS medications, doses and pack sizes reimbursable by the PCRS.

#### *4.2.8 Statistical analysis*

Overall prevalence of PIP by commission and by omission was calculated per 1000 GMS patients with 95 % confidence intervals (CI). Where one individual may have received more than one PIP, this was counted as a single episode of PIP, as a proportion of the total GMS eligible population <16years. The prevalence of PIP defined by each individual PIPc indicator was also calculated. These estimates represent the number of individuals exposed to a PIP as a proportion of all the eligible individuals within the particular age category detailed in the indicator. (i.e. all those from the included populations who were dispensed a prescription during 2014). The relative risk of exposure to PIP by commission and PIP by omission occurring in males to females was calculated. A p value of <0.05 was considered to be statistically significant. Total cost per indicator was calculated per episode of PIP

rather than per individual. Analyses on the HSE-PCRS database were performed using SAS 9.2 (SAS Institute Inc., Cary, NC, USA).



## 4.3 Results

### 4.3.1 Descriptive statistics

This study includes 414,856 children <16 years from the HSE PCRS database. Table 4.2 describes the population.

Table 4.2 Patient Demographics

Age group	Female	%
0-4	56,465	48.6
4-11	95,579	48.6
12-15	49,504	48.4

### 4.3.2 Primary outcomes: Prevalence of overall PIP

The overall prevalence of PIPc defined by indicators of commission was 35.32/1000 children (95% CI 33.69-34.80), the overall prevalence of PIP defined by indicators of omission was 115.49/1000 children (95% CI 110.95-112.97). There was one indicator in each category; the indicator relating to carbocisteine in the commissions category and the indicator relating to spacer devices in the omissions category, which heavily influenced the overall prevalence. When these indicators are removed the overall prevalence of commission of PIP was 2.9/1000 children (95% CI 2.74-3.01) the prevalence of omission of appropriate prescriptions was 25.38/1000 children (95% CI 24.89-25.87).

### 4.3.3 Secondary outcomes

#### 4.3.3.1 Prevalence of specific indicators of PIP

The most prevalent indicator describing a commission of PIP was the prescription of carbocisteine to children (32.65/1000 GMS patients) followed by prescription of intranasal beclometasone to children under 6 years (2.48/1000 GMS patients). Table 4.3 presents the prevalence of each individual indicator of commission of PIPc.

The most prevalent indicator describing an omission of an appropriate prescription was "A spacer device should be prescribed at least every 12 months to children under

12 years who are prescribed a pressurised metered-dose inhaler (pMDI).” Seventy percent of children under 12 years who were prescribed a pMDI were not prescribed a spacer device every 12 months. The second most prevalent indicator describing an omission of appropriate prescription was “An emollient should be prescribed to children prescribed greater than one topical corticosteroid in a year”. Almost 54% of children who were prescribed greater than one topical corticosteroid in a year were not prescribed an emollient. Table 4.4 presents the prevalence of individual indicators which describe an omission of an appropriate prescription.

Table 4.3 Prevalence by indicators of commission of PIPc

Indicator	No. of children with PIP	No. of eligible children	Prevalence /1000 children	95% CI
1 Carbocisteine should not be prescribed to children	13546	414856	32.65	(32.10-33.21)
*Carbocisteine should not be prescribed to children< 2years	536	46437	11.54	(10.57-12.53)
2 Intranasal beclometasone should not be prescribed to children under 6 years	358	144161	2.48	(2.22-2.74)
3 Sedating antihistamines should not be prescribed to children under 2 years.	86	46437	1.85	(1.46-2.24)
4 Codeine/Dihydrocodeine medications should not be prescribed to children under 12 years.	414	312571	1.32	(1.19-1.45)
5 Loperamide should not be used in the treatment of diarrhoea in children under 4 years	89	92874	0.96	(0.76-1.12)
6 Tetracyclines should not be prescribed to children under 12 years.	182	312571	0.58	(0.50-0.67)
7 Domperidone should not be prescribed concomitantly with erythromycin	86	414856	0.21	(0.16-0.25)

Table 4.4 Prevalence of PIPc by indicators of omission of appropriate prescriptions

Indicator		No. of children who were <b>not</b> prescribed appropriate medication	No. of children eligible to be prescribed appropriate medication	% of children who were <b>not</b> prescribed appropriate prescription	95% CI
1	A spacer device should be prescribed at least every 12 months to children under 12 years who are prescribed a pressurised metered-dose inhaler (pMDI)	39945	57010	70.07%	(69.40-70.76)
2	An emollient should be prescribed to children prescribed greater than one topical corticosteroid in a year	7479	13953	53.60%	(52.39-54.83)
3	An inhaled corticosteroid should be prescribed to children aged 5-15 years who are prescribed a long acting beta-2 agonist (LABA)	18	45	40.00%	(21.52-58.67)
4	An inhaled short acting beta-2 agonist should be prescribed to children under 5 years who are prescribed a leukotriene receptor antagonist	1914	5146	37.19%	(35.53-38.88)
5	An inhaled short acting beta-2 agonist should be prescribed to all children who are prescribed two or more inhaled corticosteroids	1410	22492	6.27%	(5.94-6.50)

#### 4.3.3.2 Association of PIP and gender

There was a significant difference in the relative risk of PIP by omission in males to females (RR 1.3; 95%CI 1.02-1.66) however the results were not significant for PIPc by commission (RR 1.03; 95%CI 0.65-1.62) as detailed in Table 4.5.

Removal of outlier indicators in both categories (carbocysteine and spacer indicators) did not affect significance.

Table 4.5 Rate of PIP by commission and omission, male to female

Type of PIP	Rate of PIP in males /1000 GMS patients (95% CI)	Rate of PIP in females /1000 GMS patients (95% CI)	p value
PIP by commission	35.8 (35.0, 36.6)	34.8 (34.1, 35.6)	p>0.05
PIP by omission	130.0 (128.4, 131.5)	100.2 (98.8, 101.6)	p<0.05

#### 4.3.3.3 Cost of PIP

The total cost of PIP defined by indicators which describe the commission of PIP was €129,225.04. For indicators which described an omission of an appropriate prescription, the cost not incurred (effectively a saving) by the state amounted to €678,816.30. Table 4.6 details the costs incurred by the state per indicator of commission of PIP and Table 4.7 details the costs not incurred by the state per indicator of omission of appropriate prescribing.

Table 4.6 Cost of commission of potentially inappropriate prescribing

	Indicator	Average cost/item	Cost based on prevalence of indicator
1	Carbocisteine should not be prescribed to children	8.18	110,853.10
2	Codeine/Dihydrocodeine medications should not be prescribed to children under 12 years	11.75	4,865.79
3	Tetracyclines should not be prescribed to children under 12 years	25.37	4,642.67
4	Intranasal beclometasone should not be prescribed to children under 6 years	12.08	4,324.90
5	Domperidone should not be prescribed concomitantly with erythromycin	34.89	3,000.91
6	Sedating antihistamines should not be prescribed to children under 2 years	10.47	900.34
7	Loperamide should not be used in the treatment of diarrhoea in children under 4 years	7.16	637.33
	Total		€129,225.04
	Total after Carbocisteine indicator removed		€18,371.94

Table 4.7 Costs not incurred by omission of appropriate prescribing

	Indicator	Average cost/item	Cost based on prevalence of indicator
1	A spacer device should be prescribed at least every 12 months to children under 12 years who are prescribed a pressurized metered-dose inhaler (pMDI)	14.48	578,403.60
2	An emollient should be prescribed to children prescribed greater than one topical corticosteroid in a year	8.69	65,038.13
3	An inhaled short acting beta-2 agonist should be prescribed to children under 5 years who are also taking a leukotriene receptor antagonist	10.69	20,476.84
4	An inhaled short acting beta-2 agonist should be prescribed to all children who are prescribed two or more inhaled corticosteroids	10.69	14,464.30
5	An inhaled corticosteroid should be prescribed to children aged 5-15 years who are taking a long acting beta-2 agonist (LABA).	24.07	433.42
	Total		€678,816.30
	Total after spacer indicator removed		€100,412.70

## 4.4 Discussion

### 4.4.1 Overall results

This study shows that using the PIPc indicators, PIP in children is uncommon in the Republic of Ireland, 35.32/1000 children in commissions of PIP which reduces to 2.9/1000 when the carbocisteine indicator is removed. The overall prevalence of omissions of appropriate prescribing was 115.49/1000 children which reduces to 25.38/1000 children when the indicator relating to the annual replacement of spacer devices is removed. The overall prevalence of PIP is lower than that found in studies of middle aged adults (42.9%) and older populations (36%) in Ireland using explicit criteria applied to the HSE PCRS dispensing database. (9) (99). The primary drivers of PIP in these populations are polypharmacy and multimorbidity both of which are uncommon in children. Few studies were found in the literature that directly examines the prevalence of potentially inappropriate prescribing in children in primary care.

A significantly higher rate of PIP was found in males than in females when measured by indicators of omissions of appropriate prescribing but the difference was not significant in commissions of PIP. The cost of medications prescribed potentially inappropriately was outweighed by the “savings” or costs not incurred by the failure to prescribe appropriate medications.

### 4.4.2 Comparison with current literature: Indicators of PIP by commission

#### 4.4.2.1 Carbocisteine should not be prescribed to children

The most common instance of PIP was prescription of carbocisteine to children (32.65/1000). This finding is in keeping with other studies from across Europe. Carbocisteine is one of the 20 drugs most prescribed by family paediatricians in Italy. (138) In Spain, the prescription rate for mucolytics is 23.4/100 person years with highest rate in under 2 year olds. (139) In the current study, the prevalence of carbocisteine prescribing in under 2 year olds was 11.54/1000 GMS children. There is very little evidence in the literature which demonstrates a beneficial effect of carbocisteine. A 2014 Cochrane systematic review of the over the counter medications for cough and cold did not find any high quality randomized control



trials which investigated carbocisteine in adults or in children. (49) An earlier Cochrane review in 2013 found three trials involving 288 participants which examined carbocisteine in acute respiratory infections in children without chronic lung disease. (140) These trials showed the effect of acetylcysteine or carbocisteine was not statistically significant except for cough after six to seven days which in the clinical context of self limiting infections is not likely to be clinically relevant. The authors of the 2013 Cochrane review caution that although the overall safety of carbocisteine was good, with mainly minor gastrointestinal tract disorders in few participants ( $n = 46$ ; 2%) that the findings should not lead to the conclusion that mucolytic agents are well tolerated in paediatric patients. The studies in the review were not sufficiently powered to detect rare adverse events, lacked detailed description of side effects and few studies included children under 2 years.

Indeed, there are growing concerns about the safety of carbocisteine in children under 2 years. An analysis of the French pharmacovigilance system concerning adverse drug reactions to acetylcysteine and carbocisteine showed 59 respiratory adverse drug reactions in children younger than six years from 1989 to 2008. (141) The respiratory adverse drug reactions reported were increased and/or prolonged cough, increased bronchorrhoea, worsening of respiratory distress, mucous vomiting and dyspnoea. Fifty one of the children were hospitalized and one child died from pulmonary oedema secondary to mucous vomiting. (141) While these were rare events, there was sufficient concern that led to the withdrawal of the license for carbocisteine and acetylcysteine in paediatric patients younger than two years of age in France and Italy in April 2010. (142) Carbocisteine is also unlicensed for use in Ireland in children under 2 years.

The reason for the increased susceptibility of children to adverse effects of carbocisteine under 2 years is not known. Mucolytic agents act by increasing bronchial mucous flow. This flow may exceed the capacity of spontaneous drainage of an infant who is limited by a small bronchial diameter and neuromuscular physiologic immaturity. (140) The adverse effects on children under 2 years could also be explained by a dose related effect as there is no clinical research which supports the recommended doses of the marketing authorization. (140)

#### *4.4.2.2 Intranasal beclomethasone should not be prescribed to children under 6 years*

The second most common PIP was the use of intranasal beclomethasone in children under 6 years, although the prevalence of use was rare (2.58/1000). Intranasal corticosteroids, particularly older agents such as beclomethasone can have adverse effects on growth and the hypothalamic-pituitary adrenal axis function in children. (143) Clinical efficacy is similar for all intranasal corticosteroids but bioavailability varies considerably and systemic absorption from beclomethasone is high compared to newer agents such as fluticasone. (144) Intranasal beclomethasone is unlicensed for use in children under 6 years in the treatment of allergic and vasomotor rhinitis. In a large study of drug use in Canadian children in British Columbia found that nasal preparations (ATC class R01) were the 8<sup>th</sup> most commonly prescribed drugs to children with a prevalence of 2.5/100 children. (145) Similarly European studies have found that respiratory drugs in particular nasal preparations are among the most commonly prescribed to all children. (146) (64)

#### *4.4.2.3 Sedating antihistamines should not be prescribed to children under 2 years*

Sedating antihistamines should not be used in children under two years because of the risk of drowsiness and paradoxical excitation. Although sedating antihistamines are unlicensed in syrup form for children under one year, they may be indicated for relief of itch in allergy conditions and in chicken pox in addition to use in emergency anaphylaxis. (37) Recent Cochrane reviews have found there was no evidence of effectiveness in children as monotherapy in the relief of itch in eczema, (147) in the treatment of the common cold, (148) or in over the counter medications for acute cough. (49) The MHRA advise that children under 6 years should not be given over the counter cough and cold medications containing antihistamines. (149) Nonetheless a large study of cough and cold medication use by children in the US found that in a given week, cough and cold medication were used by 10.1% of US children, exposure was highest to first-generation sedating

antihistamines such as chlorphenamine (6.3%). (150) Due to limitations of the PCRS database it not possible to determine the clinical indication for prescribing sedating antihistamines in this study.

#### *4.4.2.4 Codeine/dihydrocodeine should not be prescribed to children under 12 years*

The MHRA issued updated advice on the use of codeine in children in 2013 and again in 2015 due to concerns about serious adverse effects such as respiratory depression. (151) There have been a number of reported deaths of children in the US following the use of codeine for analgesia following tonsillectomy and adenoidectomy. (152) Codeine has complicated pharmacokinetics and conversion to the active metabolite depends on many factors such as age, race, genetic phenotype and use of other drugs that makes it difficult to predict the effect and adverse events. (153, 154) Regulators advise that codeine should only be used in children over 12 years to relieve moderate pain and that codeine phosphate should not be used in children under 12 years for cough and cold. The American Academy of Paediatrics stated in 1997 (reaffirmed in 2006): “no well-controlled scientific studies were found that support the efficacy and safety of narcotics (including codeine) as antitussives in children”. (155, 156) A large cross sectional study of opioid use in children in Norway Sweden and Denmark using national prescription databases showed that codeine is the most commonly used opioid in Norway with a prevalence of opioid use of 4.6/1000 children in the 0-4 year olds and 5.2/1000 children in 5-10 year olds. (154) Although prevalence of use of codeine in under 12 year olds in the current study was low (1.32/1000 GMS eligible children) there is increasing evidence that codeine should not be used at all in children under 12 years and with caution in adolescents.

#### *4.4.2.5 Loperamide should not be used in the treatment of diarrhoea in children under 4 years*

The final three indicators describing commissions of potentially inappropriate prescribing have prevalence of <1, which is unsurprising given they are well known to be contraindicated for use. Loperamide should not be used in the treatment of

diarrhoea in children as the mainstay of management in both adults and children is the prevention of dehydration by maintaining fluid intake. (157) Loperamide is not licensed for use in young children as the risk of adverse effects such as drowsiness, abdominal distension and ileus outweigh the benefits in this age group. (37) Dosing information for loperamide for chronic diarrhoea from 1 month can be found in the BNFc however this remains an unlicensed use in this age group as the marketing authorisation of loperamide in both solution and tablet formulation in the UK and in Ireland state that it is not recommended in children under 4 years. There is less clarity around duration of use; the therapeutic indication as stated in the marketing authorisation for loperamide oral solution is for acute use but allows “occasional use in intractable diarrhoea in children under specialist supervision”. (187)

#### *4.4.2.6 Tetracyclines should not be prescribed to children under 12 years*

All tetracyclines are contraindicated in children under 12 years because deposition of tetracyclines in growing bone and teeth, by binding to calcium, causes staining and occasionally dental hypoplasia. Common indications in children over 12 years include acne vulgaris, and the treatment of infections due to susceptible organisms such as chlamydia and mycoplasma. (37) While it is not possible to determine the reason for the prescription of any tetracyclines to children under 12 years in this study it may be that there is a lack of awareness of the age limit of appropriate prescribing.

#### *4.4.2.7 Domperidone should not be prescribed concomitantly with erythromycin*

The least common instance of PIPc was the use of domperidone with erythromycin (0.21/1000). A rare but significant adverse effect of domperidone is the disruption of normal cardiac electrical conduction causing a prolongation of the QT interval which may lead to sudden cardiac death. (37) Recent evidence has highlighted the risk of using drugs that increase plasma concentration of domperidone e.g. erythromycin which may result in an increased risk of ventricular arrhythmias. (158) No studies were found that determined the prevalence of this specific combination of medications, however in a recent study of French children

using a national dispensing database domperidone was the 14<sup>th</sup> most commonly prescribed drug. (146) Studies have shown it is the preferred antiemetic for the treatment of gastroenteritis in France, Spain and Italy. (159)

#### *4.4.3 Comparison with current literature: Indicators of PIP by omission of appropriate prescribing*

##### *4.4.3.1 An emollient should be prescribed to children who are prescribed greater than one topical corticosteroid in a year.*

In a 2006 community based study of the appropriateness of prescribing in childhood eczema, half (50.6%) of the children who were prescribed a topical corticosteroid were not prescribed any emollient. (116) This is consistent with the findings of the current study where 53.6% of children prescribed greater than one topical corticosteroid in a year were not prescribed an emollient. Emollients are considered the mainstay of eczema treatment and their use reduces the need for topical corticosteroids. Only 2 types of emollient are reimbursable under the GMS scheme; however there is a large variety of emollients available for purchase in most pharmacies and supermarkets thus this figure may under-represent emollient use.

##### *4.4.3.2 A spacer device should be prescribed every twelve months to children under 12 years who are prescribed a pressurised metered dose inhaler (pMDI).*

The four remaining indicators which describe the omission of an appropriate prescription relate to the management of asthma in children. The most commonly omitted prescription was spacer devices in children prescribed a pMDI. Almost 70% of children under 12 years who were prescribed a pMDI were not prescribed a spacer device every year. Effective use of MDI requires synchronization of inhalation with actuation of the device. Spacer devices are used to overcome the difficulty experienced by children in coordinating inhalation and actuation of the device. (160) Spacers have further advantages in that they improve efficacy (increase lung deposition and decrease oropharyngeal deposition) and reduce side effects from inhaled drugs. (161) Spacer devices were found to be no less

effective than nebulisers for delivering beta agonist in acute asthma in children over 2 years, and had significantly lower pulse rate and tremor in a recent Cochrane review.(162)

NICE guidelines recommend a new spacer device yearly as detachable plastic spacers are prone to developing an electrostatic charge, which causes adhesion of the drug to their surface, so reducing delivery. (163, 164) GINA guidelines recommend washing once monthly in mild detergent and air drying to reduce charge but do not make any recommendations of frequency of renewal. (165) BTS/SIGN guidelines recommend change of spacer at least every year and every 6 months if the device is used daily. (46) The effect of electrostatic charge on drug delivery from spacer devices is conflicting at present. Although it has been reported that electrostatic charge on spacer devices does not affect bronchodilation with salbutamol in methacholine challenged pre-school children, (166) other studies have reported a greater bronchodilator response after inhalation of salbutamol from a non-static spacer compared to one with static present (167) Further studies show that electrostatically charged spacers can reduce lung dose in children by more than two fold leading to a clinically significant effect. (168) Newer antistatic spacers have been shown to increase lung bioavailability of medications in young children to a variable level. (169) Although the NICE guidelines recommend renewing spacer devices annually the optimum time frame for renewal is unknown at present.

#### *4.4.3.3 An inhaled corticosteroid should be prescribed to children aged 5-15 years who are prescribed a long acting beta agonist (LABA).*

LABA monotherapy has been used as an indicator of the quality of asthma care in adults in a number of studies (13) (170) Two large trials from the US and the UK demonstrated a higher risk of asthma-related death among adults receiving salmeterol than among those receiving placebo. (171, 172) Although no such large studies were available for the newer LABA, formoterol, the aggregate evidence showed that patients taking this drug had an increased risk of severe asthma-related adverse events (173) A recent Cochrane review found that LABA monotherapy in children was associated with an increased risk of serious non-fatal adverse events which were statistically significant for formoterol but not for

salmeterol.(174) An observational study of prescribing patterns in paediatric asthma in Scotland which used primary care prescribing data from 46 primary care practices in 2012 found a similar low rate of long acting beta agonist (LABA) monotherapy with only 27 children prescribed LABA without concomitant inhaled corticosteroid (ICS). (112) In the current study only 18 children aged 5 to 15 years were prescribed LABA without ICS suggesting a high level of adherence to guidelines.

*4.4.3.4 A SABA should be prescribed to children under 5 years who are prescribed a leukotriene receptor antagonist (LTRA).*

The final indicators of omission of appropriate prescriptions describe the omission of SABA as first line treatment in presumed asthma. In the current study almost 40% of children under age 5 years who were prescribed a LTRA were not prescribed a SABA. The absence of clinical information in the PCRS database means that we do not know why there is such a high level of omission of appropriate prescribing. LTRA are indicated for use as add on therapy or as an alternative to low dose inhaled corticosteroids in mild to moderate persistent asthma. The BTS guidelines advise that all patients with symptomatic asthma should be prescribed a short acting beta agonist although the evidence in children under 5 years is based on expert opinion or extrapolated from studies on older children and adults. (46) It is possible that LTRA are being used in asthma but that alternatives bronchodilators such as ipratropium bromide are prescribed instead of short acting beta agonists. However SABA work more quickly and/or with fewer side effects than the anti-cholinergics such as ipratropium bromide.

Alternatively it may be that LTRA are prescribed for indications other than asthma namely allergic rhinitis or episodic viral wheeze. Allergy guidelines advise that LTRA are amongst second line agents used in the management of allergic rhinitis but this use is reserved for children with both asthma and allergic rhinitis and therefore these children would be expected to be prescribed a SABA in addition to a LTRA. (144) Although there is some limited evidence to support intermittent use of montelukast in children under 12 years with episodic wheeze associated with viral infections this remains an unlicensed use. (37) Furthermore a recent Cochrane review examined 5 studies on 3741 children aged one to 6 years

found there is no evidence of benefit associated with maintenance or intermittent LTRA treatment in viral episodic wheeze. (175) A Scottish study which analysed the changes in primary care prescribing patterns for paediatric asthma using a prescription database in 2012 found that 91.4% of children aged 0-4years with at least one prescription for any asthma medication in the study year received a SABA while only 8.4% of received a LTRA. (112) While directly comparable, the 2012 Scottish study suggest a lower rate of LTRA monotherapy than was found in the current study.

#### *4.4.3.5 A SABA should be prescribed to children who are prescribed two or more inhaled corticosteroids.*

Finally, in this study only 6% of children who were prescribed at least two inhaled corticosteroids were not prescribed a SABA suggesting a good level of adherence to international guidelines on the use of SABA as a first line preventer in all children with asthma. (46) This result is in keeping with the above Scottish study where 91% aged 0-11years who received any asthma medication received a SABA. (112)

#### *4.4.4 Cost of PIPc*

The overall cost of potentially inappropriately prescribed medications (€129,225.04) was lower than the cost of the omission of appropriate prescriptions (€578,403.60). This effectively results in a saving to the state over half a million euro in direct drug costs. The most expensive instance of PIP was the inappropriate prescribing of carbocisteine to children. The cost to state of the inappropriate prescription of carbocisteine was €110,853.10 which accounts for over 85% of the total cost of commissions of PIP. Although the item cost of carbocisteine to the state is relatively inexpensive at €8.18/item, the overall cost is high due to a high prevalence of potentially inappropriate prescribing. When this indicator is removed, the cost of commissions of PIP was significantly reduced to €18,371.94.

Almost 70% of children under 12 years who were prescribed a pMDI were not prescribed a spacer device every year. It is not known how many spacer devices



are purchased over the counter or received free following an admission to hospital or presentation to the Emergency department with acute asthma and therefore this figure could represent an underestimation of prevalence of use. Spacer devices cost approximately €14.48 to purchase without prescription compared to €2.50 with prescription meaning that over the counter purchases are likely to be relatively infrequent. However some types of spacers are not available on the GMS scheme e.g. Aerochamber, parents may choose to purchase these spacers as they are considered to be more child friendly. The cumulative savings or costs not incurred by the state of the remaining three indicators which relate to the appropriate prescription of short acting beta agonists and inhaled corticosteroids in accordance with BTS asthma guidelines amount to €35,374.56. The unit cost of emollients is low at €8.69 per item however the overall saving or costs not incurred by the state due to the omission of prescription of emollients is the second highest at €65,038.13. Indeed, this may possibly represent an underestimation given that there is a limited selection of emollients covered by the GMS scheme and many patients may choose to purchase their preferred emollient.

It must be stressed that the indirect costs of poorly controlled asthma such as exacerbations; hospitalisations and reduced quality of life for patients have not been examined in this study. Nonetheless, they are likely to significantly outweigh not only the direct costs of prescription of spacer devices but also the cost of appropriate prescribing of SABA's and ICS's in line with international asthma management guidelines. Similarly poorly managed eczema may result in increased healthcare visits to GPs and referrals to secondary care leading to increase health care costs overall.

The overall costs of commissions of PIP and omissions of appropriate prescribing determined in this study pale in comparison to those found in studies of PIP in older adults (€45 million) in Ireland. (9) Detailed cost effectiveness studies are required to investigate the wider economic implications of potentially inappropriate prescribing in children in primary care.

#### *4.4.5 Association between gender and PIPc*

In this study male children were significantly more likely to be exposed to PIP by omissions of appropriate prescribing but not by commissions of PIP. Although few studies examine inappropriate prescribing in children, studies which investigate drug utilisation using population based databases have found that drugs are either similarly or slightly more commonly prescribed to boys than girls especially in younger age groups. (146) Studies in Danish children found that prescription rates are slightly higher in boys mainly due to anti-asthmatic and anti -infective use. (176) Similarly in a European study of Italy, the Netherlands and the UK, drugs were equally prescribed to both sexes or more commonly to boys until adolescence when the pattern reverses. (64)

#### *4.4.6 Strengths and limitations*

This large observational study has several key strengths. Firstly the PIPc criteria have been developed for use in prescribing or dispensing databases in the absence of clinical information meaning all 12 indicators have been successfully applied to the HSE PCRS database. Although many studies have examined the prevalence of PIP in older populations, to our knowledge this is the first study to determine the prevalence of PIP in children.

There are some limitations associated with the use of large datasets for observational studies. Firstly the HSE PCRS database only contains information on prescriptions dispensed to approximately one third of the population of children under 16 years. Secondly although this study is only concerned with medications prescribed by a GP, lack of available information on over the counter medication use in the dataset could affect the accuracy of the prevalence estimates. For example PIP may be underestimated if carbocisteine is purchased over the counter and overestimated if a patient on greater than one topical corticosteroid purchases an over the counter emollient. Calculating the prevalence of use of spacer devices is further complicated by the fact that patients can receive devices from a number of sources for example by prescription, over the counter purchase, directly from a hospital or a General Practice surgery. Although use of longitudinal records of dispensed medications eliminates the issue of primary non adherence

to therapies which can occur when prescribing datasets are used, it is still not possible to determine whether patient adhere to medications which have been dispensed. Thirdly, population data in the PCRS database is recorded in age categories of 0-4 years, 5-11 years and 12-15years; in the case of some indicators relating to specific age groups for example “sedating antihistamines should not be prescribed to children under 2 years” an average of the number of children within the age group (the denominator) was made. Although the PIPc indicators were designed for use in dispensing databases without clinical information some assumptions were made in relation to clinical diagnosis for example, two or more inhaled corticosteroids was used as a proxy for the diagnosis of asthma. However the prescribing of asthma medication is a widely used as surrogate to identify children with asthma. (90, 112) A further limitation of the PCRS database is the absence of information on whether a medication originates in primary or secondary care. A patient will bring a hospital prescription to their GP to avail of free medications under the GMS scheme. A small number of medications which are licenced for use under specialist prescribing only may appear to then be prescribed by their general practitioner without specialist supervision.

Finally, in relation to the development of the indicators the level of expertise required to be a member of the Delphi panel would ideally be clearly defined prior to the beginning of the study. Nonetheless, significant efforts were made to ensure that the Delphi panel were heterogeneous in experience and setting to offset this limitation.

#### *4.4.7 Implications for future research*

The PIPc indicators can be quickly and easily applied to similar large population based datasets in other countries to determine the prevalence of PIP in children internationally. Changes in prescribing patterns can be identified across time and between geographical areas. The PIPc indicators can also be used for more specific purposes such as to examine the impact of changes in guidelines on prescribing patterns on a population level e.g. asthma care. Further studies to investigate health outcomes (hospital admissions, adverse events) are required to

identify the clinical impact of PIP in children, there is for studies which examine the factors that influence prescribing practices that result in PIP in children.

Identification and quantification of PIP in older populations has led to the development of interventions that improve prescribing. For example a randomised controlled trial of multi-faceted interventions which included pharmacist advice, web based pharmaceutical treatment algorithms and tailored patient information leaflets had positive results on PIP in older populations. (177) Integrating some of these supports into clinical decision support systems may prove to be a practical method of improving prescribing in children.

#### **4.5 Conclusion**

The application of the PIPc indicators to a national dispensing database in the ROI has shown that the overall prevalence of PIP is low. The direct cost of potentially inappropriately prescribed medications is offset by the omission of appropriate prescriptions. The PIPc indicators can be used to investigate health outcomes which may help to inform interventions designed to improve prescribing in children.

## **Chapter 5 Discussion**

### **5.1 Introduction**

The main findings from the PIPc development and validation studies are summarised in Section 5.2. Section 5.3 discusses the findings in the context of the current evidence. Section 5.4 summarises the strengths and limitations of the study overall. Section 5.5 discusses the implications of the findings, section 5.6 reflects on the research process and section 5.7 presents recommendations for future research. Section 5.8 concludes the thesis.

### **5.2 Summary of the main findings**

This thesis presented:

- 1) The development of a set of indicators of potentially inappropriate prescribing in children (PIPc) in primary care by Delphi consensus methodology.
- 2) The validation of the indicators by application of the indicators to a national dispensing database.

#### *5.2.1 Development of PIPc indicators*

The development of the PIPc indicators in primary care was informed by previous studies using the Delphi consensus methodology. The literature and guidelines were searched to identify previously developed indicators relevant to children in primary care in addition to the expert opinion of a Project Steering group. A Delphi panel of experts in the field of prescribing to children was recruited and consensus on a list of 12 indicators was reached via a two round anonymous web based questionnaire.

### *5.2.2. Application of the indicators to the PCRS database*

The 12 PIPc indicators were applied to a national dispensing database to determine the prevalence of PIP in children in 2014. The database contained anonymised data on 414,856 children under the age of 16 years, 48.5% were female. The overall prevalence of PIP as defined by indicators of commission of PIP was 35.32/1000 GMS eligible children. The overall prevalence of PIP as defined by indicators of omission of appropriate prescribing was 115.49/1000 GMS eligible children. The most common instance of PIP was the prescription of carbocisteine to children. The least common instance of PIP was the prescription domperidone and erythromycin concomitantly. The most commonly omitted prescription was prescription of a spacer device every year to children using a pressurised meter dose inhaler (pMDI). The least commonly omitted prescription was a SABA to children who are prescribed greater than one ICS. Male children were significantly more likely to be exposed to PIP by omission than female children; the difference in rates of PIP between male and female children as defined by indicators of commission of PIP was not statistically significant. The cost of PIPc was €129,225.04 by indicators of commission of PIP and the cost of omission of appropriate prescriptions was €678,816.30.

## **5.3 Context of previous research**

The 12 PIPc indicators developed in this study provide a valuable addition to the literature in this area by adding to the limited number of indicators of PIP previously for use in both children and primary care.

### *5.3.1 Indicators of PIP in children- consensus methodologies*

The Delphi consensus methodology has been used successfully in many studies to gain consensus on subjects for which there is a lack of agreement among experts or an insufficient level of evidence to support clinical decision making. The Delphi consensus method has been used to develop lists of explicit indicators of PIP in adults for many years, producing acceptable and validated lists such as the START/STOPP criteria and the Beers Criteria.(50, 78) Literature search detailed in Chapter two found only one other study which used the Delphi technique to

develop indicators of inappropriate prescribing in children (POPI). (91) The POPI indicators were developed using a two round Delphi process was used with 10 members of the panel replying to both rounds. The methodology used differs from that of the current research project in that the panellists were given feedback between rounds (including their own previous individual rating, median panel rating and frequency distribution of the agreement rating) and asked to rerate each item based on their own opinion and the group response to the previous round. This approach dilutes the main advantages of the Delphi Technique over other consensus methodologies. The use of anonymous online questionnaires without feedback between rounds of the questionnaires and the avoidance of face to face meetings reduces the risk of influence of a single dominant member of the panel. Respondents are thus less likely to “jump on the bandwagon” when their views are not in line with the majority. A consensus of opinion can be formed rather a compromised opinion by limiting the number of rounds of questionnaires and by ranking of each item by the entire group which can help make the ultimate conclusions more reliable than a single meeting. (18)

Other studies of prescribing indicators in children have used consensus methodology such as the Nominal Group Technique (NGT) and the RAND methodology. Both techniques were used to develop a set of 35 primary care quality indicators for children in the UK. (20) The Nominal Group Technique, generally used to generate ideas and solutions in response to a specific question was used by the authors of the UK study to identify aspects of care of highest priority requiring quality indicator development. The RAND methodology involved a 10 member panel of GPs who met face to face to rate the validity and acceptability of the proposed indicators on a 9 point Likert scale. The NGT technique benefits from anonymity in the generation of ideas but both methods are at risk of bias when face to face meetings are required.(18)

The authors of a Dutch study of prescribing in out of hours used the expert opinion of three different general practitioner expert panels and national guidelines to develop the indicators. (92) Three indicators related specifically to prescribing antibiotics for infections in children and are based on the availability of clinical information. In the current study indicators relating to antibiotic prescribing were

excluded as clinical information is required to determine the appropriateness of choice of antibiotic. Indicators which described comparisons such as the ratio of first to second line antibiotics were also excluded as the format was deemed to be more applicable to auditing national trends in antibiotic prescribing in the general population rather than an indicator of PIP in children in primary care.

### *5.3.2. Use of indicators as a measurement of PIP*

It is important to note the limitations of indicators applied to large databases as measures of prescribing quality; improving a patients prescription does not necessarily improve patient outcomes. (77) Prescribing indicators are process measures which may serve as a useful aid to improving prescribing but are not intended as a substitute for a prescriber's careful clinical decision-making. (178) According to a recently published systematic review of the tools used to assess appropriateness of prescribing, (77) the ideal tool should:

- ◁ cover all aspects of appropriateness (efficacy, safety, cost effectiveness, and patient preferences)
- ◁ be developed using evidence based methods
- ◁ show significant correlation between the degree of inappropriateness and clinical outcomes
- ◁ be applicable not only in research but also in daily health care practice

The PIPc indicators certainly do not fulfill all of these criteria mainly due to the lack of clinical data and patient preferences. Nonetheless a particular strength in the context of this description of an ideal indicator is that they include under prescribing or omissions of prescribing which are a frequently neglected area of PIP. They are also applicable to daily general practice as they relate to medications that are available to GPs to prescribe in the management of common clinical conditions.

During the process of study it became apparent that it would be better to frame the PIPc indicators in terms of omissions and commissions in line with the STOPP/START criteria. (78) The development of indicators as measurable aspects of care has led to financial incentivisation or pay for performance



measures in some countries such as the UK. e.g QOF framework. In an analysis of the effect of the pay for performance initiative, areas of care not incentivised by the QOF scheme improved more slowly than those aspects of care included in the scheme. (179) Other studies have also found that GPs complied better with quality prescribing indicators that were linked to financial incentives than with unincentivised indicators. (180) In Ireland, payments have been linked to completed vaccination schedules for children and more recently payment will be linked to some aspects of asthma care in children under 6 years, although these payments are not directly related to prescribing. It remains to be seen whether these changes in asthma care will lead to any improvement in patient outcomes.

### *5.3.3 Prevalence of PIPc indicators*

As highlighted in chapter 2 there are many studies which investigate the prevalence of PIP in older populations but few that examine prescribing in children. The prevalence of PIP determined in this study was much lower than studies in older adults and in middle aged adults in Ireland which used similar methodologies and similar databases. In this study there was a notable difference between the prevalence of indicators of commission of PIP and those of omission of appropriate prescribing. Even when outlier indicators were removed, the prevalence of omissions of appropriate prescribing remained much higher than that of commissions. This result likely reflects a cautious approach to prescribing in children in Irish General Practice. Nonetheless, the higher rate of PIP by omissions of appropriate prescribing suggest that prescribing could be more in keeping with relevant guidelines. It is notable that the indicators of omission of prescribing related in general to asthma care which is an area of prescribing where there are clear international guidelines freely and easily available to GPs.

#### *5.3.3.1 Interpretation of indicators of omission of appropriate prescribing*

The prescribing of a spacer device at least annually to children who are prescribed a pMDI is advised by the SIGN/BTS guidelines (46) and NICE guidelines.(163, 164) There is some evidence that electrostatic build up on spacer devices does affect drug delivery to a clinically significant level.(169) While, the evidence to support annual renewal of spacers is lacking, guidelines suggest a six monthly

renewal if it used daily. It could be reasonably inferred that the need for renewal of a spacer device should depend on the frequency of use and not a one size fits all annual time limit. The clinical relevance of this indicator may be further reduced by the development of antistatic spacer device e.g. Aerochamber Plus <sup>TM</sup> which are now available to purchase if not yet reimbursable on the GMS scheme.

Almost 40% of children under 5 years who are prescribed a LTRA did not receive a SABA. While the possible reasons for this are discussed in more detail in Chapter 4, it is notable that neither asthma nor allergy guidelines advise LTRA monotherapy (46, 144) and that the evidence for use of LTRA in episodic viral wheeze is weak. (175) When considered in the context of the indicator a SABA should be prescribed to all children prescribed greater than one ICS which demonstrated a very low level of inappropriate prescribing and therefore a good level of adherence to guidelines. It could be inferred that perhaps LTRA are not being used for appropriate or licensed uses in Irish general practice.

The remaining asthma indicator relates to monotherapy with LABA without the use of ICS. While the evidence to support this indicator is strong, the numbers of children treated inappropriately in this study were so small (18/45) that it is difficult to interpret their significance.

Finally, the high level of omission of emollient prescriptions in children who are prescribed more than two topical corticosteroids must be interpreted with the knowledge that patients may buy emollients over the counter and this figure may under represent use. In addition, the prescription of two corticosteroids in a year was used a proxy for a diagnosis of eczema as has been done in other studies , but this may not accurately reflect the number of children diagnosed with eczema.

#### *5.3.2.2 Interpretation of indicators of commission of inappropriate prescribing*

The prescription of carbocisteine to children was the most prevalent episode of PIP identified in this study. As discussed in Chapter 4 carbocisteine is a commonly prescribed medication internationally despite a lack of evidence of effectiveness and significant concerns regarding adverse effects especially infants under two years.(140) Owing to the high prevalence of use, the cost to the state of

prescriptions of carbocisteine was the highest of all the indicators of PIP at over €100,000 in 2014.

The second most prevalent indicator relating to the use of intranasal beclomethasone is clinically relevant in terms of serious long term side effects relating to growth suppression.(143) There are a number of alternative intranasal corticosteroids e.g. fluticasone which have better safety profiles and similar effectiveness. (144) These agents are reimbursable on the GMS scheme and so their use could be encouraged over older agents such as beclomethasone.

The remaining five indicators of commission of PIP have a prevalence of <2/1000 children indicating a low rate of inappropriate prescribing by GPs in Ireland. As stated previously there are few other studies that investigate PIP in children. However studies which examine off label or unlicensed use of medications in children demonstrate higher levels ranging from 13.5% to 65% depending on the methodology used (61) Given that concerns have been raised regarding the safety of codeine/dihydrocodeine as an analgesic or cough suppressant and domperidone as an antiemetic as discussed in chapter 4, these two indicators in particular may be useful in monitoring changes in prescribing patterns of GPs in response to updated guidelines.

#### *5.3.2.3 Interpretation of findings of cost*

Omissions of appropriate prescribing resulted in a state saving over five times that spent on commissions of inappropriate prescribing. However it is important to interpret this result in the broader context of health services spending in particular where the inappropriate management of some conditions in primary care can lead to significant direct and indirect costs in secondary care. As no studies were identified that examined the cost of PIP in children, this study provides new data to add to this field of research.

#### *5.3.4 Off label and unlicensed prescribing*

Although this study was not designed to consider prescribing in terms of licensing or labelling, 5 of the 12 PIPc indicators described off label/unlicensed prescribing. Off label prescribing is defined as prescribing outside the specifications of the SPC and unlicensed drugs are those with no valid marketing authorisation. Unlicensed

use of medications means the prescription or administration of drugs outside of the marketing authorisation. The main reason for off label or unlicensed use of medication in the current study was the prescription of medications below the age limits recommended in the marketing authorisation. Of the indicators which described off label/licence use of medications, the highest prevalence of use was the prescription of mucolytic carbocysteine to children, followed by intranasal beclomethasone to children under 6 years and sedating antihistamines to children under 2 years. These results are in keeping with other studies which demonstrate a high level of off label use of nasal decongestants, sedating antihistamines and corticosteroids. (61, 64, 146) Given the absence of clinical information in the PCRS database it was not possible to identify whether medications were also being prescribed for unlicensed indications

## **5.4 Impact of findings**

There are four broad areas where health research may have an impact (181)

- < research related impacts
- < policy impacts
- < service impacts
- < societal impacts

The PIPc study has potential impacts across these areas as discussed below.

### *5.4.1 Research impact*

This study has significantly contributed to the field of paediatric prescribing by developing an explicit set of indicators of PIP applicable to children in primary care for use in prescribing databases without clinical information. This study adds new knowledge to the area of rational prescribing in children, which has not been researched adequately to date. The study also contributes to the current literature on the use of the Delphi technique as a means of consensus methodology by providing a framework for future studies. The indicators developed in this study provide an opportunity for researchers in other countries to investigate PIP by applying the indicators to other similar databases e.g. the Enhanced Prescribing

Database in Northern Ireland in a process which will enhance the external validity of the PIPc indicators. Importantly the PIPc indicators could be used to explore the link between inappropriate prescribing and adverse clinical outcomes in children, which is an area where there is no clear evidence at present. To date, one article on the development of the indicators has been submitted for publication from this research with plans to disseminate the findings of the second part of the study; the application of the indicators to the PCRS database by publication in a peer reviewed journal. The study has been presented at a national general practice academic conference, the Association of University Departments of General Practice in Ireland (AUDGPI) and an abstract submitted to an upcoming international academic primary conference, the Society of Academic Primary Care. (SAPC)

#### *5.4.2 Service impacts*

A number of service related impacts may arise from this study. Firstly the development of acceptable valid indicators of PIP relevant to primary care in Ireland provides a means by which PIP in children can be identified and the scale of the problem investigated on a national level. This has led to improved information on the quality of care provided to children in Ireland. The development of effective evidence based interventions may lead to an improvement in the quality of care itself. On an individual level GPs could use the PIPc indicators for auditing their prescribing practice to continuous professional development (CPD) points. The study highlights an opportunity for cost- containment for the state, in terms of a reduction in unnecessary spending on potentially inappropriate medicines which are ineffective or harmful. Additionally, there is an opportunity to improve prescribing in chronic diseases in terms of omitted prescriptions in primary care, which in turn could lead to a reduction in excessive spending in secondary care due to poorly managed conditions. In particular, this study highlights the high level of omitted prescriptions in asthma care. A cycle of care for patients with asthma has been developed in a new under 6's contract with GPs which encourages accurate diagnosis and management of children with asthma. The contract ensures a financial incentive for GPs to review patients with asthma at least annually in terms of symptom control, medication review, provide vaccinations, document household smoking status and provide a written asthma

management plan.(182) Currently there is no assessment of the appropriateness or quality of prescribing in the contract however the PIPc indicators could be used to support GPs in their prescribing in this context.

#### *5.4.3 Policy related impacts*

Health services research can influence and inform policy at a local and national level. This thesis can potentially influence policy on both levels. There are a number of national policies developed by the HSE to improve the quality and safety of care provided to patients. The Medication Safety Programme is one of the National Safety Programmes supported by the HSE Quality Improvement Division. (183) The programme aims to reduce medication-related harm and improve patient safety. The PIPc study highlights the use of medications in children which are ineffective or have serious adverse effects and therefore this work could be used to inform and influence such policies. The Medicines Management Programme is a national policy developed by the HSE to improve cost effective prescribing. (35) The programme produces a list of preferred drugs/devices when prescribing e.g. it recommends the use of a spacer device for children under 6 years to optimise drug delivery. The findings of this study show that spacers are not currently prescribed to the majority of children who use inhaler devices. As the state provides free health care at the point of contact to all children under 6 years since 2015 there is an even greater need to provide cost effective healthcare at a national and local level.

Changes in health policy have resulted in changes to how primary care is delivered to patients. GPs are working increasingly in primary care teams with other health professionals including community pharmacists. In the UK, GPs can access their individual prescribing data via the Health and Social Care Information Centre website (184) The PIPc indicators could be modified for use in a UK setting and used to by GPs to determine their own level of PIPc. This type data is not available to GPs in Ireland; however the PIPc indicators could be integrated into individual practices or pharmacies via practice software to reduce PIP at a local level.

#### *5.4.4 Societal related impacts*

This study has the potential to have some societal related impacts if successfully communicated to an audience beyond that of academic medicine. It could impact on the knowledge, attitudes and behaviours of parents seeking medications for their children. If parents were aware of the potential inappropriateness of certain treatments they may be less likely to request unnecessary medications and more likely to demand better information and treatments from their general practitioner. This may in turn lead to an improved quality of life for children in terms of the effective treatment of illnesses and the avoidance of potentially harmful side effects and trauma of administering ineffective treatments. Without doubt, much further qualitative and quantitative research would be required to draw such conclusions. The idea of rationalising healthcare is underpinned by the “Choosing Wisely” campaign began in the United States in 2012, founded by the American Board of Internal Medicine (ABIM) Foundation (185) The campaign helps specialists to agree lists of interventions that should be used with more caution because they are often unnecessary and therefore wasteful and potentially harmful. This campaign, supported by the Academy of Royal Colleges in the UK argue that doctors have an ethical responsibility to reduce this wasted use of clinical resource because, in a healthcare system with finite resources, one doctor’s waste is another patient’s delay.(186) The findings of this study in particular in relation to the use of carbocysteine in children in this study could be used to inform this campaign.

### **5.5 Strengths and limitations**

The individual strengths and limitations of the process to develop of the PIPc indicators and their application to a national dispensing database have been outlined in Chapters three and four respectively. The PIPc indicators are relevant practical and applicable to general practice in Ireland and, with some modifications internationally. While the Delphi consensus process was carried out in line with best practice, the validity of the indicators also rests on the quality of the evidence supporting them. Unfortunately, rational prescribing in children, particularly in primary care, has not received much focus for many years for reasons outlined in

chapter 2. Thus as has been the case with other studies that developed indicators of prescribing in children, there is a lack of high quality evidence for some of the indicators (20)

The main strength of the application of the PIPc indicators to the PCRS database is that this is the first such study to investigate the extent of this problem in an Irish setting and there are very few comparable studies internationally as described in Chapter two. The main limitation of the study rests with the PCRS database which contains only limited data about prescribing. There is no clinical information recorded and it is not known whether prescriptions originate in primary via the GP or secondary care via an emergency department or a specialist clinic and therefore it is difficult to interpret the appropriateness of prescribing in some instances. In addition, the PCRS database records data on medications prescribed through the GMS scheme, only one third of the population is eligible for this scheme with the socially deprived being over represented. The results of the study must be interpreted in this context.

## **5.6 Research Reflection**

I have developed my research skills throughout this project, from learning about study methodology to statistical analysis and academic writing and presentation skills. I also gained leadership, teamwork and organisational skills in directing the Project Steering group and the Delphi panel. With the benefit of experience, there are a number of elements of this study that I would improve if it was to be repeated.

Development of the indicators: The members of the Delphi panel were equally distributed between Ireland and the UK. They were representative of the relevant specialities of general practice, paediatrics and pharmacy however it would have been preferable to clearly identify the level of experience and expertise necessary to be defined as an expert and invited on the Delphi panel at the outset of the study. While this information was generally available, the Delphi panel were not explicitly asked to outline their experience.



Validation of the indicators: A personal lack of familiarity with the PCRS database meant that obtaining prevalence data was more time-consuming and complex than was necessary. In hindsight, I would have spent more time understanding the limitations of the database for example the effect of age banding, and the effect this would have on statistical analysis. If I were to repeat this project I would have liked to obtain more detailed prevalence data for example on multiple episodes of PIP, and to examine patterns of prescribing within geographical area and at individual prescriber/practice level.

### **5.7 Recommendations for further research**

The PIPc indicators are the first set of indicators to be developed which allow examination of PIP using large population based prescribing or dispensing datasets which do not contain any clinical information. These datasets are available in other countries such as the UK and Northern Ireland and could be applied to determine the prevalence of PIP in children in these countries. The PIPc indicators were developed primarily from UK and Irish guidelines, the BNFc was an important point of reference throughout the study and finally half of the experts on the Delphi panel were UK or NI based. Therefore the indicators are generalisable across these health systems and could easily and quickly be applied to UK databases. Repeated studies using the same indicators by different research groups and using different databases will also add to the validity and reliability of the PIPc indicators.

This study makes a contribution to current knowledge on the methods of identifying PIP in children and prevalence of PIPc in Irish primary care. Recent studies in adult prescribing have identified a link between PIP and health outcomes. Further research is needed to investigate the clinical significance of PIP in children. Studies are required to determine the association between both omissions and commissions of PIP on health outcomes such as morbidity, mortality, hospital admissions and adverse events.

Studies in recent years have shown that multimorbidity and polypharmacy are important factors which contribute to PIP in older adults, however it is not known

whether these factors are also relevant to children. Studies have shown that off licence prescribing may be one such contributing factor. Other factors which may be relevant include age, gender, health status, frequency of attendance to healthcare providers, family health status, child/parental education level, socioeconomic conditions, access to and availability of healthcare etc. The PIPc indicators could be used to help to identify which, if any, of these factors may increase the risk of PIP in children.

This study highlighted the overlap between off label or unlicensed medications and potentially inappropriate prescribing. The literature examining the relationship between medication error and adverse drug events is conflicted and there is a lack of studies investigating the health impact of unlicensed and off label medication in children. On the level of biomedical sciences research, more studies are required to improve data on the safety and efficacy of medicines in children to support regulatory and licensing information

This study also highlighted a high level of under-prescribing or the omission of appropriate prescribing particularly in relation to asthma management. The PIPc indicators could be useful in investigating the reasons why GPs do not prescribe medications appropriately even when there are clear clinical guidelines available to assist in decision making. The PIPc indicators could be used for evaluation or assessment of prescribing as part of the new asthma cycle of care programme as described in section 5.4.2.

As the primary care environment in which GPs prescribe to children changes on a socioeconomic level through the implementation of policies such as free health care for under six year olds, it may also be useful to investigate the affect these changes may have on prescribing patterns across time within Ireland. The PIPc indicators could be used to examine the impact of changes in guidelines on prescribing patterns on a population level e.g. asthma care. Further more detailed cost effectiveness studies on PIP in children could inform both local practice and national medications policy.

Identification and quantification of PIP in older populations has led to the development of interventions that improve prescribing. Some of the issues which

influence PIP in children differ to those in older adults, research into the factors which influence PIP in children would be useful to inform the development of interventions tailored to paediatric prescribing. It may also be useful to focus such interventions on specific types of PIP in children for example, those with the highest prevalence of occurrence or those with the highest potential harmful effect clinically or the most costly.

## **5.8 Conclusion**

PIP in children is an important area of health services research as rational prescribing in children has been under investigated to date. This study has developed 12 explicit indicators of PIP which were applied to a national dispensing database without clinical information. The prevalence of PIPc overall was found to be low with some specific indicators demonstrating a high level of PIP, resulting in significant cost consequences to the state. This study offers some groundwork in identifying and quantifying the problem of PIP in children in Ireland. Further research is required to develop interventions that will improve this problem.

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## Appendix 1 Literature Review Search Terms

### PubMed MeSH terms

Inappropriate prescribing and indicators	(inappropriate or appropriate or optimal or suboptimal or ineffective or unnecessary) and (medication or prescribing)) AND ((prescribing indicator or prescribing indicators) or (quality indicator) or (guideline adherence) or (prescribing tool or prescribing tools)) = 1227 references. No limits/filters applied
Prescribing indicators in children	(youth) OR child) OR minor) OR paediatric) OR infant) OR preschool) OR schoolchild) OR adolescent) AND prescribing indicators) OR quality indicators) OR prescribing criteria)) AND (((((polypharmacy) OR multidrug) OR medication appropriateness) OR prescribing pattern) AND children)) AND (appropriate prescribing) OR optimum prescribing) OR inappropriate prescribing) OR unnecessary prescribing) OR incorrect prescribing) OR excessive prescribing) OR multiple prescribing) AND children) = 16 references
Indicators of potentially inappropriate prescribing in children	(potentially inappropriate prescribing) OR inappropriate prescribing) misprescribing) OR overprescribing) OR under prescribing) AND child) OR infant) OR adolescent) AND prescribing indicators) AND healthcare))) = 49 references
Indicators of quality prescribing in children	(child) OR paediatric) OR infant) OR preschool) OR schoolchild) OR adolescent) AND prescribing indicators) AND quality)) AND quality indicators) AND health care = 47 references
Indicators of inappropriate	potentially inappropriate prescribing) OR inappropriate prescribing) misprescribing) OR overprescribing) OR under prescribing) AND child) OR infant) OR



prescribing in children	adolescent) AND prescribing indicators) AND healthcare)))))) AND quality = 26 references
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## **Appendix 2 List of information sources.**

PubMed Search 2014 and 2015

British National Formulary for Children online

Irish Medicines Formulary 14<sup>th</sup> Edition 2013 and 16<sup>th</sup> Edition 2014

Cochrane Database of Systematic reviews

British Medical Journal Clinical Evidence

Clinical Knowledge Summaries (pre 2014 when still available from ROI)

References of References

Medicines and Healthcare products Regulatory Agency website (MHRA)

European Medicines Agency website (EMA)

U.S Food and Drug Administration website (FDA)

St James Hospital National Medicines Information Centre Therapeutic Update  
Bulletins

Guidelines including those produced by

- ◁ National Institute for Health and Care Excellence (NICE)
- ◁ British Thoracic Society (BTS)
- ◁ Scottish Intercollegiate Guidelines Network (SIGN)
- ◁ European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)
- ◁ British Society for Allergy and Clinical Immunology (BSACI)
- ◁ Royal College of Paediatrics and Child health (RCPCH)

### Appendix 3 Project Steering Group

Dr Emma Barry	GP	RCSI
Prof Susan Smith	GP and Supervisor	RCSI
Dr Kirsty O'Brien	Researcher and Supervisor	RCSI
Dr Patrick Redmond	GP	RCSI
Frank Moriarty	Pharmacist	RCSI
Prof Tom Fahey	GP	RCSI
Dr Janine Cooper	Pharmacist	QUB
Prof Carmel Hughes	Pharmacist	QUB
Prof Kathleen Bennett	Pharmacoepidemiologist	RCSI

## Appendix 4 Table of indicators excluded by Steering group

Indicator by system	Reason for exclusion
Rationale for inclusion	
<b>A Gastro-intestinal system</b>	
<b>1 Metoclopramide should not be prescribed to children under the age of 1 year</b> Metoclopramide can induce acute dystonic reactions such as facial and skeletal muscle spasms and oculogyric crises.	Low prevalence
<b>2 Domperidone should not be prescribed concomitantly with Ketoconazole</b> Ketoconazole inhibits Domperidone metabolism; Domperidone levels may be increased up to 3-fold. This resulted in a small mean increase in QT prolongation.	Low prevalence
<b>3 Anti-obesity drugs are generally not recommended for children under the age of 16 years</b> Diet and exercise are the preferred methods of weight loss in children.	Medications not reimbursed through PCRS from 2012.
<b>4 Df c h c b · Di a d · = b \ ] V ] h c f g · fl DD = Dg L · g \ c i · X · b c f of 2 years</b> The efficacy of PPIs for children younger than 2 years of age with GORD is inconsistent and is insufficient to support the use of PPIs. In addition, evidence suggests that PPIs are associated with an increased risk of lower respiratory tract infections and gastroenteritis.	May be initiated by specialist.
<b>5 Histamine H2 antagonists should not be prescribed to children under the age of 2 years for gastro-oesophageal reflux disease (GORD)</b> Evidence is insufficient to support the use in primary care of histamine-2 receptor antagonists (H <sub>2</sub> RAs) for children younger than 2 years of age with GORD. Limited evidence indicates that H <sub>2</sub> RAs are associated with an increased risk of lower respiratory tract infections and gastroenteritis.	Lack of evidence.

#### Appendix 4 Table of excluded indicators cont.

<b>B Respiratory system</b>		<b>Reason for exclusion</b>
<b>6</b>	<b>Number of items for cough suppressants or nasal decongestants/patient</b> Known to be of limited effectiveness.	Format not appropriate to the aims of the study. Elements included in other indicators
<b>7</b>	<b>Children who have been prescribed Theophylline should not be prescribed Erythromycin, Ciprofloxacin or Azithromycin</b> Theophylline has a narrow margin between therapeutic and toxic dose. Plasma concentration increased by antibacterials mentioned.	Low prevalence
<b>8</b>	<b>Ratio of corticosteroid to bronchodilator as indicator of quality of asthma prescribing</b> A low ratio indicates poor prescribing.	Format not appropriate to the aims of the study. Elements included in other indicators
<b>C Central Nervous system</b>		<b>Reason for exclusion</b>
<b>9</b>	<b>Children under the age of 16 yrs should not be prescribed systemic Aspirin</b> Risk of Reye's syndrome.	Low prevalence
<b>10</b>	<b>Children under the age of 16 yrs should not be prescribed topical oral pain relief products containing salicylate salts (e.g. teething gels)</b> The CHM (2009) has advised that topical oral pain relief products containing salicylate salts should not be used in children under 16 years, as a cautionary measure due to the theoretical risk of Reye's syndrome.	Not reimbursed by PCRS
<b>11</b>	<b>Phenothiazines should not be prescribed to children under 1 yrs</b> Extrapyramidal side effects and respiratory depression may occur in susceptible children.	Low prevalence
<b>12</b>	<b>7 \ j ` X f Y b ` i b X Y f ` %* ` m f g ` g \ c i ` X ` b c h ` V Y ` d f Y g V</b> Identified as a clinically questionable prescribing in previous studies.	Low prevalence

#### Appendix 4 Table of excluded indicators cont.

- |    |   |                                |
|----|---|--------------------------------|
| 13 | <b>Females taking enzyme inducing antiepileptic drugs (EIAED) including Phenobarbitone, Primidone, Phenytoin, Carbamazepine, Oxcarbazepine and Topiramate should not be prescribed a combined oral contraceptive (COC), patch or vaginal ring</b><br>EIAEDs increase metabolism of estrogens and progesterone thereby affecting contraceptive efficacy. | Low prevalence                 |
| 14 | <b>Tricyclic and tetracyclic antidepressants should not be prescribed to children under 16 years</b><br>Lack of efficacy and can have serious side effects in some children.  | Clinical information required. |
| 15 | <b>Paroxetine and Venlafaxine should not be prescribed to children under 16 years</b><br>Clinical trials have failed to show efficacy and have shown an increase in harmful outcomes.   | Low prevalence                 |
| 16 | <b>Children under the age of 16 yrs should not be prescribed a single subclass in a 90 day period.</b><br>Identified as a clinically questionable prescribing in previous studies   | Low prevalence                 |
| 17 | <b>Children under the age of 16 yrs should not be prescribed a single subclass in a 90 day period)</b><br>Identified as a clinically questionable prescribing in previous studies. Risk of dependence   | Low prevalence                 |
| 18 | <b>Benzodiazepines should not be prescribed for greater than 30 days</b><br>Risk of dependence.   | Clinical information required  |
| 19 | <b>Children under the age of 16 yrs should not be prescribed a high total number of doses</b><br>High risk of side effects.   | Clinical information required  |

#### Appendix 4 Table of excluded indicators cont.

20	<b>Ratio of the number of children under the age of 6 yrs prescribed any psychotropic medication divided by the number of youths under 18 yrs who were prescribed any medication.</b> There has been a drastic increase in recent years in the number of very young children being prescribed psychotropics.	Format not applicable to this study
<b>E</b>	<b>Endocrine system</b>	<b>Reason for exclusion</b>
21	<b>In children aged 5-16 yrs who are on long term steroid tablets (e.g. longer than three months) or requiring frequent courses of steroid tablets (e.g. three to four per year) an inhaled corticosteroid should also be prescribed as well as a short acting beta 2 agonist, and a trial of a LABA.</b> Patients on long term steroid tablets (e.g. longer than three months) or requiring frequent courses of steroid tablets (e.g. tree to four per year) will be at risk of systemic side effects.	Clinical information needed. Some elements included in other indicators.
<b>F</b>	<b>Dermatological system</b>	<b>Reason for exclusion</b>
22	<b>Proportion of children prescribed more than one topical corticosteroid that have been prescribed Fucidin or prescribed a corticosteroid cream with Fusidic acid</b> There are high rates of resistance to Fusidic acid.	Lack of evidence
23	<b>If Isotretinoin is prescribed there should be evidence of failure of previous acne therapy (within the last 12 months)</b> Many side effects including changes in bone density and growth as well as suicidal ideation and depression	May be initiated by specialist.

#### Appendix 4 Table of excluded indicators cont.

G	General	Reason for exclusion
24	<b>A high rate of generic prescribing</b> A high rate of generic prescribing is considered to be a marker of cost consciousness.	Format not applicable to the study
25	<b>Consumption of antibacterials for systemic use expressed in DID</b> This is likely to best indicate the size of the pressure driving antibiotic resistance which is highly relevant for public health.	Format not applicable to the study. Public health indicator
26	<b>Consumption of beta lactamase sensitive penicillins expressed as a percentage of the total consumption of antibacterials for systemic use</b> Generally, narrow-spectrum antibacterials are preferred to broad-spectrum antibacterials unless there is a clear clinical indication e.g. life-threatening sepsis.	Format not applicable to the study. Public health indicator
27	<b>Consumption of 3<sup>rd</sup> and 4<sup>th</sup> generation of cephalosporins expressed as a % of the total consumption of antibiotics for systemic use.</b> Antibiotic-associated colitis may occur with the use of broad-spectrum cephalosporins, particularly second- and third-generation cephalosporins.	Format not applicable to the study. Public health indicator
28	<b>Ratio of number of items for Co-Amoxiclav to number of items for all antibiotics</b> Co-Amoxiclav is generally considered a second line antibiotic for most common conditions requiring antibiotic treatment and therefore the ratio of this antibiotic to all antibiotics prescribed should reflect this.	Format not applicable to the study. Public health indicator.
29	<b>Ratio of number of items for quinolones to number of items for all antibiotics</b> Quinolones not generally recommended in children unless growth is complete, there is a risk of musculoskeletal damage.	Format not applicable to the study. Public health indicator.



#### Appendix 4 Table of excluded indicators cont.

30	<p><b>Ratio of 2<sup>nd</sup> line (or broad spectrum?) antibiotic to the number of items for any antibiotic</b></p> <p>Second line and broad spectrum antibiotics should be prescribed at a much lower level than narrow spectrum and first line antibiotics.</p>	Format not applicable to the study. Public health indicator.
31	<p><b>Ratio of the consumption of broad spectrum antibiotics to the consumption of narrow spectrum antibiotics</b></p> <p>Second line and broad spectrum antibiotics should be prescribed at a much lower level than narrow spectrum and first line antibiotics.</p>	Format not applicable to the study. Public health indicator
32	<p><b>Seasonal variation in the total antibiotic consumption</b></p> <p>Marked variation in antibiotic use is likely to reflect poorer practice since it represents higher use of antibiotics for respiratory infections which has a poor evidence base.</p>	Format not applicable to the study. Public health indicator
33	<p><b>Mefloquine should not be prescribed to children under 16 years with a history of convulsions</b></p> <p>Mefloquine is an anti-infective agent for protection and treatment of malaria, there is an increased convulsion risk with epilepsy.</p>	Clinical information needed

## Appendix 5 Members of the Delphi Panel

Name	Area of Expertise	Location
Dr Sumi Dunne	Academic and clinical General Practice	ROI
Dr John Delap	General Practice	ROI
Dr Muireann de Paor	Academic and clinical General Practice	ROI
Dr Turlough Bolger	General Practice and Paediatrics	ROI
Dr Carol Blackburn	Paediatrics	ROI
Dr Aoife Carroll	Paediatrics	ROI
John Hayden	Academic and clinical Pharmacy	ROI
Paul Dillon	Academic and clinical Pharmacy	ROI
Anne Teresa Morgan	Academic and clinical Pharmacy	ROI
Dr Bill Beeby	General Practice	UK
Dr Beth Rimmer	General Practice	UK
Dr Simon Hurding	Academic and clinical General Practice	Scotland
Prof Alastair Sutcliffe	Academic and clinical Paediatrics	UK
Prof Michael Shields	Academic and Clinical Paediatrics	NI
Dr Dan Hawcutt	Paediatrics and Clinical Pharmacology	UK
Dr Paul McCague	Paediatric academic pharmacist	NI
Sharon Conroy	Paediatric Clinical and academic pharmacist	UK
Dr Catherine Tuleu	Paediatric academic Pharmacist	UK



## **Appendix 6 Description of analytic approach used to apply the indicators of commission of PIP**

### **1. Intranasal beclometasone should not be prescribed to children under 6 years.**

Number of children <6 years old with at least one prescription for R01AD01 between Jan 2014 and Dec 2014 inclusive DIVIDED by population of GMS eligible children <6 years old (i.e. 0-5 years inclusive)

### **2. Carbocisteine should not be prescribed to children**

Number of children <16 years old with at least one prescriptions for R05CB03 between Jan 2014 and Dec 2014 inclusive DIVIDED by population of GMS eligible children <16 years old (i.e. 0-15 years inclusive)

### **3. Sedating antihistamines should not be prescribed to children under 2 years**

Number of children <2 years old with at least one prescriptions for R06AD02 or R06AB04 or N05BB01 or R06AX17 or R06AD01 between Jan 2014 and Dec 2014 inclusive DIVIDED by population of GMS eligible children <2 years old (i.e. 0-1 years inclusive)

### **4. Loperamide should not be used in the treatment of diarrhea in children under 4 years**

Number of children <4 years old with at least one prescriptions for A07DA03 or A07DA53 between Jan 2014 and Dec 2014 inclusive DIVIDED by population of GMS eligible children <4 years old (i.e. 0-3 years inclusive)

### **5. Tetracyclines should not be prescribed to children under 12 years**

Number of children <12 years old with at least one prescriptions for J01AA between Jan 2014 and Dec 2014 inclusive DIVIDED by population of GMS eligible children <12 years old (i.e. 0-11 years inclusive)

### **6. Codeine/Dihydrocodeine medications should not be prescribed to children under 12 years**

Number of children <12 years old with at least one prescriptions for R05DA04 or N02AA59 or N02AA79 or N02AA08 or N02AA58 between Jan 2014 and Dec 2014 inclusive DIVIDED by population of GMS eligible children <12 years old (i.e. 0-11 years inclusive)

### **7. Domperidone should not be prescribed concomitantly with erythromycin**

Number of children <16 years old with at least one prescription for A03FA03 and J01FA01 on the same day (i.e. same claim) between Jan 2014 and Dec 2014 inclusive DIVIDED by population of GMS eligible children <16 years old (i.e. 0-15 years inclusive)

## **Appendix 7 Description of the analytical approach used to apply indicators of omission of appropriate prescribing.**

### **An inhaled short acting beta-2 agonist should be prescribed to all children who are prescribed two or more inhaled corticosteroids**

Number of children with at least 2 prescriptions for R03BA (ICS) between Jan 2014 and Dec 2014 who DID NOT have a prescription for R03AC02 or R03AC03 (SABA) in the previous 12 months from the date of second prescription for R03BA DIVIDED by number of the number of children with at least 2 prescriptions for R03BA between Jan 2014 and Dec 2014.

### **An inhaled short acting beta-2 agonist should be prescribed to children under 5 years who are prescribed a leukotriene receptor antagonist**

Number of children under 5 years with at least one prescription for R03DC03 (LTRA) who DID NOT have a prescription for R03AC02 or R03AC03 (SABA) in previous 12 months from date of first prescription for R03DC03- DIVIDED BY the number of children under 5 years with at least one prescription for R03DC03 between Jan 2014 and Dec 2014 inclusive.

### **An inhaled corticosteroid should be prescribed to children aged 5-15 years who are taking a long acting beta-2 agonist (LABA).**

Number of children aged 5-15 years with a prescription for R03AC12 or R03AC13 (LABA) who DID NOT have a prescription for a R03BA (ICS) within a month (before or after) the prescription of R03AC12 or R03AC13 DIVIDED BY the number of children between 5 and 15 years old with at least one prescription for either R03AC12 or R03AC13 between Jan 2014 and Dec 2014 inclusive.

### **A spacer device should be prescribed at least every 12 months to children under 12 years who are prescribed a pressurised metered-dose inhaler (pMDI)**

Number of children with at least one prescription for R03AC or R03BA (pMDI) who DID NOT have a prescription for V07AY98 (spacer) in previous 12 months from date of first prescription for R03AC or R03BA DIVIDED BY the number of children <12years old with at least one prescription for either R03AC or R03BA between Jan 2014 and Dec 2014 inclusive.

### **An emollient should be prescribed to children who are prescribed greater than one topical corticosteroid in a year.**

Number of children with at least two prescription for D07A or D07B or D07C or D07X (topical corticosteroids) who DID NOT have a prescription for D02A (emollient) in previous 12 months from date of second prescription for D07A or D07B or D07C or D07X DIVIDED by the number of children < 16 years old with at least two prescriptions of D07A or D07B or D07C or D07X between Jan 2014 and Dec 2014 inclusive.

## **Appendix 8 Delphi panel invitation**

Study Title: The PIPc study: Development and validation of indicators of potentially inappropriate prescribing in children.

Dear Dr X

I am writing to invite you to participate in the above study. The aim of this study is to develop and validate an explicit list of indicators of potentially inappropriate prescribing for use in children in primary care. These prescribing indicators will be developed using a Delphi technique, with a two round process. To undertake this, a panel of experts from across the Republic of Ireland and the United Kingdom will be recruited. You have been approached to participate in this Delphi panel because of your clinical and research expertise.

If you accept this invitation to participate, you will form part of the Delphi panel and will be asked to use an online survey to rate your level of agreement with a series of statements about prescribing in children. We estimate this will take about 20 to 30 minutes of your time.

This study has received ethical approval from the RCSI research ethics committee.

Please find enclosed a study information sheet which provides further information about the study.

I would like to thank you for taking the time to consider your involvement in this study. If you are happy to be involved in this study please reply by email.

Yours Sincerely,

Dr Emma Barry

If you would like further information on this study please do not hesitate to contact the researchers:

Dr Emma Barry or Prof Susan Smith

Contact details: [emmabarry@rcsi.ie](mailto:emmabarry@rcsi.ie) or [susansmith@rcsi.ie](mailto:susansmith@rcsi.ie)

## **Appendix 9 Delphi panel information leaflet**

## Delphi Panel Participant Information Sheet

Study Title: The PIPc study: Development and validation of indicators of potential inappropriate prescribing in children.

Please read the following information. If you have any questions in regards to this study please contact a member of the research team. Contact details can be found at the end of this information sheet.

What is the purpose of this study?

The objective of the proposed study is to develop and validate an explicit list of indicators of quality prescribing for use in children. Development of the list will be achieved through the formation of a Delphi panel, consisting of academic GPs, general and specialist paediatricians and pharmacists. This will ensure representation from a diverse range of specialities and from across the Republic of Ireland and the UK. Validation of the indicators will entail application of the developed list of indicators to an anonymised PCRS (Primary Care Reimbursement Service) dataset held by the Department of Pharmacology,

T r i n i t y   R e s e a r c h   C e n t r e ,   S t .   J a m e s '   H o s p i t a

Why have you been chosen?

You have been invited to participant in this Delphi panel because of your clinical and research expertise in paediatric care.

What will you have to do in this study?

You will be sent, via email, a weblink which will bring you to an on-line questionnaire. This will consist of a series of statements about the prescribing of specific drugs and you will be asked to indicate your level of agreement with the statements. Approximately six weeks later, a further email will be sent to you with another weblink bringing you to a revised questionnaire, which you will complete in the same way as before. You will have the opportunity to also include any comments that you may wish to make on the statements.

Will you be able to withdraw from the study?

You are free to withdraw from the study at any stage. If you decide to withdraw from the panel before the completing the second questionnaire, any information recorded in the first questionnaire will not be used.

Will your details be kept confidential?

All information collected as part of the study will be treated in a confidential manner and your anonymity is assured. All identifiable information (such as consent forms) will be stored securely at the HRB Centre for Primary Care Research, RCSI Dublin and will then be destroyed in accordance with the Data Protection Act (1998). The study data will also be stored for 5 years.

All studies conducted within the University are required to be monitored to ensure a high standard of research. As a result, information collected as part of this research may be called for review by the research governance team of the Royal College of Surgeons in Ireland.

How will the results of the research be disseminated?

The Delphi process and the final validated prescribing indicators will be published in a high impact journal and presented at relevant conferences. All results will be anonymous and you will be provided with a report of the results at the end of the study.

Who is organising and funding this research?



This project is for an MSc by research. This project is funded by the Health Research Board Centre for Primary Care Research, Royal College of Surgeons in Ireland.

Who has reviewed the research?

The study has been approved by the research ethics committee of the RCSI Dublin.

If you would like further information on this study please do not hesitate to contact the researchers listed below:

Dr Emma Barry

Prof Susan Smith

HRB Centre for Primary Care Research

HRB Centre for Primary Care Research

Royal College of Surgeons

Royal College of Surgeons

Beaux Lane House

Beaux Lane House

Mercer Street Lower

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Dublin 2

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Tel: +353 (01) 4022408

Email: [emmabarry@rcsi.ie](mailto:emmabarry@rcsi.ie)

Email: [susansmith@rcsi.ie](mailto:susansmith@rcsi.ie)

## Appendix 10 Consent Form

Delphi panel members consent form

Study Title: The PIP study: Development and validation of indicators of potential inappropriate prescribing in children.

Please initial the following statements as appropriate.

I have read the information sheet provided in relation to the above study and I have asked any necessary questions.	
I understand my role in participating in above study.	
I understand that I may withdraw from the study at any time without giving a reason.	
I understand that my personal information (including consent forms) will be confidential and stored in a safe manner in the HRB Centre for Primary Care Research, RCSI, Dublin	
I understand that relevant data collected during the study may be looked at by individuals involved in the study and the University for audit purposes.	
I agree to provide the information about myself described in the information sheet.	
I agree to take part in the Delphi panel described in the information sheet.	

Please complete below.

Participant Name (Print):

Participant Signature:

Date:

Researcher Name (Print):

Researcher Signature:

Date:

## Appendix 11 Research Ethics Committee Approval

Royal College of Surgeons in Ireland  
The Research Ethics Committee  
121 St. Stephens Green, Dublin 2, Ireland.  
Tel: +353 1 4022205 Email: recadmin@rcsi.ie

Dr David Smith, Acting Chair  
Dr Niamh Clarke, Convenor

7<sup>th</sup> July 2014

Dr Emma Barry  
HRB Centre for Primary Care Research,  
RCSI, 123 St. Stephens Green  
Dublin 2



Ethics Reference No:	REC926
Project Title:	The Children's PIP study
Researchers Name (lead applicant):	Dr Emma Barry
Principle investigator	Professor Susan Smith
Other Individuals Involved:	Dr Kirsty O'Brien, Dr Patrick Redmond and Prof Tom Fahey, HRB centre for Primary Care, RCSI; Dr Anthony Cummins, Dept of General Practice, RCSI; Dr Janine Cooper and Professor Carmel Hughes - School of Pharmacy, Queens University Belfast; Dr Fiona Boland, Population Health Sciences, RCSI; Dr Udo Reulbach, Our Lady's Children's Hospital Crumlin, Ms Arelene Cock-Wall, Irish Medicines Formulary; Professor Kathleen Bennett, Trinity Centre for Health Sciences, St James's Hospital.

Dear Dr Barry,  
Thank you for your Research Ethics Committee (REC) application. We are pleased to advise that ethical approval has been granted by the committee for this study.

This letter provides approval for data collection for the time requested in your application and for an additional 6 months. This is to allow for any unexpected delays in proceeding with data collection. Therefore this research ethics approval will expire on **7<sup>th</sup> January 2017**.

Where data collection is necessary beyond this point, approval for an extension must be sought from the Research Ethics Committee.

This ethical approval is given on the understanding that:

- All personnel listed in the approved application have read, understand and are thoroughly familiar with all aspects of the study.
- Any significant change which occurs in connection with this study and/or which may alter its ethical consideration must be reported immediately to the REC, and an ethical amendment submitted where appropriate.
- Please submit a final report to the REC upon completion of your project.

We wish you all the best with your research.

Yours sincerely,

*Niamh Clarke*  
PP Dr. Niamh Clarke (Convenor)  
Dr David Smith (Acting Chair)

## Appendix 12 Example of Surveygizmo questionnaire

The screenshot shows a web browser window with the URL [www.surveymzmo.com/s3/2636946/PIPc-study](http://www.surveymzmo.com/s3/2636946/PIPc-study). The questionnaire is titled "PIPc study" in a blue header. Below the header, the section is titled "Respiratory system". The first question is: "1. Carbocisteine should not be prescribed to children under 2 years". The rationale provided is: "Rationale: There is a lack of evidence for its efficacy in the general population". A link to "Evidence: Cochrane Systematic Review" is also present. The response options are: "Strongly disagree", "Disagree", "Neutral", "Agree", and "Strongly agree", each with a radio button. Below the response options is a "Comments" section with a text input field. A "Submit" button is located at the bottom right of the question area. A progress bar at the bottom indicates 0% completion.

PIPc study

Respiratory system

1. Carbocisteine should not be prescribed to children under 2 years

Rationale: There is a lack of evidence for its efficacy in the general population

[Evidence: Cochrane Systematic Review](#)

Strongly disagree   Disagree   Neutral   Agree   Strongly agree

Comments

Submit

0%

# BMJ Open PIPc study: development of indicators of potentially inappropriate prescribing in children (PIPc) in primary care using a modified Delphi technique

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The PIPc Project Steering group

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## ABSTRACT

**Objective:** There is limited evidence regarding the quality of prescribing for children in primary care. Several prescribing criteria (indicators) have been developed to assess the appropriateness of prescribing in older and middle-aged adults but few are relevant to children. The objective of this study was to develop a set of prescribing indicators that can be applied to prescribing or dispensing data sets to determine the prevalence of potentially inappropriate prescribing in children (PIPc) in primary care settings.

**Design:** Two-round modified Delphi consensus method.

**Setting:** Irish and UK general practice.

**Participants:** A project steering group consisting of academic and clinical general practitioners (GPs) and pharmacists was formed to develop a list of indicators from literature review and clinical expertise. 15 experts consisting of GPs, pharmacists and paediatricians from the Republic of Ireland and the UK formed the Delphi panel.

**Results:** 47 indicators were reviewed by the project steering group and 16 were presented to the Delphi panel. In the first round of this exercise, consensus was achieved on nine of these indicators. Of the remaining seven indicators, two were removed following review of expert panel comments and discussion of the project steering group. The second round of the Delphi process focused on the remaining five indicators, which were amended based on first round feedback. Three indicators were accepted following the second round of the Delphi process and the remaining two indicators were removed. The final list consisted of 12 indicators categorised by respiratory system (n=6), gastrointestinal system (n=2), neurological system (n=2) and dermatological system (n=2).

**Conclusions:** The PIPc indicators are a set of prescribing criteria developed for use in children in primary care in the absence of clinical information. The utility of these criteria will be tested in further studies using prescribing databases.

## Strengths and limitations of this study

- The members of Delphi panel in this study were heterogeneous in experience and setting, and represented the professions involved in prescribing and dispensing to children.
- The Delphi process used in the study followed predefined methodology in line with best practice.
- Dispensing databases may not contain clinical information, limiting the application of indicators that require such information for interpretation.
- The reliability of the Delphi technique as a method for achieving consensus has been debated but its potential limitations are similar to other consensus techniques.

## BACKGROUND

Quality of prescribing for children has been identified as an area of concern since the late 1970's, when it was reported that 60% of children under 14 years received at least one prescription a year from their family practitioner.<sup>1</sup> Currently, children represent over 25% of the population and receive an average of three prescription medications before 5 years of age.<sup>2</sup> There are ongoing concerns over the quality of prescribing for children, but there is a lack of studies in this area.<sup>3</sup> Potential consequences for children may be adverse drug events leading to unplanned hospital admissions and preventable deaths.<sup>4</sup>

Medicines are generally considered appropriate in an adult population when they have a clear evidence-based indication, are well tolerated in the majority of patients and are cost effective.<sup>5</sup> Medicines or prescribing patterns that do not fit this description can be considered inappropriate; this term includes



misprescribing, underprescribing and overprescribing.<sup>6</sup> Misprescribing includes the incorrect prescription of an indicated medication and can be divided into drug choice, dosage, duration of therapy, duplication of drugs of the pharmacological class and drug-disease or drug-drug interactions or drug-food interactions. Underprescribing includes the omission of a prescription that is needed and overprescribing; the prescription of a medication that is unnecessary.<sup>7</sup> The term 'potentially inappropriate prescribing' acknowledges the reality of prescribing in clinical practice, whereby the prescription of an inappropriate medication may be justified by the individual needs of a particular patient.<sup>8</sup> For example, sedating antihistamines may be considered inappropriate for young children because of the risk of side effects such as sedation, paradoxical excitation and potential cardiac toxicity. However, they may, in some instances, be useful in the treatment of insomnia relating to itch caused by eczema.

Research into potentially inappropriate prescribing in adults has focused on the development of indicators or explicit criteria of prescribing, which are measurable criteria against which quality standards can be set and audited. Explicit indicators, such as the Screening Tool to Alert doctors to the Right Treatment/Screening Tool of Older Peoples' potentially inappropriate Prescriptions (START/STOPP) criteria, were devised to identify PIP in older adults and have been found to be valid, reliable and generalisable across international primary care settings.<sup>9</sup>

To date, many quality indicators of care of children in primary care relate to specific diseases or conditions such as mental health or diabetes.<sup>10–13</sup> More recent work in France has led to the development of the first set of indicators of inappropriate prescribing in children for use in hospital and community settings.<sup>12</sup> Researchers in the UK have also developed primary care quality indicators for children that include some prescribing indicators but focus on broader issues such as the management and assessment of clinical conditions, child development and child protection.<sup>13</sup> Other criteria have been developed for use in the out-of-hours setting and in paediatric emergency departments.<sup>14–15</sup>

Recent studies have highlighted that explicit prescribing indicators are not sufficient to assess whether prescribing is appropriate or not in the context of assessing daily prescribing practices.<sup>16</sup> Ideally, a prescribing indicator would be based on a thorough review of patient records with access to the full clinical and treatment history of the patient. Nonetheless, this process is time consuming and can be extremely complex.<sup>17–18</sup> Although the evidence base for developing explicit prescribing indicators is limited, combining expert professional opinion with consensus methodology can create quality indicators in areas where it would not otherwise be possible.<sup>19</sup> Explicit indicators can be useful in assessing the quality of prescribing using large national prescribing databases without clinical information.<sup>20</sup>

This study aims to create indicators that are based on commonly prescribed medications to children in primary care and are supported by international best practice guidelines.

## METHOD

### Study design

A modified Delphi consensus technique was used to develop these prescribing criteria. This technique allows an estimate of an overall group opinion to be reached by improving agreement between a panel of experts through rounds of questionnaires.<sup>21</sup> The Delphi panel was modified as direct feedback would not be provided to the Delphi panel members between rounds. Ethical approval for this study was obtained from the Royal College of Surgeons in Ireland (RCSI) Research Ethics Committee, Dublin, Ireland in April 2014.

### Compilation of initial indicators

We undertook a comprehensive literature search using PubMed to identify any previously developed indicators relating to potentially inappropriate prescribing in children (PIPC). Online supplementary file 1 shows the search string used. As very few indicators from lists devised for adults or older adults are applicable to children, the search strategy was limited to include only those articles involving infants, children or adolescents. The search was performed initially in April 2014 and updated in August 2015.

A set of initial indicators were identified from the literature search. Clinical guidelines, web sources and PubMed were used to identify the best available evidence to support each indicator. Online supplementary file 2 details a full list of information sources used. The British National Formulary for Children (BNFc)<sup>22</sup> and the Irish Medicines Formulary (IMF)<sup>23</sup> were used as reference resources for indication, dosages and licensing information.

A project steering group was formed to guide the development of the indicators using predefined inclusion and exclusion criteria. The steering group consisted of academic/clinical general practitioners (GPs), three academic/clinical pharmacists, a pharmacoepidemiologist/statistician and a postdoctoral researcher, all members of either the HRB Centre for Primary Care Research at the RCSI Dublin or the School of Pharmacy at Queen's University Belfast.

Inclusion criteria are as follows: indicators had to:

- ▶ describe a pattern of prescribing that was potentially hazardous or known to be ineffective
  - ▶ describe a pattern of prescribing that was not in keeping with best practice or current guidelines
  - ▶ apply to the population of interest; children <16 years
- Exclusion criteria are as follows:
- ▶ medications currently unavailable in the study setting
  - ▶ criteria which could not be applied in the absence of clinical information



- criteria containing medications with a low prevalence of use (to define uncommon use, a cut-off of <0.5/1000 General Medical Scheme (GMS) patients was agreed by the project steering group)

Members of the project steering group applied the inclusion and exclusion criteria and examined the evidence supporting each indicator. For example, the criterion 'Fluoxetine is the most appropriate antidepressant for children, other SSRIs should not be prescribed' was removed by the project steering group during this screening stage as the criterion related specifically to patients with depression and could not be successfully applied in the absence of clinical information. Some criteria identified from literature were modified by the project steering group to make them applicable to dispensing database without clinical information, for example, 'Children with eczema should be prescribed an emollient' was altered to 'An emollient should be prescribed to children who are prescribed greater than one topical corticosteroid in a year', where the prescription of greater than one topical corticosteroid in a year was considered a proxy for a diagnosis of eczema. Supplementary file 3 details the indicators removed and the reasons for exclusion by the project steering group.

#### The primary care reimbursement service database (PCRS)

The prevalence of individual drug use in children in 2011 was determined using dispensing data from the Health Service Executive-Primary Care Reimbursement Service (HSE-PCRS). The PCRS is a national dispensing database in Ireland; it stores information on all medications and other health services, provided without charge to people eligible for free medical services in Ireland under the GMS. Eligibility for free medical care is established via means testing and therefore the data collected by the PCRS is not fully representative of the entire population of Ireland. Approximately 39% (414 856) of the total population (1 072 220) of children <16 years in the Republic of Ireland were eligible for the scheme in 2014. The PCRS contains data on prescriptions originating in primary and secondary care for all children who are eligible for free medical services. Children who receive a prescription from a hospital specialist will have their prescription transcribed to a GMS prescription by their GP in order to avail of free medication. The PCRS does not record data on whether a prescription has originated in primary or secondary care. An Anatomical Therapeutic Chemical Classification System (ATC) code was assigned to each indicator to allow for extraction from the dispensing database.

#### Selection of the Delphi panel

In total, 30 specialists from the UK and Republic of Ireland were invited *a priori* (via email) to participate in a Delphi panel to develop these criteria. Although no specific standard was applied to define an expert, the specialists invited to participate on the panel were peer recognised as experts in their fields by the project

steering group and consisted of academic and clinical GPs, paediatricians and pharmacists. A total of 18 specialists agreed to participate. The panel consisted of nine experts from the Republic of Ireland (three GPs, three paediatricians, three pharmacists) and nine from the UK (three GPs, three paediatricians, three pharmacists). Written consent was received before starting the process.

#### Data collection and analysis

The consensus process involved two rounds of web-based questionnaires. The questionnaire was piloted among the project steering group and GP members of the Department of General Practice, RCSI with minor modifications made subsequently. The first and second rounds of the questionnaires were sent to the Delphi panel between January 2015 and May 2015 and between June 2015 and July 2015, respectively. For each round, panel members were emailed a link to a questionnaire which was maintained on an online survey software tool (SurveyGizmo). Panellists were presented with each indicator and an accompanying rationale for the indicator, categorised by physiological systems (gastrointestinal system, respiratory system, central nervous system, dermatological system) along with a hyperlink to a supporting evidence resource, for example, Cochrane systematic review, the BNFc or national or international guidelines. Panellists were asked to indicate their level of agreement with each indicator using a five-point Likert scale,<sup>24</sup> (where 1 was strongly disagree and 5 was strongly agree) and to provide comments within a free text box.

Following completion of the first round of questionnaires, the median response and the IQR for each indicator were calculated from the Likert scale. The level required for consensus between the panel members was decided prior to starting the study. When the upper quartile was  $\leq 2$ , this indicated there was consensus by the Delphi panel members on rejection of the indicator. When the lower quartile was  $\geq 4$ , this indicated there was consensus by the Delphi panel members on acceptance of the indicator. When the IQR included 3, this indicated there was a lack of agreement between the panel members and a need for further review of the particular indicator. These indicators were reviewed by project steering group and were either revised and included in the second questionnaire or rejected based on the comments received from the Delphi panel. Panellists did not receive feedback from the first questionnaire. The second questionnaire was presented in the same format as the first. Again, the median response and the IQR were calculated, and the project steering group reviewed these measures of agreement along with any additional comments. If consensus was not reached following the second round, the criterion was rejected.

#### RESULTS

Figure 1 summarises the development of the indicators. Literature searches identified 47 potential indicators.

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**Contributors** EB assisted in the compilation of the initial indicators, revised the indicators, developed the online survey, engaged the Delphi panel and drafted the manuscript. SMS conceived and supervised the study. KOB devised the initial indicators. KB extracted the prevalence data. FB provided statistical support. FM, JC, PR, CMH, TF and SMS formed the project steering group and reviewed the indicators throughout the study. All members of the project steering group revised the manuscript.

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Table 3 Accepted indicators

<b>Respiratory system</b>	
1	Intranasal beclometasone should not be prescribed to children under 6 years.
2	Carbocysteine should not be prescribed to children
3	An inhaled short-acting $\beta$ -2 agonist should be prescribed to all children who are prescribed two or more inhaled corticosteroids for presumed asthma
4	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.
5	An inhaled corticosteroid should be prescribed to children aged 5–15 years, who are taking a long acting $\beta$ -2 agonist (LABA)
6	Children under 12 years who are prescribed a pressurised metered-dose inhaler (pMDI) should also be prescribed a spacer device at least every 12 months
<b>Gastrointestinal System</b>	
7	Loperamide should not be prescribed to children under 4 years.
8	Domperidone should not be prescribed concomitantly with erythromycin.
<b>Dermatological system</b>	
9	An emollient should be prescribed to children who are prescribed greater than one topical corticosteroid in a year.
10	Tetracyclines should not be prescribed to children under 12 years.
<b>Neurological system</b>	
11	Codeine/dihydrocodeine medications should not be prescribed to children under 12 years.
12	Sedating antihistamines should not be prescribed to children under 2 years.
LABA, long-acting $\beta$ -2 agonist; pMDI, pressurised metered-dose inhaler.	

significant efforts were made to ensure that the Delphi panel were heterogeneous in experience and setting to limit this potential bias. There may be variation in knowledge underpinning panel members' views, but the Delphi panel was provided with the best available evidence to mitigate this effect. It may have been useful to provide the panel with a more objective rating of the evidence, for example using the GRADE system to further aid decision-making, but this was beyond the scope of the current study.<sup>29</sup>

Explicit prescribing criteria are limited in that they do not address individual differences among patients or the complexity or appropriateness of entire medication regimens.<sup>30</sup> Furthermore, they need to be regularly updated in line with evidence, and country-specific adaptations are necessary where countries differ in their guidelines, standards and approved medications.

Finally, the database used in this study to determine the prevalence of the indicators is not fully representative of the entire population of children in Ireland. The PCRS database contains information on prescriptions

dispensed under the means-tested GMS scheme for which ~39% of the population under 16 years were eligible in 2014. Poorer health has been reported in socio-economically deprived areas<sup>31</sup> with an increased prevalence of prescribing; therefore, the use of this database would have inflated the prevalence of prescribing, thus mitigating against the effects of this potential source of bias. Unfortunately data on non-eligible patients are not routinely collected in the Republic of Ireland.

#### Implications for research and practice

The examination of individual clinical information to assess the appropriateness of prescribing can be time-consuming and difficult. These indicators can be applied quickly and easily to large population-based data sets in the absence of clinical information to identify PIPc unexamined to date. A study to validate the indicators developed in this study is currently underway using the PCRS database. Changes and unwarranted variation in prescribing patterns can be identified across time and geographical area. Researchers in other countries outside of Ireland and the UK could use these indicators with translation and some modifications based on country-specific guidelines, clinical practices and drug formularies.<sup>7</sup> The indicators can be used to examine the impact of changes in guidelines on prescribing patterns on a population level, for example asthma care. The cost of PIPc can also be examined.

The indicators may be used as a screening tool at the level of individual clinical practices and could be used to support detailed medication review of individual patients. Community pharmacists, who routinely dispense medications without clinical information, could also use these indicators as a resource for clinically checking prescriptions for children.

Identification and quantification of PIP in older populations has led to the development of interventions that improve prescribing. For example, a randomised controlled trial of a multifaceted intervention which included pharmacist advice, web-based pharmaceutical treatment algorithms and tailored patient information leaflets had a positive effect on PIP in older populations.<sup>32</sup> Integrating some of these supports into clinical decision support systems may prove to be a practical method of improving PIPc.

#### CONCLUSION

To date, research into paediatric prescribing in primary care is lacking. This study offers a set of 12 evidence-based explicit prescribing indicators to identify PIPc in primary care. The application of these indicators will enable investigation of the prevalence of PIPc and allow examination of changes in PIPc over time.

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Table 2 Exemplar comments received from the Delphi panel on rejected indicators

Rejected following round 1 Indicator Rationale	Comments
<b>Domperidone should not be prescribed to children under 1 year, and for children over 1 year, it should not be prescribed for more than 7 days.</b> Efficacy in GORD and gastroenteritis is uncertain in this age group. Extrapyramidal side effects occur in young children. Can be used for short-term treatment of nausea and vomiting, maximum duration of use should not normally exceed 1 week.	<i>'domperidone is not evidence based for little ones'</i> <i>'would not prescribe...because of risk of extrapyramidal side effects'</i> <i>'have used this longer term in many cases with no adverse effects But am aware of recent questions'</i> <i>'efficacy of this drug is unproven, any drug which may mask symptoms or disease progression should never be prescribed for apparent gastroenteritis'</i> <i>'occasional use necessary- if a child can't sleep won't grow...'</i> <i>'very rare situations this might be appropriate'</i> <i>'agree unless prescribed by a consultant'</i> <i>'if child has severe eczema they may be needed for a short period of time'</i> <i>'possibly under dermatology guidance for rare severe eczema'</i>
<b>Very potent or potent topical corticosteroids should not be prescribed to children under 1 year</b> Topical corticosteroids can cause adrenal suppression and Cushing's syndrome.	
Rejected following round 2 Indicator Rationale	Comments
<b>Other than in children with asthma, systemic corticosteroids should not be prescribed to children aged 5–15 years.</b> Systemic corticosteroids can cause serious side effects including adrenal suppression, immunosuppression and mood disturbances. In the general paediatric population, there are few indications for systemic corticosteroids apart from asthma and croup. Croup commonly affects children under 5 years.	<i>'Agree unless there is a clinical indication such as flare of juvenile rheumatoid arthritis'</i> <i>'Exceptions being serious diseases where specialists might prescribe. e.g. glomerulonephritis'</i> <i>'there are relatively rare indications for systemic steroids in children- they would always be initiated by a specialist'</i>
<b>Long-acting <math>\beta</math> agonists (LABAs) should not be prescribed to children under 5 years.</b> Use of LABAs is associated with increased risk of asthma exacerbations, hospitalisations and asthma-related deaths in children and adults. It is not known if combination use with inhaled corticosteroids reduces this risk.	<i>'Not recommended by the British thoracic guidelines in under 5s'</i> <i>'Lack of fear of their pernicious side effects plus a lack of understanding of the definition of asthma is to blame'</i> <i>'The Cochrane review summary that is attached says that LABA does not significantly decrease exacerbations or hospitalisations as opposed to your statement of increasing the risk based on the SMART trial'</i> <i>'I have seen evidence of poor response to short acting bronchodilators in those on long acting bronchodilators'</i>

GORD, Gastro-oesophageal reflux disease; LABA, long-acting  $\beta$  agonists; SMART, Salmeterol Multicenter Asthma Research.

order to remove any potential bias of panellists altering their responses to fit those of the groups. The Delphi consensus method allowed the expert panel members to inform the development of these criteria through their level of agreement and additional comments. Some criteria were rejected by the panellists due to the difficulty in determining the appropriateness of a prescribed medication without knowledge of whether a treatment had been initiated by a specialist. Medications which were considered to be appropriate 'under specialist supervision only' were therefore removed. Finally, to ensure relevance to clinical general practice each indicator was presented with a clear rationale that described either a lack of clinical effectiveness or the potential serious side effects of the relevant medication. The rationale for the indicator was supported by the highest level of evidence available, provided to the panel in an

easily accessible format to facilitate informed decision-making.

The main limitation of this study relates to use of the Delphi technique. While it is a commonly used technique, the reliability of the Delphi method for achieving consensus has been debated in the literature. 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.<sup>27</sup> In this study, a panel size of 15 experts with clinical and academic expertise in prescribing to children was used to mitigate this limitation. This is thought to be a sufficient panel size when the experts have a similar training and general understanding of the field of interest.<sup>28</sup> Ideally, the level of expertise required to be a member of the Delphi panel would be clearly defined prior to the beginning of the study.<sup>28</sup> Nonetheless,



Table 1 Continued

Indicator	Round 1		Round 2	
	Median	Revised Indicator	Median	Outcome
14. An emollient should be prescribed to children who are prescribed more than one topical corticosteroid in a year.	4 (4-5)	Accepted	NA	Accepted
15. Very potent or potent topical corticosteroids, for example, clobetasol propionate should not be prescribed to children under 1 year.	4 (3-4)	Revision required	NA	Rejected
16. Tetracyclines should not be prescribed to children under 12 years.	5 (4-5)	Accepted	NA	Accepted

Following a two-round Delphi process, the final list of indicators consisted of 12 indicators by system: respiratory n=6, gastrointestinal n=2, dermatological n=2, neurological n=2. Table 3 summarises the accepted indicators. Online supplementary file 4 details the PIPc indicators with supporting references. LABA, long-acting  $\beta$ -2 agonist; NA, not applicable; PIPc, potentially inappropriate prescribing in children; PMDI, pressurised metered-dose inhaler; SABAs, short-acting  $\beta$ -2 agonist.

quality indicators for children were also developed in the UK in 2014 using a multistep consensus methodology.<sup>13</sup> These quality indicators are based on routine and chronic care in addition to child development and child protection and include six prescribing indicators of a total number of 35 indicators overall. There is an overlap between two of these prescribing indicators and the indicators developed in this study: 'Children with asthma should be prescribed a spacer' and 'Children with atopic eczema should be prescribed emollients' overlap in both studies. However, in the UK study clinical and diagnostic information is required to implement the indicators, which were designed for auditing computerised primary care records, which contain codes for clinical conditions and have yet to be validated.<sup>13</sup> A cross-sectional study performed in the Netherlands in 2007 examined prescribing and referral in a single out-of-hours setting using 24 indicators developed from national guidelines and a GP expert panel.<sup>14</sup> These indicators focused on drug choice, primarily antibiotics, in the management of infections. In our study indicators relating to antibiotic prescribing were excluded as clinical information is required to determine the appropriateness of choice of antibiotic. Nonetheless, our indicators remain relevant to general practice as they relate to commonly prescribed medications such as anti-asthmatics. The largest cohort study to date of drug use in children in Europe found that antifebriles, respiratory drugs and dermatological agents had the highest prevalence of use across all age groups of children.<sup>25</sup>

#### Strengths and limitations

This study followed a well-defined process that has been refined by others in the development of similar criteria in populations other than children, for example, The START/STOPP criteria for detection of PIP in older adults and the PRPrescribing Optimally in Middle-aged People's Treatment (PROMPT) criteria for detection of PIP in middle-aged adults.<sup>9-26</sup> The PIPc criteria were constructed from two sources—a literature search and the expertise of the project steering group whose members had experience in clinical medicine in primary care settings and in the development of quality indicators of prescribing in other population groups. A second strength was the broad and representative sample of medical professionals involved in paediatric prescribing on the Delphi panel. The panel members were distributed across academic and clinical experience in specialities, such as paediatrics, general practice and pharmacy, providing a high level of (face) validity to the process and were representative of geographically diverse areas of Ireland and the UK. Out of 18, 15 members who agreed to participate completed both rounds of the questionnaires. The number of rounds and consensus method were decided in advance of questionnaire distribution with predefined limits for the acceptance, revision or rejection of indicators. Feedback was not provided to the panellists between rounds in

**Table 1** Progression of indicators through the Delphi process

	Indicator	Round 1 Median IQR	Outcome	Revised indicator	Round 2 Median IQR
1	Systemic antihistamines should not be prescribed to children under 1 year.	3 (2.5–4)	Revision required	<i>Sedating</i> antihistamines should not be prescribed to children under 2 years	4 (4–4)
2	Intranasal beclometasone should not be prescribed to children under 6 years	4 (4–4)	Accepted	NA	NA
3	Mucolytics should not be prescribed to children under 2 years	4 (3.5–5)	Revision required	Carbocysteine should not be prescribed to children	4 (4–5)
4	An inhaled SABA should be prescribed to all children who are prescribed two or more inhaled corticosteroids for presumed asthma	5 (4–5)	Accepted	NA	NA
5	An inhaled SABA should be prescribed to children under 5 years who are also taking a leukotriene receptor antagonist for presumed asthma.	5 (4–5)	Accepted	NA	NA
6	An inhaled corticosteroid should be prescribed to children aged 5–15 years who are taking a LABA	5 (4–5)	Accepted	NA	NA
7	LABAs should not be prescribed to children under 5 years.	4 (3.5–4)	Revision required	LABA's ( <i>either in combination or on their own</i> ) should not be prescribed to children under 5 years. New evidence presented	4 (3.5–4)
8	Children under 12 years who are prescribed a pressurised metered-dose inhaler (pMDI) should also be prescribed a spacer device at least every 12 months.	4 (4–5)	Accepted	NA	
9	Loperamide should not be used in the treatment of diarrhoea in children under 4 years.	4 (3.5–5)	Revision required	Loperamide should not be prescribed to children under 4 years. New evidence presented.	4 (4–5)
10	Domperidone should not be prescribed to children under 1 year, and for children over 1 year, it should not be prescribed for >7 days.	<1 year 5 (3.25–5) <7 days 4.6 (3.25–5)	Revision required	Rejected based on comments of panel. Lack of evidence to support.	NA
11	Domperidone should not be prescribed concomitantly with erythromycin.	4 (4–5)	Accepted	NA	NA
12	Codeine/dihydrocodeine medications should not be prescribed to children under 12 years.	4 (4–5)	Accepted	NA	NA
13	Systemic corticosteroids should not be prescribed to children aged 5–15 years without evidence of asthma.	3 (2.5–4)	Revision required	<i>Other than in children with asthma</i> , systemic corticosteroids should not be prescribed to children aged 5–15 years.	4 (2–4)

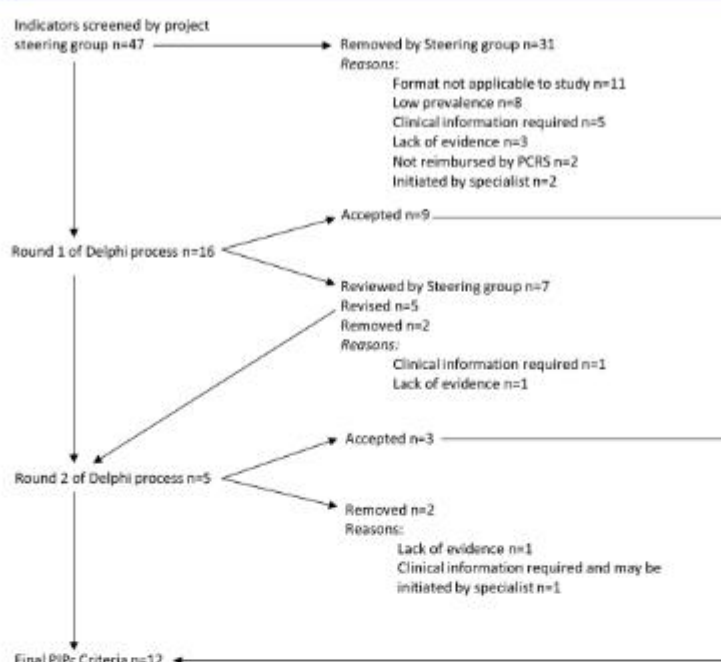


Figure 1 Flow diagram potentially inappropriate prescribing in children (PIPc) Study.

Out of the total identified, 31 indicators were removed following the application of the inclusion and exclusion criteria along with a detailed examination of the evidence by the project steering group. Remaining 16 indicators were presented to the Delphi panel in the first round. Out of 18, 15 experts who consented to participate completed each round of the questionnaire. Three experts did not complete either round. Consensus was reached for nine indicators on the first round with no indicators being rejected; consensus was not reached on seven indicators. From these seven indicators, two were rejected by the project steering group on the basis of the clinical comments of the Delphi panel. Five indicators were then presented to the Delphi panel in round two. Consensus was reached on three indicators and none was rejected outright. Consensus was not reached on the remaining two indicators which were then removed by the project steering group, following review of the comments of the Delphi panel. Table 1 summarises the progression of the indicators through the Delphi process and table 2 provides an example of some of the comments of the Delphi panel.

## DISCUSSION

We have developed a set of twelve indicators of potentially inappropriate prescribing for use in children in primary care through a modified Delphi method. These

12 indicators can be easily and quickly applied to large prescribing or dispensing data sets in the absence of clinical information. The indicators developed in this study were not designed as an exhaustive list of PIPc, but rather represent a list of commonly prescribed medications in Ireland and the UK, which may be used to explore the prevalence of PIPc. The usefulness and validity of these indicators will be investigated in future studies using national prescription-based databases.

## Comparison with existing literature

Concerns about the quality of care received by children in the USA were highlighted in a large study in 2007, which examined the management of common medical conditions in primary care using 175 quality indicators applied to the medical records of 1536 children.<sup>5</sup> A screening tool consisting of 104 explicit criteria for identifying the omission of prescriptions and inappropriate prescriptions (POPI) in children has recently been developed in France using a Delphi process.<sup>12</sup> The POPI tool includes propositions or indicators of inappropriate prescribing including omissions of prescribing in the treatment of commonly encountered paediatric health problems, for example, management of pain and fever. Although intended for community and hospital settings, this tool was developed without the input of GPs and has not yet been validated.<sup>12</sup> A set of 35 primary care



- criteria containing medications with a low prevalence of use (to define uncommon use, a cut-off of <0.5/1000 General Medical Scheme (GMS) patients was agreed by the project steering group)

Members of the project steering group applied the inclusion and exclusion criteria and examined the evidence supporting each indicator. For example, the criterion 'Fluoxetine is the most appropriate antidepressant for children, other SSRIs should not be prescribed' was removed by the project steering group during this screening stage as the criterion related specifically to patients with depression and could not be successfully applied in the absence of clinical information. Some criteria identified from literature were modified by the project steering group to make them applicable to dispensing database without clinical information, for example, 'Children with eczema should be prescribed an emollient' was altered to 'An emollient should be prescribed to children who are prescribed greater than one topical corticosteroid in a year', where the prescription of greater than one topical corticosteroid in a year was considered a proxy for a diagnosis of eczema. Supplementary file 3 details the indicators removed and the reasons for exclusion by the project steering group.

#### The primary care reimbursement service database (PCRS)

The prevalence of individual drug use in children in 2011 was determined using dispensing data from the Health Service Executive-Primary Care Reimbursement Service (HSE-PCRS). The PCRS is a national dispensing database in Ireland; it stores information on all medications and other health services, provided without charge to people eligible for free medical services in Ireland under the GMS. Eligibility for free medical care is established via means testing and therefore the data collected by the PCRS is not fully representative of the entire population of Ireland. Approximately 39% (414 856) of the total population (1 072 220) of children <16 years in the Republic of Ireland were eligible for the scheme in 2014. The PCRS contains data on prescriptions originating in primary and secondary care for all children who are eligible for free medical services. Children who receive a prescription from a hospital specialist will have their prescription transcribed to a GMS prescription by their GP in order to avail of free medication. The PCRS does not record data on whether a prescription has originated in primary or secondary care. An Anatomical Therapeutic Chemical Classification System (ATC) code was assigned to each indicator to allow for extraction from the dispensing database.

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#### Data collection and analysis

The consensus process involved two rounds of web-based questionnaires. The questionnaire was piloted among the project steering group and GP members of the Department of General Practice, RCSI with minor modifications made subsequently. The first and second rounds of the questionnaires were sent to the Delphi panel between January 2015 and May 2015 and between June 2015 and July 2015, respectively. For each round, panel members were emailed a link to a questionnaire which was maintained on an online survey software tool (SurveyGizmo). Panellists were presented with each indicator and an accompanying rationale for the indicator, categorised by physiological systems (gastrointestinal system, respiratory system, central nervous system, dermatological system) along with a hyperlink to a supporting evidence resource, for example, Cochrane systematic review, the BNFc or national or international guidelines. Panellists were asked to indicate their level of agreement with each indicator using a five-point Likert scale,<sup>24</sup> (where 1 was strongly disagree and 5 was strongly agree) and to provide comments within a free text box.

Following completion of the first round of questionnaires, the median response and the IQR for each indicator were calculated from the Likert scale. The level required for consensus between the panel members was decided prior to starting the study. When the upper quartile was  $\leq 2$ , this indicated there was consensus by the Delphi panel members on rejection of the indicator. When the lower quartile was  $\geq 4$ , this indicated there was consensus by the Delphi panel members on acceptance of the indicator. When the IQR included 3, this indicated there was a lack of agreement between the panel members and a need for further review of the particular indicator. These indicators were reviewed by project steering group and were either revised and included in the second questionnaire or rejected based on the comments received from the Delphi panel. Panellists did not receive feedback from the first questionnaire. The second questionnaire was presented in the same format as the first. Again, the median response and the IQR were calculated, and the project steering group reviewed these measures of agreement along with any additional comments. If consensus was not reached following the second round, the criterion was rejected.

#### RESULTS

Figure 1 summarises the development of the indicators. Literature searches identified 47 potential indicators.

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## PIPC study: development of indicators of potentially inappropriate prescribing in children (PIPC) in primary care using a modified Delphi technique

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