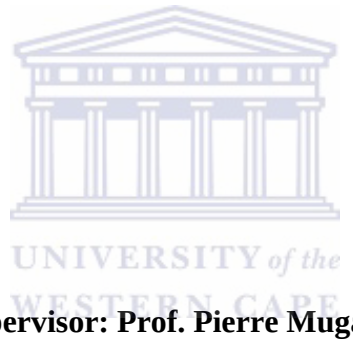
TITLE: PRESCRIBING PRACTICE AT A TERTIARY LEVEL PAEDIATRIC HOSPITAL IN SOUTH AFRICA

by Hyder Sablay

A thesis submitted in partial fulfillment of the requirements for the degree of Magister Pharmaceuticae in the Department of Pharmacy of Science, University of the Western Cape



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Declaration

I declare that this thesis, "Prescribing practice at a tertiary level paediatric hospital in South Africa", is my own work; that it has not been submitted before for any degree examination at any other university; and that all the sources I have used or quoted have been indicated and acknowledged by complete reference.

Hyder Sablay November 2014

Signed: …….

Dedication

I dedicate this thesis to my loving wife, Dr Zakira Mukuddem-Sablay, and our children Zakiyyah, Yusra and Salmaan Sablay, for their sacrifice, and support and encouragement to me as I embarked on and undertook this study.

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Keywords

prescribing practice

paediatric population

paediatric hospital

South Africa

prescription chart

prescribing errors

drug-drug interactions (DDIs)

drug-disease interactions (DDiS)

off-label (OL)

determinants

Abstract

Prescribing Practice at a Tertiary Level Paediatric Hospital in South Africa

Introduction: Prescribing for paediatric patients can be challenging for any prescriber. There are few studies on prescribing practice in paediatrics compared to that of adults. The paediatric population is usually excluded in clinical trials at the time when the actual medicines are developed. Thus the outcome of medicine use in the paediatric population can result in adverse events when rational use of medicine is not practiced by the prescribers. This motivated the researcher to embark on a study that focused on prescribing practice at RCWMCH.

Objectives: The objectives of the present study were to describe the type and frequency of prescribing errors and error frequency, to determine the error frequency for different drug classes, to identify potential drug interactions and drug-disease interactions to point out off-label prescribing and to evaluate risk factors of prescribing errors.

Methods: This prospective cross sectional study was conducted over a period of 6 months from July 2012 to December 2012 in 2 specialist wards and 2 general medical wards at Red Cross War Memorial Children's Hospital in Cape Town in South Africa. Only prescriptions generated by doctors in the above mentioned wards were assessed. Convenience sampling was used to select 200 prescription charts for analysis. Information relating to prescribing error, potential drug interaction, potential drug-disease interactions, off-label prescribing and potential risk factors of prescribing error were entered into excel spreadsheet and analysed using STATA versions 11&12. The mass of the patients was converted into weight-for-age z-score (WAZ) using WHO 2006 child growth standards. Univariate analysis and multiple logistic regression were used to identify risk factors of prescribing errors.

Results: Of the 200 children on whom prescribing information was analysed, 40 (20%) were severely underweight and a further 25(12.5%) were moderately underweight. A total of 1402 prescribing errors were documented in 1282 drug items prescribed, a rate of 1.09 errors per drug item prescribed. Incomplete prescription information was the most common type of prescribing error, present in 65.6% of all drug items prescribed. The error frequency was high for all drug classes ranging from 57.9% of all respiratory drug items prescribed to 86.4% of all gastro intestinal system drug items prescribed. The number of potential drug-drug interactions was low i.e. 20 potential pharmacodynamic and 49 potential pharmacokinetic drug interactions were identified. The number of potential drug-disease interactions was also low i.e. 39 or 0.03% per drug item prescribed. Furthermore 57 off-label prescribing incidences were recorded. Senior doctors posed a significant risk factor for prescribing errors, an OR 1.95, 95% CI 1.46 – 2.61. Conversely, prescriptions written up in the general wards compared to the speciality wards (an OR 0.65. 95% CI 0.47-0.90) and prescribing during weekends compared to weekdays (an OR 0.71, 95% CI 0.53-0.96) were associated with lower prescribing error risk.

Conclusion: This study provided valuable information about prescribing practices in children at RCWMCH. There is a need to improve prescribers' practice at RCWMCH considering the type of errors observed viz. missing information, use of wrong drug name, abbreviations, legibility concerns and lack of clarity of the prescriptions, among others. Based on this study results further intervention studies are recommended to investigate the level of medical student's training w.r.t prescribing practice.

Contents

List of Abbreviations

ABCB1	ATP binding cassette, sub-family B, a glycoprotein
AAP	American Academy of Paediatrics
ACE	Angiotensin Converting Enzyme Inhibitor
ADE	Adverse drug events
ADI	Adverse drug interaction
AGE	Acute gastroenteritis
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
APL	Acute promyelocytic leukemia
ARDS	Acute respiratory distress syndrome
ARF	Acute renal failure
ART	Antiretroviral treatment
ARV	Antiretroviral
AUC	Area under the plasma concentration
BHCD	Brooklyn Hospital for Chest Diseases
BNF	British National Formulary
CCF	Congestive cardiac failure
CD 4 T-cell	cluster of differential 4 T-cell, a glycoprotein
CGE	Chronic gastroenteritis
CI	95% confidence interval
CLD	Chronic lung disease
CMV	Cytomegalovirus

CNS	Central nervous system
COHASA	Council for Health Service Accreditation of Southern Africa
CP	Cerebral palsy
CYP3A5	CYPA5 encodes a member of the cytochrome P450 enzymes
DCMO	Dilated cardiomyopathy
DDI	Drug-drug interaction
DDiS	Drug- disease interaction
ED	Emergency department
EU	European Commission
FTT	Failure to thrive
g.i.t.	Gastro-intestinal tract
GORD	Gastro-oesophageal reflux disorder
HD	Haematological disorders
HE	Hepatic encaphalopathy
HLH	Haemophagocytic lymphohistocytosis
HI	Hepatic impairment
HIV	Human immunodeficiency virus
ICU	Intensive care unit
INH	Isoniazid
INR	International normalised ratio
IPH	Idiopathic pulmonary hemosiderosis
ITP	Idiopathic thrombocytopenic purpura
LRTI	Lower respiratory tract infection
ME	Medication error

MI	Myocardial infarction
MUPS	Multiple unit pellet system
NDoH	National Department of Health (South Africa)
NDP	National drug policy (of South Africa)
NF	Neutropenic fever
NGT	Naso-gastric tube
NICU	Neonatal intensive care unit
NSAID	Non-steroidal anti-inflammatory drug
OL	Off-label
OM	Otitis media
OR	Odds ratio
PBM	Pharmacy Benefit Management
PCW	Paediatric cardiac ward
PDD	Prescribed daily dosage
PGWC	Provincial Government of the Western Cape (in South Africa)
PICU	Paediatric intensive care unit
PJP	Pneumocystic jiroveci pneumonia
PK	Pharmacokinetic
PRISM	Paediatric risk of mortality
PZA	Pyrazinamide
RCWMCH	Red Cross War Memorial Children's Hospital
RMP	Rifampicin
SAHIVCS	SA HIV Clinicians Society
SAMF	South African Medicines Formulary

SHO	Senior house officer
STG	Standard treatment guidelines
TB	Tuberculosis
TOF	Tetralogy of fallot
URTI	Upper respiratory tract infection
UTI	Urinary tract infection
UWC	University of the Western Cape
VSD	Ventricular septal defect
WAZ	Weight-for-age
WHO	World Health Organization

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Chapter 1

Introduction

"Quality healthcare is not negotiable" (Van Zyl, 2011). This was the opening remark of the chairman of the Council for Health Service Accreditation of Southern Africa (COHSASA), made at the launch of the Safecare Initiative Conference in Cape Town in March 2011. Unfortunately, in the developing world, quality healthcare appears to be the exception rather than the norm. Interestingly, according to the World Health Organization (WHO), one of the ten main domains for concerns regarding healthcare in developing countries is preventable adverse drug events. Thanushya Pillay (2011), president of the South African Hospital and Institutional Pharmacists (SAAHIP), notes that pharmacists in India form an integral part of the healthcare team at the ward level in hospitals and are also involved in drug selection at the point of prescribing, almost serving in the role of "consultant". The argument, then, which this thesis is concerned with, is: is it not perhaps time for South African pharmacists to become custodians of medicine in the true sense of the word as part of the healthcare team, serving in an advisory capacity with regards to all aspects of the prescribing of medication?

1.1 Prescribing practice

Prescribing of medication is one of the most common interventions used to treat patients. Prescribing is a doctor's written direction (order) for the preparation, compounding and administration of a medicine. While it is commonly believed that practice makes perfect, the same, however, cannot be said about the prescribing practice in pharmacy. Moreover, prescribing for a paediatric population can be more of a challenge than for adults, and since there are very few available studies on prescribing practice in paediatrics compared to that of

adults, a study of this nature was undertaken towards the Master's degree to assist in discovering the concerns and challenges experienced by prescribers, in general, and more specifically, with regard to children in South Africa. Good prescribing is not an easy discipline to master as prescribers are not necessarily trained to write prescriptions. Junior doctors, who generally have less practical experience with paediatric patients, are expected, at times, to prescribe without the necessary supervision from the senior doctors.

Unnecessary prescribing or over prescribing is not an uncommon practice, especially when doctors with less experience in healthcare of children are faced with the challenge of prescribing. As part of this Master's study, a memorandum on correct prescribing practice was developed by the pharmacists involved and forwarded by hospital management to different departments at the Red Cross War Memorial Children's Hospital (RCWMCH) in November 2013. Standard clear instructions about who may write and sign a prescription, emphasis on legibility, process regarding alteration of an item, and particulars about what must appear on a prescription, for example, prescriber and patient details and prescribed medicine details, were specified in the memorandum. Whilst on ward rounds during the undertaking of the research in real time, it became quite apparent that most prescribers failed to follow or read the memorandum detailing correct prescribing. This finding clearly highlighted an area of concern regarding prescribing practice, both in terms of junior and senior prescribers, prescribing practice referring to the lack of prescribing knowledge, be it the style of writing or in the decision-making process of prescribing. Thus, in the current study, it became a point of interest to know whether prescribing practice at the RCWMCH influences the prescribing error rate, potential drug-drug interactions (DDIs), and potential drug-induced diseases drug-disease interactions **(**DDiS), as well off-label (OL) prescribing.

An assumption can and was made at the outset of this study that prescribing practice has become habitual (whether good or bad is beside the point) at times, with prescribers knowingly or un-knowingly prescribing medicines that interact with one another, not always considering the disease state of the patient, and also in some cases prescribing medicines classified as off-label. Moreover, the increasing number of new medications released into the market is a major challenge for physicians. Additionally numerous studies have found that pharmacists can improve patient safety and outcomes by preventing adverse events by recommending optimal therapies and dosages (see, for example, Bond et al.,1999; Kaboli et al., 2006). Recently, all operational departments at teaching hospitals in Cape Town, South Africa, were audited by assessors as part of the National Core Standard audit in 2011; although the overall outcome of the audit was outstanding, one area of the medication management system was criticized—the prescribing habits of physicians, thus confirming the need for intervention by pharmacists at the ward level. It is thus necessary that prescribers reassess their prescribing habits in light of our present social and economic circumstances in South Africa, that is, with the view of instituting more rational drug prescribing and reducing medicine usage to effect a favourable outcome. Prescribers must avail themselves of easily accessible information regarding good prescribing practice, which, in the long-term, will enhance drug therapy and reduce the incidence of adverse drug events due to inappropriate or incorrect prescribing.

1.2 Prescribing errors

It is a known fact that prescribing errors contribute majorly to medication errors in the medication management system, with prescribing for children a big challenge for any

prescriber in any healthcare setting. The need for calculations, dilutions, and manipulations of paediatric medicines, together with the need to dose on an individual patient basis taking into account age, gestational age, weight, and body surface area means that children are more prone to the effects of medication errors (Conroy, 2007). Moreover, prescribing is a high volume activity, meaning that even a small percentage of errors can lead to scores of serious adverse events (Conroy, 2007).

Although the main theme of this thesis will focus on prescribing errors, potential drug-drug interactions (DDIs) and drug-disease interaction (DDiS), off-label (OL) prescribing will also be looked at in order to reveal and highlight concerns relating to prescribing practice at paediatric tertiary hospitals, such as RCWMCH, the site of this study.

Error reporting is becoming common practice in some parts of the world, but, unfortunately, healthcare professionals in South Africa generally fail to report medication errors, let alone prescribing errors. This lack or non- reporting of errors means that managing prescribing errors is virtually non-existent in the country. Yet, prescribing errors are potentially tragic and costly both in human and economic terms for patients and professionals alike (Cohen, 2000). For example, failure to standardize prescribing terms often leads to inappropriate use of dangerous abbreviations, acronyms, and coined names, thus enabling the easy misinterpretation of prescribing information (Cohen, 2000). However, research studies on interventions by pharmacists with regard to phramacovigilance in the healthcare system suggest that many medication errors occur and that clinical intervention by pharmacists helps to prevent adverse drug events (see, for example, Guy, 2003; Barber, 1997).

Teaching hospitals in South Africa have for many years been the training ground for many a healthcare professional, including those from other parts of the world, with **deleted**)RCWMCH no exception in this regard. RCWMCH is one of very few paediatric

referral hospitals in Africa and, at any given time, has an interesting patient population that varies in age and co-morbid disease(s). This, coupled with the practice of poly-pharmacy and off-label prescribing, makes it the ideal place to monitor, detect, evaluate, and report prescribing errors. Currently, there are no clinical interventions and prescribing error reporting mechanisms by pharmacists at the ward level at RCWMCH, an indication that the skills and knowledge possessed by pharmacists are not being fully utilized with regard to pharmacovigilance.

1.3 Factors influencing prescribing

Clinical training of medical students focuses more on the theory than the practice of pharmacology. As a result, most medical students remain unsure about the actual requirements, methods and best practice of prescribing, that is, how to actually prescribe. To begin with, pharmacology reference books, drug-centered and clinical textbooks rarely discuss therapeutic recommendations, that is, they do not discuss why certain therapies are chosen and so forth, thus leaving the potential prescriber to figure out on his or her own the therapeutic drug regimen for the underlying condition (de Vries et al.,1994).

Moreover, prescribing is influenced by such factors as effectiveness and harm of a medicine, external influences, and cognitive biases. The poor choice of a medicine, poly-pharmacy, co-prescribing of potentially interacting drugs, prescribing for a self-limiting condition, and continuing to prescribe for a period longer than is necessary are a few of the factors contributing to irrational prescribing. Irrational prescribing influences morbidity and mortality, especially in the treatment of childhood infections or chronic diseases, such as hypertension, diabetes, epilepsy, and mental disorders. Irrational or incorrect prescribing can

affect public health at large; for instance, in the case of antimicrobials, resistance can result from irrational prescribing, especially in children.

The procurement and prescribing of pharmaceuticals, both important chains in the medicine management system, are governed by various guidelines. Such guidelines are critical for sustaining medicine stocks for patient care at RCWMCH. The Standard Treatment Guidelines (STG) for paediatrics, Western Cape (PGWC) code list, the National department of Health (NDoH) tenders, the Pharmacy and Therapeutics Committee, and the PGWC procurement policies all provide guidelines in this regard. There are many challenges in maintaining adequate stock levels of pharmaceuticals as a result of the above guidelines; in addition, formularies and the various guidelines are not aligned with each other, thus influencing prescribing directly or indirectly. To start with, not all medicines on the PGWC code list are on the NDoH tenders, which results in a medicine needing to be procured as a buy-out. Secondly, NDoH tenders are renewed every two years and often medicines on the PGWC code list are removed from the tender. This then necessitates a change in the code list, affecting both procurement and prescribing. Thirdly, paediatric formulations of medicines are often not placed on the NDoH tenders but incorporated in the STG. In addition, prescribers do not necessarily refer to all these guidelines. There are other factors too, such as newly recruited health professionals from the private sector, foreign doctors, and experienced doctors (used to certain treatment regimens) who are each comfortable in prescribing in accordance with very different and personal styles. Pharmaceutical companies also influence prescribers, with teaching hospitals not excluded from this tendency, especially as concerns the use of new or existing drugs in certain drug trials. The prescriber, in such cases, is obliged to prescribe the medication during the trial period in lieu of certain incentives provided by the drug company to the prescriber. Certain drugs are no longer registered in South Africa (Section 21 drugs) and are not easily obtainable, resulting in patients not receiving the

intended drug on time or even not at all. Prescribers are then obliged to search for alternatives to the requested drug; sometimes, such alternatives are non -existent.

1.4 Possible determinants or predictors of prescribing errors

A study in 1998 on drug related problems at Addington Hospital by Moodley (2000) South Africa focused on geriatric patients. According to the study, the most common prescription interventions centered on problems involving drug therapy monitoring, safety of drug therapy, indication of drug therapy, prescribing errors, prescription information and omission. The study at RCWMCH focuses on the type of prescribing errors due to the prescribing practices of doctors, where, amongst others, age, poly-pharmacy and off label prescribing act as possible contributing risk factors associated with potential prescribing errors. Possible determinants or predictors of prescribing errors included: level of qualification of the prescriber (that is, senior versus junior doctor status), day of the week the item was prescribed, age of the patient (in terms of infant and child groups), location of the ward (that is, specialty versus general medical wards), drug formulation, class of the drug, number of drugs prescribed and formulary status of a drug. All these possible determinants have a direct influence on the prescriber, thus contributing to potential errors.

Chapter 2, following, on reviewing the literature will cover topics related to the main theme of study, namely, prescribing errors, drug-drug interactions (DDIs), drug-disease interactions (DDiS) and off label (OL) prescribing. It will also present the study's research question and hypothesis with regard to adherence of prescribers to the Medicines and Related substance Act 101 of 1965 (Medicines and Related Substance Act101 of 1965, Regulations as amended,2014:28) The aims and objectives are also outlined, providing the focus on type of

prescribing errors, error frequency per different classes, potential drug interactions, drug-disease interactions off label prescribing and determinants of prescribing errors.

Chapter 3 concentrates on the materials and method used and outlines the study design, site and population, inclusion and exclusion criteria, sample size, parameters assessed and definitions of the type of prescribing errors. In addition, drug-drug interactions, drug-disease interactions and off label prescribing are explained in terms of types of parameters, respectively. Nutritional status is also defined in terms of weight for age for the study population. The methods of statistical analysis are explained in this chapter as well as the timeframe and ethic consideration as per the different institutions.

Chapter 4 presents the results of the study, including the sample size, age distribution, and the presenting conditions of the patients in the study. The results are presented in tabular form, with 31 tables provided. Each table succinctly describes the legends contextually, with a brief description of the contents of the respective tables provided as a footnote.

Chapter 5 discusses the findings as reflected in Chapter 4, namely the results. The findings of other similar studies are also discussed and comparisons are made between the findings of the present study at RCWMCH and those conducted in other parts of the world.

Chapter 6, summarizes and discusses key points, anomalies and essentially contextualizes the study in terms of its wider relevance, that is, beyond the site of study at RCWMCH. Recommendations with regard to limitations noticed or aspects needing further research are discussed.

Chapter 2

Literature Review

2.1 Introduction

In this chapter, literature review will be presented on the topic of prescribing errors, which will be covered in sections 2.2. to 2.6. This will be followed by an outline of the parameters of the study introducing the research question, hypothesis, aim and objectives and potential value of the study.

The focus of this literature review was the following: (a) to highlight themes covered in the thesis, namely, prescribing errors, drug-drug interactions (DDIs), drug-disease interactions (DDiS) and off-label (OL) prescribing, and (b) to help address the research question (see 2.7.2 page 47, chapter 2) The review focused on key paediatric research findings in relation to the research findings at RCWMCH.The literature review covers, in particular, the central theme of this study, namely, prescribing errors while also focusing on drug-drug interactions, drug-disease intteractions and off label prescribing as possible co-factors in prescribing errors. Most of the literature search was accomplished digitally through electronic databases, including Science Direct, Ebsco Host search and references of reviewed articles searched from useful sources (that is, ACADEMIC SEARCH, CINAHL, HEALTH and MEDLINE). Search terms included “prescribing error”, “paediatric population”, “drug-drug interaction”, “drug-disease interactions” and “off-label”. Hand searching of locally published journals was also undertaken to identify studies located in South Africa. A total of 201 articles published between 1980 and 2013 were retrieved overall.

2.2 Paediatric population

Children are not small adults and thus pose a challenge to any prescriber, be it a senior or a junior doctor. Children, especially the very young (infants), have immature organ systems; thus the effect of drugs on them is of major concern, with potential harm caused by medicines if these are not prescribed and administered in the correct manner.

Growth assessment and nutritional status are important indicators of child health. The significance of detecting poor growth in early life is reflected in poor cognitive function and educational performance, and when accompanied by excessive weight gain later in childhood, increases risk of nutritional-related chronic diseases (Victora et al., 2008). In 2004, child growth monitoring practices worldwide were reported as part of the construction of the WHO standards. Growth charts are since widely used in paediatric care and weight-for-age has been adopted almost universally, followed by length/height-for-age and weight-for-length/height (de Onis et al, 2006).

Under-nutrition in childhood is one of the main contributing factors to high mortality rates in developing countries. A study carried out in 2012 in a slum in the state of Uttar Pradesh in India (Srivasta et al., 2012), assessed the influence of nutritional status on the health outcome of children aged 5 to 15. In the study, underweight (weight-for-age z-scores less than -2.00) reflected chronic and acute under-nutrition. It is important to note that nutritional status in children reflects the socio-economic status of the family, and in turn, the social well-being of the community and the health care system in general.

Children are subjected to many of the same diseases that adults suffer from and are

often treated with the same drugs used to treat adults. However, many drugs used in children are not licensed for use in them or are prescribed outside the terms of the license, that is, they are used "off label". The consequence of this practice, which is very common, can place children more at risk with regard to potential adverse drug events. Data needed for effective and safe drug treatment cannot be linearly abstracted from adult data and specific research is necessary. Unfortunately, obstacles for the conducting of research among children are many, including issues of a financial, ethical, scientific and practical nature. In order to further progress in paediatric research, rules and requirements in this research area need adjustment. An important step was taken by the European Commission (EU) on 28 September 2004 in adopting a proposal for the regulation on medicinal products for paediatric use. This proposal aims to improve the health of children in Europe by increasing research, development, and authorization of medicines for use in children. (Masoli et al., 2004)

The benefits of the findings of future studies among children, as per the above proposal, may influence the way prescribing is practiced for the paediatric population not only in Europe but globally. Nonetheless, there is a need for ongoing studies to be conducted among children in both developed and developing countries. However, challenges in developing countries, including South Africa, are many, including limited resources, funding constraints and, perhaps, most importantly, obtaining the permission of caregivers to enroll their children as participants in research studies. There are many barriers to efficiently reduce the burden of disease in childhood.

Such barriers include poverty, poor education, poor infrastructure, inherent barriers in the organization of healthcare services in terms of geography, type of professional responding, education and training systems, public and private care and the tendency of care to be "acute" rather than "routine". It is common practice for prescribers and pharmacists to make educated guesses and to rely solely on their individual clinical experience when it comes to the issue of

prescribing. However, decisions regarding the safety and efficacy of medicines need to be considered with more efficiency because, in the first place, sufficient data is not available for children. Very often clinical decisions made by prescribers are based on the extrapolation of empirical data from studies on adults. This kind of practice is continued in clinical settings despite the fact that large differences exist between adults and children, even among children themselves (Masoli et al., 2004)

Proper use of medicines among children is critical. Infectious diseases are one of the leading causes of deaths in children despite the availability of various vaccines and treatments for different infectious diseases. Indeed, one can question the accurate use of existing medicines and vaccines since current experience shows a crucial need to train and educate public health officials, physicians, and parents in the correct use of available vaccines and medications. A recent influenza campaign at RCWMCH (Blake, 2013a) indicated the importance of communicating vital information both to the prescriber and caregiver of the child patient. Prescribers were informed in advance about the availability of the vaccine as well as the target population to receive the vaccines at RCWMCH, that is, the compromised and very sick child patients. Parents were also educated about the influenza vaccine and its benefit, ensuring the success of the influenza vaccination campaign. The memorandum on the influenza vaccination campaign was forwarded to the doctors and assisted in ensuring communication to all patients targeted; the result was that the target population was administered with the influenza vaccine in time, with minimal influenza cases reported.

2.3 Prescribing error

Pharmacology training focuses more on theory than on practice. The result of this is that many medical students remain unclear about how to prescribe a drug or what drug information to give their patients. The study material available to students is more likely than

not to be drug-centered, that is, concentrating on indications, side effects and so forth. In contrast, in clinical practice, a practical approach is required. Patients differ in age, gender, size, and socio-cultural characteristics, all of which may influence treatment choices. Since practical prescribing skills remain weak, prescribers may face more challenges when serving special population groups such as children (de Vries et al., 1994).

Bad prescribing habits lead to ineffective and unsafe treatment, prolongation of illness, distress to the patient, and higher costs to the state and patient or their families or care givers. Bad prescribing habits also make the prescriber vulnerable to influences that can cause irrational prescribing, for example, patient pressure and high-powered salesmanship by sales representatives of pharmaceutical companies. Yet, changing existing prescribing habits is very difficult. Good training, it is argued, is needed in the first place to prevent the development of poor habits (de Vries et al., 1994).

There is no universal agreement as to what constitutes a prescribing error, with research studies varying in their definitions of the event. Often, studies include all medication errors and fail to distinguish clearly between prescribing and other types of errors (for example, administration errors, supply errors and so forth). For example, one study gives the general definition as a "mistake made at any stage in the provision of a pharmaceutical product to a patient" (Wilson et al., 1998). In the specific category of prescribing errors, the researchers included incorrect drug selection, incorrect dose or frequency, incorrect route, incomplete information (for example, a prescription not signed or a dose not stated), illegible prescription, unforeseen drug interactions, inadequate monitoring of drug levels and infusion error (Wilson, 1998). This particular study was conducted at the Congenital Heart Disease Centre at the University Hospital of Wales, with the hospital consisting of a 15-bed paediatric cardiac ward (PCW) and a four-bed cardiac Intensive Care Unit (ICU). Errors were documented by nurses, pharmacists, or doctors, using standardized incident report forms.

Individuals responsible for errors remained anonymous, creating a non-punitive environment and the Medication Error (ME) Committee, consisting of one senior doctor, one junior doctor, one nurse from each clinical area and a senior pharmacist, met at three-monthly intervals to analyze reports. The findings of the ME Committee were reported back to the unit staff in the form of written updates, along with recommended changes in practice. During the 24-month study period, there were 682 admissions for a total of 5 315 inpatient days. A total of 441 error reports were submitted by nurses (61%), pharmacists (35%), and doctors (4%). Prescription errors accounted for 68% and included incomplete prescription (36%), incorrect dose (36%), incorrect frequency (11%), transcription error (7%), incorrect drug selection (4%), drug interaction (3%), and illegible prescription (3%). Interestingly, nurses, doctors, and pharmacists were all actively involved in reporting errors, be it supply, administration or prescription errors.

Another study stated that a clinical meaningful prescribing error occurs when, as a result of a prescribing decision or prescription writing process, there is an unintentional significant (1) reduction in the probability of the treatment being timely and effective, or (2) increase in the risk of harm compared with generally accepted practice (Ghaleb et al., 2005). Interestingly, Ghaleb et al., (2005) used what is known as the two-stage Delphi technique over other methods to avoid direct communication between groups of experts while still allowing for a certain level of interaction between them. In this methodology, the views of a panel of expert participants about situations that should or should not be included as prescribing errors in paediatric practice was taken into consideration. Ghaleb et al., (2005) further mention that a practitioner-based definition of a prescribing error has been developed in the United Kingdom for use both in research and practice, but that the one limitation of this definition is its developed use for the adult setting with issues specific to paediatric practice such as the prescribing of drugs based on individual weight or age not considered. Ghaleb et

al. (2005) further state the objective of the study as being an intention to develop a practitioner-led definition of a prescribing error that could be applied to a paediatric setting, which could act as the foundation for future research into prescribing errors in paediatrics. It is with the similar aim in mind that current study was undertaken, that is, researching the prescribing practices at a paediatric hospital in South Africa to highlight the trend and associated risk factors, for example, age of the patient, level of experience of doctor and class of drug(s).

According to the Delphi technique used in the study by Ghaleb et al. (2005), the definition of the prescribing error was raised in the form of a question, that is, what constitutes an error? Different scenarios of what represents a prescribing error were forwarded to the different participant's, namely, the doctors, nurses, pharmacists, and other healthcare members. In the first stage of the Delphi technique, participants had to indicate their extent of agreement with the proposed definition of a prescribing error. In the second stage, participants restored agreement or disagreement for prescribing error scenarios where consensus was not reached in the first round. In this round, consensus was reached and thus there was no need to conduct a third round. The following definitions were specified before data was analyzed, namely, "consensus", "agreement", and "disagreement". Where consensus existed, it was agreed that the scenario would be included as a prescribing error if the median score fell within the 7–9 range, excluded if it fell within the 1–3 range, and regarded as equivocal if it fell within the 4–6 range. Ethical approval was obtained from the Thames Valley multicenter ethics committee (Ghaleb et al., 2005).

After consensus was reached, the authorities in the research study decided to retain the initial proposed definition of a prescribing error, that is, "a clinically meaningful prescribing error occurs when as a result of a prescribing decision or prescription writing process, there is an unintentional significant reduction in the probability of treatment being

timely and effective or increase the risk of harm when compared with generally accepted practice" (Ghaleb et al., 2005).

Interestingly, of this definition could be applied to any paediatric setting, including a hospital such as the RCWMCH. The guidelines offered in the study Ghaleb et al. (2005) also pertain to the scenarios for inclusion and exclusion with regard to prescribing errors and can be useful in the local RCWMCH context as well. However, the drawbacks of the methodology used in the above study are of equal concern, especially considering the needs surrounding a prospective descriptive study in a teaching hospital like the RCWMCH. Firstly, involving different participants from different specialties would appear to be an impractical task; secondly, as with the Delphi technique, response rates would likely be less than 100% and the results therefore probably biased, that is, missing responses of participants would need to be considered. On the other hand, the high response rate would conclude the validity of the study. Nonetheless, the current advantage of the study by Ghaleb et al. (2005) is that globally there exists no standard definition of prescribing error, hence the definition and the scenarios can possibly be used internationally as a "rough" guide regarding what constitutes a prescribing error, thus allowing its use in research studies, such as the current one undertaken at a paediatric hospital like the RCWMCH.

In an interesting retrospective cohort study carried out at the emergency department (ED) of the Hospital for Sick Children in Toronto Canada in 2000 , it was found that trainees are more likely to commit prescribing errors and, not surprisingly, seriously ill children are more likely to be subjected to prescribing errors (Kozer et al., 2002). In this study, the charts of 1 532 children treated in the ED of the paediatric tertiary care hospital were reviewed during 12 randomly selected days. The objectives of the study were to estimate incidence and type of errors and identify the possible factors (variables) likely to increase the risk of prescribing errors. Approval from the hospital ethics committee was obtained for the study

and two medical students served as research assistants. The data was extracted (under the supervision of one of the investigators) and incorporated into a database, which included information about patient demographics, clinical condition, diagnosis, acuity of the condition (based on the triage category), the prescribing physician and all the medication prescribed and administered to the patient. Drug doses differing from the recommended dose, deviation by two hours or more from the recommended interval between doses, wrong units and route of administration from the recommended regimen were all flagged as potential errors. Medication prescribed and not given, that is, omissions, and medication given without a properly written prescription, that is, prescriptions not legally compliant, were also flagged as errors. Medication errors due to prescribing errors were classified as: (a) insignificant/minimal risk, for example, a child receiving 5mg dexamethasone instead of 3mg, (b) significant, for example, a drug error that could cause non-life threatening consequences or an error that would result in a less effective treatment for child's condition (for example, a tenfold lower dose of amoxicillin for otitis media(OM)), or (c) severe, that is, if a medication error could cause death or decrease the chance of successful treatment of a life threatening condition, for example, a tenfold error in insulin dosage or significant under-dosing of antibiotics for a patient with meningitis. Potential errors in medications prescribed and administered at the ED or for home use were identified using 403 charts. A senior investigator reviewed a random sample of 50 charts and identified one additional error (not picked up by the research assistants). In 330 cases (81.8%), there was initial agreement between the reviewers regarding whether an error had occurred and the ranking of the error. In 49 of the remaining 73 cases, agreement was achieved between the reviewers after each case was discussed on an individual by individual basis. Twenty four cases were reviewed by a third researcher. Prescribing errors were identified in 154 charts (10%).The most common types of errors were wrong dose (49.1%), wrong frequency (43.2%), wrong route (2.6%),

wrong drug (1.8%), inadequate information (2.6%) and other (0.7%). The drugs most commonly involved in errors were acetaminophen followed by antibiotics, asthma medications, and antihistamines. Moreover, these were also found to be the most commonly prescribed drugs in the ED.

The incidence of medication errors was calculated and logistic regression used to assess the likelihood of medication errors among patients for whom a medication was prescribed. The independent relationship between each variable and the outcome variable (error versus no error) was examined. Variables found to be significantly linked with drug errors or those that might confound the relationship between other variables and drug errors were included in a multivariate analysis. Multivariable logistic regression was used to identify factors such as age, gender, level of training of the physician, shifts, patients waiting time and triage category that independently influenced the rates of medication/prescribing errors (Kozer et al., 2002).

Factors associated with an increased risk of medication errors included medication prescribed by a trainee as opposed to a staff physician and seriously ill patients being the most affected as compared with least ill patients.

In another study conducted by Lesar et al. (1997) in a 631 bed tertiary teaching hospital in New York from July 1 1994 to June 30 1995, potential prescribing errors were defined as medication orders for the wrong drug, inappropriate dose, frequency, route, dosage form, inappropriate indication, ordering of unnecessary duplicate/redundant therapy, contraindicated therapy, medications to which the patient was allergic, prescriptions for the wrong patient, or missing information required for the dispensing and administration of the drug. All prescriptions were handwritten and copies of the originals sent to the pharmacy. All the prescriptions were reviewed by centralized staff pharmacists and entered into a pharmacy

computer system prior to dispensing. The pharmacy computer system had automated programs for dose-checking, duplicate therapy checking, allergy-checking and drug interaction checking capabilities. All prescriptions jointly determined by the physician and pharmacists to be in error, and subsequently changed, were considered "confirmed prescription errors". A total of 905 prescribing errors were detected and confirmed during the 1 year study period, with 522 (57.7%) of the errors detected rated as significant, that is, potentially fatal, potentially serious and potentially significant, classified A, B, and C respectively. A total of 289 411 prescriptions were written during the study period, with a daily average of 793 prescriptions. The overall prescribing error rate was 3.13 per 1 000 prescriptions (0.31%) and there were 1.80 significant prescribing errors per 1 000 prescriptions (0.18%). The overall frequency of medication prescribing errors was 0.44 per 100 patient days (0.44%) and 0.25 significant errors per 100 patient days (0.25%).

Medication prescription errors most frequently involved antimicrobials, which accounted for (23.1%) of all errors and 28.5% of all significant errors. Overdose was the most frequent type of error, occurring in 28.7% cases and accounting for 38.9% of significant errors. Prescribing errors involving missing information accounted for 22.3% errors but did not contribute to significant errors because of the low potential of such prescriptions being carried out. The most common medications involved in the 696 prescribing errors were antimicrobials, cardiovascular drugs (122 or 17.5 %), gastrointestinal agents (51 or 7.3%) and non-narcotic analgesics and antipyretics (46 errors or 6.6%). Error rates varied significantly among medication groups ($P<0.001$). Of the 696 errors, 43 (6.2%) were rated as A (potentially fatal or severe), 96 (13.8%) were rated as B (potentially serious errors), and 557 (80 %) were rated as C (potentially clinically significant). The error rates were as follows: for surgical patients, 3.51 per 1 000 prescriptions, for medical patients, 4.12 per 1 000 prescriptions for obstetric-gynecologic patients, 4.51 per 1 000 prescriptions, for

paediatric patients, 5.89 per 1 000 prescriptions and for emergency patients, 5.05 per 1 000 prescriptions ($p < .001$, the difference among all groups). Interestingly, the most common specific factor related to prescribing errors was the presence of pathophysiological status or disease (such as cardiac failure, renal impairment, or hepatic failure) that required alteration of drug therapy (Lesar et al., 1997).

A study such as the one above highlights the importance of knowledge of the drug, patient factors related to drug therapy, namely, age, disease state, for example renal impairment, and knowledge about the correct use of the drug. Although the Lesar et al. (1997) study focused mainly on the adult population, children were not excluded, as was noted in the error rates above. Thus, irrespective of the age of the patient, this study revealed that prescribing errors are a concern for children as well. The definition of prescribing errors used in the above study almost fits the one used in the current study conducted at the RCWMCH, but differs in that the Lesar et al. (1997) study included administration errors, whereas the study conducted at the RCWMCH did not include errors in the administration stage of medication management as a prescribing error. Furthermore, the study carried out by Lesar et al. (1997) involved a group of investigators and had the advantage of using an automated computer system to detect errors, which the current study did not.

To illustrate the clinical significance of tenfold medication dose prescribing errors, from 1 July 2000 to 4 January 2002, in another study Lesar et al. (2002) identified and quantified the characteristics of such errors in a 631 bed tertiary care teaching hospital in New York (the same hospital used in the previous study conducted by Lesar et al. (1997)) between June 1994 and July 1995. This time around, the study also included the paediatric population, the said population group occupying 120 beds, including a neonatal intensive care unit (NICU) and paediatric ICU (PICU) as well as general paediatric beds. For all paediatric patients weighing less than 50kg, hospital policy required inclusion of the weight (gestational

age required for neonatal intensive care unit (NICU) patients), the equation used to calculate the drug dose and a final calculated dose amount. Medication prescribing error data for the study analysis were concurrently and systematically collected over an 18-month period as part of an ongoing error prevention/quality improvement program. As with the earlier study by Lesar et al. (1997) in the very same hospital, pharmacists routinely made use of all available information to evaluate the prescription for appropriateness, with a prescription in question discussed between the pharmacist and the prescriber, then changed or discontinued and considered a potential prescription error. In the 2002 study, potential tenfold prescribing error was defined as medication prescriptions with a drug dose prescribed that was 10, 100 or 1 000 fold greater or lesser than the correct dose for the patient. The mechanism for each error was determined as either adding a zero or omitting a zero or misplaced decimal point, the latter practice of which was found to be a common problem that appears to be frequently associated with medications with the dose <1 (for example, 0.05mg intended, prescribed as 0.5mg) or doses containing multiple zeroes (for example, 3 000 units intended, prescribed as 30 000 units). Failure to place a leading zero before a decimal point (for example, 1mg) include a zero following a decimal point (for example, 1.0mg) or use trailing zeroes (for example, 0.150) are a common cause in tenfold errors, especially in the interpretation of written prescriptions. This study also showed that the potential for patient harm resulting from errors in prescribing are greater than that for errors in preparation, dispensing or administration. It is important to note that in paediatric patients doses of the same drug vary so widely between patients that errors are not easily recognized. Of the 200 confirmed significant medication tenfold prescribing errors detected between 1 July 2000 and 4 January 2002 in the Lesar et al.(2002) study, 161 (80.5%) occurred among adults and 39 (19.5%) among paediatric/neonatal patients. The tenfold errors accounted for 5.33% (200 of a total of 3 758 detected prescribing errors) of all clinically significant prescribing errors detected by

pharmacists during the study period. During the 18 months in which the study was conducted, tenfold prescribing errors were detected at a rate of 0.53 errors per 100 total admissions and 0.98 per 1 000 total patient days compared with a rate of 0.52 per 100 total admissions and 0.77 per 1 000 patient days among adults. Overdoses occurred in 122 cases and under doses in 78 cases. The detected errors were rated as potentially severe or serious in 90 (45%) of cases. The mechanism for the tenfold error in prescribing was pinpointed to a misplaced decimal point in 87 cases, the addition of an extra zero in 63 cases, and the omission of a zero in 50 cases.

In a study that focused on antimicrobial prescribing errors for children in Christchurch, New Zealand, the appropriateness of antimicrobial treatment of children admitted to a paediatric unit was assessed (Grimwood, Cook & Abbott, 1983). During the audit period, 255 children were studied; their ages ranged from five days to 12 years and they made up 52% of 487 children admitted to hospital for treatment of infection. All prescriptions were written by junior doctors, and after reviewing the recorded information, that is, drug, dose, frequency, route and duration, the auditors made a collaborative assessment about the appropriateness of the therapy. When the auditors differed, consensus was reached via favoring a practical over an ideal therapeutic approach. Prescribing errors for each antimicrobial were classified into the following categories: (1) antimicrobial not indicated; (2) incorrect choice; (3) incorrect dosage; (4) incorrect frequency; (5) incorrect route; and (6) incorrect duration. Of the 203 antimicrobials dispensed, 130 (64%) were found to have been used appropriately. Errors tended to occur most frequently in the area of dosage, with 55 (27%) of prescriptions incorrect in this regard. There was a tendency to chart dosages too low for the diseases for which they were prescribed, with this practice observed most commonly for oral agents. Prescribing of aminoglycosides in 20 patients was considered inappropriate in 11 (55%), the major error being failure to adequately monitor serum levels and alter the

dosage or frequency accordingly. Chloramphenicol was used to treat 10 patients, with its use considered inappropriate in four (40%). Errors included a wrong dose and prolonged ampicillin/chloramphenicol combination treatments in three children with bacterial meningitis. This combination was used for three or four days despite there being microbiological data indicating the nature and sensitivity of the infecting organism 12 to 24 hours after commencement of treatment. Incorrect choice of drugs was infrequent (7%) and related mainly to using broad-spectrum agents such as amoxicillin where penicillin would have been more appropriate (Grimwood, Cook & Abbott, 1983).

The above study, conducted 31 years ago, indicated the increased prevalence of resistant bacteria to be the direct result of antimicrobial misuse. Unfortunately, this practice is still observed in most hospital settings globally and is unlikely to change any time soon as newer antibiotics, considered more sophisticated, continue to be released into the market. Antimicrobial resistance, once very uncommon in children, has increased in this age group, posing a challenge for infectious disease physicians, especially in patients with co-morbid diseases. However, prescribing errors can be reduced if physicians adhere to proper prescribing guidelines and consult with the expertise in the field of infectious disease, failing which the war against micro-organisms will fail.

To date, most medication error studies have been carried out for adults. However, potential adverse drug events (ADE's) (this term includes adverse drug reactions (ADR's) and medication errors (ME)) may be up to three times more common in children than in adults (Kaushal et al., 2001). Most potential reported ADE's show dosing errors and errors involving IV administration. The Department of Health in the United Kingdom has recognized that children constitute a particular challenge as regards the safe use of medicines. Recently published literature reviews have established medication errors as a significant problem in paediatric practice there (Ghaleb & Wong, 2006; Walsh, Kaushal & Chessare,

2005). In one such systematic review (Wong et.al., 2004), researchers found the true incidence of paediatric dosing errors to be approximately 500 000 per year in England. Based on these findings and the fact that ADRs and MEs are under-reported or hardly ever reported in South African hospitals, there is thus an urgent need to minimize any further such potential errors. Although hospital formularies and standard treatment guidelines (STGs) are readily available for prescribers to use, it is still not common to comfortably locate prescriptions within the fold of good prescribing protocols. The American Academy of Paediatrics (AAP) has also recognized the importance of identifying and managing MEs in children. The Drug and Therapeutics Committee of the Hospital Care section of the AAP emphasizes the importance of systems change in detecting and preventing MEs among inpatients. It enumerates substantial recommendations covering not only prescribers, pharmacists, and nurses, but also the hospital system and parents (Koren, Barzilay and Greenwald 1986).

It was of paramount importance that a definition of paediatric prescribing errors be established before conducting a study at a paediatric hospital such as the current one at RCWMCH. The definition of a prescribing error is vital to the study, seeing as such a definition can significantly influence the number of errors identified. For the study at RCWMCH prescriptions complying with the defining terms constituting a correct prescription, that is, prescriptions in accordance with the Medicines and Related Substance Act 101 of 1965 (Medicines and Related Substance Act 101 of 1965, Regulations as amended,2014: 28) were regarded as correct for the purpose of this study.The act requires the following information with regard to the prescriber, patient, and drug: (a) name, qualification and practice number, and address of the prescriber, (b) name, address, age, and sex of the patient, and (c) approved name of the drug, dosage form, strength of dosage form, and quantity of medicine to be supplied. In the case of Schedule 6 drugs, the quantity is to be written in figures and words, with instructions for the administration of the dosage, frequency

of administration, and the duration clearly stipulated on the prescription. In addition, the date of the prescription must be clearly recorded, with the whole prescription needing to be in legible hand written or typed print.

2.4 Drug-drug interactions

Prescribers often prescribe a number of drugs belonging to different classes, each with their own side effect profile. Drug-drug interactions (DDIs) are often overlooked. This oversight can and does interfere with the outcome of drug treatment, that is, causing therapeutic failure and drug toxicity. It is true that not all DDIs are bad, that is, some drug interactions are seen as synergistic or even beneficial to the patient. Prescribers, however, must take into consideration the potential for harm that drugs may have when they are administered in combination as part of a therapeutic drug regimen. Antiretroviral (ARV) drugs are not to be ignored when it comes to DDIs. The treatment of HIV-infected patients is a challenge for many a healthcare professional, made more complex in the case of HIV-infected children. Drug interactions involving metabolism are the most difficult to predict and constitute the most common problems for prescription errors. Some drugs may interact in more than one way, acting as an inhibitor and inducer of different CYP450 enzymes. The prescriber dealing with HIV-infected children has to prescribe responsibly to ensure that prescribed medication has more benefit than risk to the patient. It is predictable that drug interactions occur in almost all patients being treated for HIV/AIDS, due largely to the average number of drugs prescribed for treating the virus and the opportunistic infections it causes (Katenda-Kyenda et al., 2011).

ARV's have transformed HIV/AIDS into a chronic disorder that can be managed effectively, with the right of all HIV-infected adults and children to receive standard care endorsed by the SA HIV Clinicians Society (SAHIVCS). ART guidelines recommending

different treatment combinations are also provided for. With the increased number of approved ARVs, the risk of prescribing errors increases, as well as the dispensing of incorrect dosages and/or dose frequencies and incorrect reporting of drugs by the patient to the prescriber, all of which lead to treatment failure. DDIs are an under recognized consequence of medication prescription errors, resulting in significant healthcare costs. DDIs determine both positive and negative consequences of treatment for HIV- infected patients and SAHIVCS and the NDoH in South Africa have made recommendations with regard to a number of drug combinations and adjustment of dosages concerning certain co-administered drugs (Katende-Kyenda et al., 2011).

In a non-experimental retrospective quantitative study Katende-Kyenda et al. (2011) described the prevalence of ARV prescriptions with potential DDIs and evaluated their prescribed daily dosages (PDDs) with specific reference to the prescriber and age group. The study was performed over a 24-month period on data received from a South African Pharmacy Benefit Management (PBM) company. Confidentiality was strictly maintained to ensure non-identification of patients, medical practices, pharmacies, or medical schemes involved. Permission to conduct the study was granted by PBM and ethics approval was obtained from the research and ethics committees of the North West University and the Walter Sisulu University. Potential DDIs between ARVs were identified and classified as clinically major, moderate, or minor. The study was performed using 49 995, 81 096, and 88 988 ARV prescriptions made for 7 664, 10 162, and 10 061 HIV patients in 2005, 2006, and 2007, respectively. ARV prescriptions represented 0.59% (N = 49 995), 0.90% (N = 81 096), and 1.11% (N = 88 988) of the medical aid claims for the three years. ARV prescriptions from general practitioners (GPs) with potential DDIs and incorrect PDDs increased from 12.33% in 2005 to 24.26% in 2007. Prescriptions from specialist practitioners (SPs) increased from 15.46% in 2005 to 35.30% in 2006 and decreased to 33.16% in 2007. The highest

numbers of incorrect PDDs with DDIs were identified in ARV combinations as follows: lopinavir-ritonavir 1066.4mg/264mg with efavirenz 600mg , and lopinavir/ritonavir 1 066.4mg/264mg with nevirapine 400mg, followed by indinavir 1 600mg with ritonavir 800mg, ritonavir 600mg with efavirenz 600mg and saqinavir 800mg with efavirenz 800mg for both GPs and SPs. Although combination ARV therapy is potent and effective for HIV infection, ARVs frequently interact among themselves as many are metabolized through the same CYP450 system.

A study such as the one above clearly illustrates the importance of appropriately prescribed ARVs for adult and children, more so in children who are not sufficiently pharmacokinetically developed to buffer serious adverse effects due to DDIs. The outcomes of interactions are not always easy to measure in the absence of a concerted effort by healthcare professionals to keep records of unexpected adverse drug events. As stated earlier, while it should be noted that not all drug interactions are harmful, with some drug interactions possibly beneficial with potential synergistic use to produce a desired outcome, the concern should be on those that are not.

As previously mentioned, paediatric patients react to drugs differently than do adults. In particular, extended half-life of metabolised drug and reduced excretion may result in toxicity problems. A descriptive study of drug interactions in hospitalised children undertaken by Martinbiancho et al. (2007) and others from January 2005 to December 2006 in a teaching hospital in Brazil helped to verify rates of drug interactions and their clinical meaning in prescriptions for paediatric patients during the period of hospitalisation. The study included patients aged 0–12 years with four or more drugs in their prescriptions, excluding topical drugs. The study excluded patients hospitalised in emergency areas, ICUs, and the oncology unit. Patients' electronic prescriptions were analysed three times a week by a pharmacist and two scholarship holders in pharmaceutics. The Micromedex/Drug Reax

program was used to analyse drug interactions and incompatibilities. Based on the interactions found, an analysis was performed on their relevance to the patients' respective conditions and the medical team informed of the findings. The drug interactions were classified in terms of interaction severity, effect start, and literature documentation. For the duration of the study period, 3 170 patients were investigated, with 11 181 prescriptions analysed, producing a mean of 3.5 prescriptions per patient. The mean quantity of items per prescription was 10. These prescriptions contained 6 857 drug interactions, that is, 1.9 interactions per prescription and seven interactions per patient. The most frequent drug interactions were ampicillin and gentamycin in 220 (3.2%) prescriptions, diazepam and chloral hydrate in 215 (3.1%), and valproic acid and phenobarbitone in 214 (3.1%) prescriptions. In total, 1 201 (5.6%) drug interactions were brought to the notice of medical teams, with 204 (17%) of severe level, 672 (56%) of moderate level, and 325 (27%) of mild level.

The above study showed that although the number of clinically relevant drug interactions was considered low, many hospital admissions were linked to effects caused by the interactions of utilised drugs. The computerised system used to identify and verify potential drug interactions is an excellent means of helping health professionals prevent severe drug interactions. In a dynamic working environment and specialised teaching hospital such as the RCWMCH, the Micromedex/Drug Reax system, if adopted, could prove of great benefit in the future. Interestingly, the drugs identified in the study to be most frequently involved in drug interactions are drugs also commonly used at the RCWMCH, for example, the concurrent prescribing of valproic acid and phenobarbitone, ampicillin and gentamycin, and chloral hydrate and diazepam.

In a study carried out by Goldberg et al. (1994), an analysis of high risk population involved in potential drug-drug interaction was considered. This study only included subjects

50 years and older. Yet, based on the findings by these researchers, one cannot discount the possibility that perhaps children, if they had been included, may have shown similar outcomes since most of the drugs involved in the study are drugs also commonly used in the paediatric population. The retrospective study by Goldberg et al. (1994) was carried out the EDs of two facilities, namely, a community hospital ED (referred to in the study as facility 1 and a general teaching hospital ED (facility 2). The general hospital has a volume of approximately 160 000 ED visits per year and the community hospital that of 30 000. Three 24-hour periods were randomly selected at each facility during the months of January and February 1994. All patients receiving three or more medications and any patient 50 years of age or older taking at least two medications were included in the study. Data collected included: age, gender, reason for admission, medications taken prior to ED visit, medications administered in or prescribed at the ED, and discharge diagnosis. Potential drug interactions were analysed using the Drug Master Plus computer software program, with the editors defining a moderately significant interaction as one in which the potential for interaction is increased and possible harm to the patient with prolonged use of the drug combination. A total of 205 patients were studied, 111 from facility 1 and 94 from facility 2; the study groups were similar with respect to mean age and number of patients with hypertension, diabetes, renal failure, and congestive heart failure.

Overall, 89 of 191 patients (47%) had a total of 226 potential adverse drug interactions (ADI's), 50% of which were related to ED treatment. No significant differences between the facilities were found. The potential for ADIs increased with the number of medications administered, with 13% of patients taking two medications at risk for ADI as compared to 38% taking five medications and 82% taking seven or more medications. Of a total of 226 potential drug interactions, 11 drugs accounted for 223 (98%). An analysis of these drugs in terms of relative risk of drug interaction between patients administered versus

those not administered commonly interactive drugs showed that digoxin and furosemide had significant p values ($p<0.0001$),nifedipine ($p<0.0098$), enalapril ($p<0.0070$), ranitidine ($p<0.0015$), and glyburide ($p<0.0423$). P values with respect to relative risk failed to reach significance for prednisone, prochlorperazine, dilantin, and aspirin.

That these studies were carried out only in the EDs of the hospitals does not mean that similar results could not have been obtained in the general wards of the same hospitals, since all the drugs indicated above are commonly used throughout the hospitals. Children also form part of the patient pool that visit the EDs of hospitals, thus a significant population group was excluded in the study, that is, the relative risk of potential drug interaction could have shown more interesting results if they had been included.

In a study performed in two cities in Pakistan, namely, Faisalabad and Sargodha, in 2009 by Sajid et al. (2011) a comparative assessment of drug interactions in children at private and public sector hospitals illustrated the importance of including the paediatric population when researching drug interactions. Interestingly, the researchers considered drug interactions as a type of prescribing error.

The medication records of hospitalised paediatric patients from May to August 2009 were screened for drug interactions. The study included hospitalised children aged 12 years and below with three or more drugs in their prescriptions. Topical drugs were excluded, as were children hospitalised in emergency and intensive care units. A computerised software program developed by Medical Letter 2002 was used to analyse potential drug interactions classified as severe, moderate, or mild. Comparative data of a total 1 420 prescriptions were collected, with a total of 950 drug interactions found, that is, 66.90%. Among the total drug interactions found, the public sector hospital showed 820 out of a total of 1 100 prescriptions, that is, 74.55%. In the private sector hospitals in both cities, the total number of drug

interactions found was 130 out of 320 prescriptions, that is, 40.63%. The total number of paediatric patient admissions in the public sector hospital in Faisalabad was 2 681 from May 2009 to August 2009, with 680 prescriptions selected. The number of drug interactions found was 430 out of the 680 prescriptions, that is, 63.24%. The data of 420 from 1 680 admissions from the sole public sector hospital in the city of Sargodha were also collected. The total number of drug interactions found was 92.86%, with 390 out of 420 prescriptions. Regarding the types of drug interactions, 19 types were found in the public sector hospital studied in Faisalabad, 24 (3.5%) of these being severe, 242 (35.6%) moderate, and 164 (24.1%) mild. Examples included interactions between ampicillin and cefotaxime (16.2%) and isoniazid and rifampicin (2.3%). In the public sector hospital in Sargodha, 20 types of interactions were observed, with 3.8% being severe, 73.3% moderate, and 15.7% mild.

In the private sector hospital, from May to August 2009, a total of 320 prescriptions were analysed, with 200 from two hospitals in Faisalabad and 120 from two hospitals in Sargodha. The total number of drug interactions found in the private sector of Faisalabad were 40 out of 200 prescriptions (20%), with six types, 18 of which (9.0%) was mild and 22 (11%) moderate; no severe drug interactions were found. A total of 90 (75%) drug interactions of nine different types were found in the private sector hospitals in Sargodha, with 19 (15.8%) being mild, 65 (54%) moderate, and 6 (5.0%) severe. These findings show that the public sector hospitals of both cities experienced a greater percentage of drug interactions compared to the private sector hospitals. The public hospitals of Faisalabad showed a better performance (63.24%) where specialised prescribers were available, compared to the public sector hospital of Sargodha, in which the whole city had only two to three specialist paediatricians. On the other hand, both public sector hospitals had pharmacists, but these were involved in purchasing of medicines and not in clinical activities. The private sector hospital of Faisalabad showed only 25% of drug interactions as compared

to the private sector hospital in Sargodha, which had 75% of drug interactions. This could be attributed to the Faisalabad hospital having more pharmacists than did the private sector hospital in Sargodha.

The above study clearly demonstrates the potential for drug interactions in the paediatric population, irrespective of the type of healthcare setting, that is, private or public. It also highlights the importance of specialists involved in the role of prescriber rather than junior doctors as well as the presence of clinical pharmacist on the ward rounds.

2.5 Drug-disease interactions

A drug-disease interaction (DDiS) occurs when a medicine worsens a pre-existing disease (Lindblad et al., 2005). This is a concern, especially for elderly patients who may have more than one chronic condition and also for the paediatric population, who have immature organ function, thus placing them more at risk for DDiS.

Choosing the correct drug and correct dose can thus be a challenge in the face of a chronic disease. Interestingly, the most profound interactions will occur when the disease process affects organs involved in drug disposition. Important examples of drug-disease interactions are described in the list that follows: (a) Cirhossis and other liver diseases can impair the ability of the liver to metabolise drugs. Drug toxicity may result if hepatic impairment is not considered, with therapeutic drug monitoring being important in patients with pre-existing liver diseases. (b) In patients with renal disease, prostaglandins assists in maintaining residual renal function. If drugs, such as non-steroidal anti-inflammatory drugs, are used in compromised patients, inhibition of cyclo-oxygenase will take place, resulting in a decline in residual renal function and consequently impaired renal excretion may occur (c) Viral infection suppresses hepatic cytochrome P450, perhaps as a result of interferon

induction. A patient with a plasma drug concentration at the upper end of the therapeutic range could therefore suddenly show signs of drug toxicity during a viral infection. (d) Achlorhydria (lack of stomach acid) may affect the site of absorption of drug formulations with a pH dependant coating. (e) The choice of a diuretic for a patient with cardiovascular disease is influenced by whether the patient has osteoporosis. Hydrochlorthiazide is a diuretic that does not increase renal elimination of calcium, which makes it the diuretic of choice in this type of patient. (f) Anticholinergics can increase cognitive impairment in patients with Alzheimer-type dementia (Page et al., 2002). Children, especially the very young, are disadvantaged when one considers their immature organ systems *vis a vis* the drugs that needs to be administered, metabolised, and excreted by the liver and kidneys, especially in the case of a chronic condition, such as chronic liver disease or end stage renal disease, add to the malfunction of their very same immature organs.

To illustrate the interactions of age, genetics, and disease severity on tacrolimus (an immune-suppressive drug) dosing requirements after paediatric kidney and liver transplantation, de Wildt et al. (2011), conducted a retrospective study in paediatric liver and kidney transplant patients who received tacrolimus in the first 14 days after transplant. Children, aged between 0–18 years eligible for study purposes had at the time of liver or kidney transplant received tacrolimus during the first 14 days post-transplant. The study was conducted on such patients between 2000 and 2008 at the Hospital for Sick Children in Toronto, Canada. All patients who received tacrolimus in the first two weeks after transplant were approached for informed consent when they visited the out-patient clinic between November 2006 and February 2008. All the patients received the transplant immune-suppression protocol therapy, namely, methylprednisolone, mycophenalate mofetil, and tacrolimus. The tacrolimus starting dose was 0.1mg/kg orally twice daily for all patients, adjusted by routine pre-dose tacrolimus concentrations to reach the preset target tacrolimus

concentration of 10–15ng/ml. Doses were adapted by the transplant physician in collaboration with the pharmacist. Tacrolimus doses (date/time) and morning pre-dose blood concentrations (date/time) were collected. The primary outcome measure was median tacrolimus dosing requirement and secondary outcome measures were median tacrolimus concentrations and concentration/dose ratio. The independent variables included recipient age, CYP3A5 and ABCB1 genotype, and PRISM (paediatric risk of mortality) score, a measuring score widely used in paediatric intensive care setting assessing the severity of illness and the potential risk of mortality in critically ill children. The total transplant cohort at the transplant unit as of February 2008 was 124 kidney and 91 liver transplant patients, with approximately 80% having received tacrolimus in the first two weeks of transplant. Overall, 42 paediatric liver recipients and 48 kidney recipients were enrolled in the study. The liver recipients were much younger than the kidney recipients, with the median range as follows: 1.5 years (range: 0.05–14.8) and 11.5 years (range: 1.5–17.7), respectively. Median durations of mechanical ventilation and stay at the ICU were longer in the liver patients than in the kidney patients. Children aged younger than 5 years needed higher tacrolimus doses per kilogram of bodyweight than did older children for both kidney and liver transplants. For kidney transplant patients, the median was 0.15 (range: 0.07–0.35) versus 0.09 (0.02–0.20) mg/kg 12-hourly, p = 0.046. For liver transplant patients, the median was 0.12 (range: 0.04–0.32) versus 0.09 (range: 0.01–0.18) mg/kg 12-hourly, p = 0.038). The PRISM mortality scores were not correlated with tacrolimus dosing requirements, tacrolimus trough concentrations, or concentration/dose ratios in both transplant groups.

Although a study such as the one above did not find any relation between disease severity and drug disposition, DDiS cannot be overlooked, as the following study revealed.

In a study carried out at two separate facilities, namely, a general teaching hospital and a community hospital in the United States in 1994, no significant difference was found

between the two facilities with regards to the analysis of DDiS and the relative risk of DDIs. This study was undertaken by Goldberg et al. (1994) to determine not only the potential for drug-disease interactions, but also for potential adverse drug interactions, as has been previously mentioned in section 2.4 above of this literature review. A sample of ED records from each hospital was reviewed for potential drug-disease interaction. Existing medical conditions and newly diagnosed medical conditions were entered into the computer software program and compared with a list of the patient's medication. Clinical interaction was defined by the program editors based on the drug manufacturers' current package labelling and data derived from standard medical references. Relative risks were derived for the incidence of drug-disease interactions between groups who had and did not have the disease. Overall, 44 of 205 patients (21.5%) had a total of 94 potential drug-disease interactions, of which 32 (34%) were related to ED treatment. Leading drug-disease interactions included: albuterol-hypertension (4.8%); furosemide-diabetes (3.9%); prednisone-hypertension (2.9%); ibuprofen-hypertension (1.9%); albuterol-diabetes (1.95%), and prednisone-diabetes (1.4%). Goldberg et al. (1994) found that patients in this study population appeared to have substantial risk for drug-disease interactions (22%). Furthermore, the study revealed that approximately a third of potential DDiS were attributable to medications administered or prescribed in the ED. The outcome for the relative risk of drug-disease interaction between patients versus those with commonly encountered diseases showed interesting results. For example, patients with congestive heart failure (CHF) had a higher incidence of drug-disease interactions (54%) compared to those without (19.4%); hypertension (42.4%) compared to those without (14.4%); diabetes (51.5%) compared to those without (18.4%), and renal (57.1%) compared to those without (20.9%).

This study clearly illustrated that DDiS should be considered in all population groups, including children, the latter who despite their young age, may suffer from the same adult

disease(s) mentioned in the above study, with physicians prescribing similar medications for children as for adults. This is even more pertinent if one considers that it is not uncommon to see children with advanced HIV and tuberculosis (TB) as a co-morbid disease, especially in the developing world and at the RCWMCH where the current study was conducted.

A study conducted by Sahai et al. (1997) illustrated the importance of considering the drugs and disease state of the patient at the time of prescribing. This study found that reduced total drug exposure to rifampicin and pyrazinamide was associated with d-xylose malabsorption in persons with HIV infection and that peak drug exposure to isoniazid was lower in patients with diarrhoea. A total of 48 TB-free persons took part in the study and included: 12 healthy participants who were HIV- uninfected (Group 1); 12 HIV sero-positive asymptomatic patients with a CD4 T-cell counts greater than 200 cells per cubic mm (Group 2); 12 HIV seropositive patients with a CD4 T-cell counts less than 200 cells per cubic mm (Group 3); and 12 HIV seropositive patients with a CD4 T-cell count of less than 200 cells per cubic mm and persistent diarrhoea (Group 4). Exclusion criteria were age below 18 years, pregnancy, abnormal liver function tests, serum creatinine levels >200 micromole/L, haemoglobin levels <100g/L, active opportunistic disease, and known hypersensitivity to any of the medications involved in the study. Study participants received 300mg isoniazid, 600mg rifampicin, 1 000mg of pyrazinamide, and 1 000mg of ethambutol daily, administered at the same time over three consecutive mornings. Therapy with other medications was stopped at least 24 hours before the study commenced and for its duration (five days). In order to measure the absorptive function of the intestines, with participants receiving 25g of D-xylose with 400ml water 24 hours after administering of the final dose of the anti-TB drugs. In this study, concentrations of all the anti-TB drugs were measured with high-performance liquid chromatography; however, analytic difficulties precluded the measurement of ethambutol. A colorimetric method was used to measure D-xylose. A comparison was made between the

plasma drug concentrations and time. It included data such as highest observed drug concentrations (Cmax), the time to Cmax (tmax), the terminal disposition half-life, and the area under the plasma concentration time curve (AUC) over the 24 hour dosing interval. Fast acetylators were distinguished if they had an isoniazid half-life of less than 130 minutes. There were 4, 10, 6, and 7 fast acetylators in groups 1, 2, 3, and 4 respectively. Fast acetylators had a shorter half-life and lower AUC value than slow acetylators. The trend analysis indicated a significant linear decrease in mean AUC with group order for pyrazinamide ($p = 0.0002$) as well as a significant linear decrease in Cmax for rifampicin ($p = 0.0006$), and isoniazid ($p = 0.046$). Consistent with the trend for decreasing AUC and Cmax values from groups 1 to 4, statistically significant decreases of 18% to 41% in these variables were seen for some of the group contrasts for each drug. This study revealed that total systemic drug exposure was reduced for rifampicin by 32% and for pyrazinamide by 24% in persons with HIV-infection compared with the healthy controls, probably reflecting decreased bio-availability. Isoniazid was generally well absorbed in HIV-infected patients compared with healthy controls, which may partially explain a lack of correlation with the D-xylose AUC. The 39% decrease in peak exposure and 0.74-hour increase in time to peak exposure suggested that diarrhoea reduced the rate of isoniazid absorption in symptomatic patients. The significant correlation between the D-xylose AUC and rifampicin and pyrazinamide AUC implies an absorptive defect. However, gastrointestinal malfunction may also increase rifampicin clearance by reducing its reabsorption during enterohepatic circulation, which explains why rifampicin was associated with the largest decreases in total and peak exposure.

A study such as the one above demonstrated that HIV-infected patients, especially those in the advanced stage of the disease, have lower plasma concentrations of one or more anti-TB drugs, particularly rifampicin, compared with healthy subjects. That HIV-infected

children were not included in this study does not exclude them from being considered at risk, considering the challenges posed when anti-TB drugs are administered to them as part of the similar treatment they receive as for adults. As mentioned previously, children are pharmacokinetically more challenged than are adults and parameters such as half-life, bio-availability, and plasma under the concentration-time curve should be considered at the time of prescribing, especially when other co-morbid conditions, for example, diarrhoea and failure to thrive (FTT), are present. The situation can be a bit more complex when the prescriber is faced with the challenges of HIV-infected patients with multiple drug resistant (MDR) and extreme drug resistant (XDR) TB, where treatment regimens need to be revised. Right at the onset of making a prescribing decision, the prescriber must take into account the potential for drug-disease interaction when prescribing for a vulnerable group, such as HIV-infected patients with TB.

A study by Schaaf et al. (2009) in Cape Town between 2004 and 2006 illustrated that both HIV- infected and HIV-uninfected children with TB required higher doses of rifampicin. A total of 60 children (26 HIV-infected and 34 HIV-uninfected children) were enrolled for the study at the Brooklyn Hospital for Chest Diseases (BHCD), a referral hospital for TB in Cape Town. The study period spanned January 2004 to December 2006. Fixed dose combinations of rifampicin (RMP) 60mg, isoniazid (INH) 30mg, and pyrazinamide (PZA) 150mg (rimcure) was used during the intensive phase, with rifampicin 60mg and isoniazid 30mg used during the continuation phase of TB. Rifampicin plasma concentrations were measured within a week of admission to BHCD and again four months after commencement of treatment to evaluate the possible influence of nutrition, disease state, and intra-individual variation on RMP pharmacokinetics. In the course of the study, four children (all HIV-infected) were transferred back to referral hospitals due to complications that could not be managed at the BHCD, and a further two discharged (one HIV-infected and HIV-uninfected).

The remaining children received a mean RMP dosage of 9.61mg/kg for the pharmacokinetic study on enrolment and 9.63mg/kg during the four-month study. The mean calculated 2-hour RMP concentrations of the HIV-infected and HIV-uninfected children on enrolment were 3.90 and 4.78 mcg/ml, respectively, with the standard deviation (SD) of the HIV-infected group (3.25) significantly greater than that of the HIV-uninfected group, (1.67). At the first pharmacokinetic evaluation on enrolment, only five children (9%) had calculated two-hour concentrations >8mcg/ml, while 25 (47%) had values <4 mcg/ml, although more HIV-infected than HIV-uninfected children had values as low as 57% and 41%, respectively. Four months after the start of treatment, three children (6%) had two-hour RMP concentrations >8 mcg/ml and 25 (43%) values <4 mcg/ml, with 39% HIV-infected and 43% of HIV-uninfected children showing such low values. While the results of the above study may perhaps be of little or no consequence in the management of less serious forms of TB in children, it might well be relevant in more severe forms of the disease, such as those encountered in the developing world, especially in association with HIV infection (Schaaf et al., 2009).

2.6 Off-label prescribing

Medical practice in recent years changed in numerous ways as compared to the past. The natural healer or physician of the past prescribed custom-made prescriptions, based on the individual's needs, with the pharmacist practising what is called *secundum artum* (according to the accepted practice of a profession, for example, pharmacy for dispensing) to an individual patient. Medical practice in the past, in essence, fashioned itself as per the custom made prescription. In contrast, medical practice presently is now shaped by a huge drug market, with the pharmaceutical industry as the supplier, the patient as the customer, and the physician as the prescriber, the latter, ideally prescribing drugs based on evidence and according to standard treatment guidelines (STGs). Along with the benefits that came with

new diagnostic procedures and drug supply as the practice of medicine grew, a number of dramatic setbacks may also be observed. For example, adverse physical effects of new drugs developed by the ever-expanding pharmaceutical industry on patients, such as, diethylstilbestrol induced cancer in some girls, Grey's syndrome in new-borns caused by chloramphenicol, coagulation factor preparations infecting patients with HIV, not forgetting hundreds of babies born with malformations induced by thalidomide. As a result, governments continue to develop laws to oversee correct marketing, selling, and consumption of drugs, with pharmaceutical companies legally obliged to provide pre-clinical efficacy and safety data from testing on animals, as well as results of clinical trials on humans to prove safety profiles and efficacy for the intended indication of a new drug before it is released in to the market. Thus the label was born. When a drug is approved for market release, the indications and dosages form part of the package insert and it is for the particular situations indicated that the risk-benefit ratio would have been reviewed and accepted by the regulatory authorities. However, different dosages, modifications of the formulation, for example, crushing tablets to make "special formulations" for children, and different routes of application (such as parenteral solutions for oral administering) mean that drugs are used without the legal protection of their labels, that, off-label (OL) use.

If there is an argument for the need to control the drug market, gained from historical lessons learnt about the developing organs of children which place them at risk from systematic drug toxicities, why is it common practice for children to be subjected to off-label (OL) drug prescribing? (Boos, 2003). In fact, the few studies done on the subject reveal the various concerns relating to off-label prescribing and show that the younger the patient and the more critical and rare the illness, the more likely will be the need for treatment that is off-label.

A study conducted in the English Midlands in 1997 by Conroy et al. (2000) showed that off-label prescribing is common practice. It would be wrong to assume or generalise that unlicensed or "off-label" medicines are either potentially harmful to children or that they do not cause any harm, since in many cases they prove to be of great therapeutic benefit. Nonetheless, in the absence of testing and licensing, we cannot know if this is the case, nor can we know if children have suffered actual harm from taking medicines prescribed OL. It is also surely wrong that clinicians treating children should be faced with a situation of having to guess the "appropriate" dose and route of a medicine for a child patient. It would thus be interesting to know the prescribing habits of physicians as far as unlicensed and off- label prescribing is concerned.

In one such study, prescribing habits with regard to unlicensed and off- label medicines in neonatal ICU patients were assessed (Conroy, McIntyre &Choonara, 1999). This was a prospective study conducted over a 13-week period in1998 in the United Kingdom and the clinical research pharmacist designed a data collection form that included patient's hospital number, date of birth, weight, gestation, diagnosis, drug prescribed and administered, date and route of administration, dose, frequency, and indication for use. In this study, unlicensed drugs referred to: (1) modifications to licensed drugs, for example, preparation of a total parenteral nutrition infusion by a hospital pharmacy's aseptic service unit, (2) use of "special" formulations of licensed drugs produced under a manufacturing license, that is, suspension of a drug licensed in a solid dose form but formulated into a liquid preparation by a "specials" manufacturer, for example, dexamethasone, and (3) "new" drugs, for example tolazoline injection for the treatment of pulmonary hypertension. Off- label, that is, drugs used outside the terms of their product license, included the administration of a drug to a patient of an age not covered by the product license, in a dose other than that specified in the license, by an alternative route, or for an indication not included in the license. In this

study, 70 patients were admitted to the neonatal intensive care unit (NICU) at a hospital in the United Kingdom during the study period, with 49 babies being premature and requiring intensive care. The median gestational age was 33 weeks. The babies received a total of 455 prescriptions episodes (each episode being a course of a drug or a single once-off dose). Of the prescriptions, 161 (35.4%) were licensed drugs, 45 (9.9%) were unlicensed drugs, and the remaining 249 (54.7%) were drugs used in an off- label manner. Further, 63 (90%) babies received at least one unlicensed or off-label drug. The unlicensed drugs fell into three categories, namely, (a) modification, which included drugs such as morphine, phenobarbitone, dopamine, and total parenteral nutrition (all prepared in the hospital pharmacy), (b) the "new" drug prepared by "special" manufacturer included caffeine, and (c) "special" formulation of licensed drugs, which included drugs such as chloral hydrate, dexamethasone, adrenaline, and spironolactone. It was found that off- label use was far more common than unlicensed drug use in this population and included drugs like morphine, folic acid, benzylpenicillin, vitamin K, flucloxacillin, albumin, and gentamycin. Similarly, at the RCWMCH, where the present study was conducted, it is also common practice for prescribers to order "special" manufactured drugs like caffeine (used as a respiratory stimulant) and sildenafil (for pulmonary hypertension). In addition, drugs such as gentamycin are also prescribed outside its licence terms, for example, as part of a bowel cocktail in patients with gastro-enteritis.

It is interesting to note further, that according to Ghaleb et al. (2010), drugs are often used off-license, leading to less clear dosing guidance. In addition, a small mistake, which might be tolerated in adults, can have significant consequences in a young child.

2.7 Parameters of the current study

2.7.1 Preamble

The rationale for the study was driven by the observance of the inconsistencies in prescribing practice and the large number of prescribing errors both by junior and senior prescribers at RCWMCH

The research studies, as highlighted in the literature review above, indicated the prevalence of prescribing errors, irrespective of the volume of prescriptions. For example, the study carried out in a 15-bed paediatric cardiac ward and four bed cardiac ICU at University Hospital in Wales (Wilson et al., 1998), showed a total of 441 error reports submitted during the 24month period, of which prescribing errors accounted for 68%. Doctors, nurses and pharmacists all participated in reporting errors, a practice not readily observed in hospitals in South Africa. The study by Kozer et al. (2000) at the Hospital for Sick Children in Toronto, Canada, found that healthcare trainees were more likely to contribute to prescribing errors. Prescribing by junior doctors is not unique to that hospital setting. My own experience of working at the RCWMCH shows that some of the wards have junior doctors who are also involved in the process of prescribing. Moreover, as highlighted by the study carried out in Christchurch, New Zealand (Grimwood et al., 1983), there is a concern with incorrect prescribing of antibiotics, be it in regard to the dose, frequency, or incorrect choice of antibiotics. Another concern with regard to prescribing practice is that of drug disease interaction. The local study at the BHCD in Cape Town (Schaaf et al., 2009) illustrated the concern of low serum levels of RMP concentrations in children, the great majority who received the recommended standard dosage of 8 to 12mg/kg. Prescribers need to consider higher dosages for RMP, especially in a country like South Africa where serious cases of TB coupled with HIV-infected children is common. More studies and on-going education with

regard to prescribing for patients with HIV and TB are needed. Drug interactions are also to be taken into consideration, especially in situations where prescribers decide to change the therapeutic regimen, as shown in the study by Martinbiancho et al. (2007). One particular DDI of note in the current study is that of valproic acid and phenobarbitone, drugs commonly prescribed for epileptic children, which is used at the RCWMCH. Both drugs enhance each other's toxicity and thus need close monitoring, a practice not always carried out.

2.7.2 Research question

The research question the proposed research study poses and sets out to answer is: are prescribers fully compliant with the legal prescription requirements, as set out by the Medicines and Related Substance Act 101 of 1965 (Medicines and Related Substance Act101 of 1965, Regulations as amended, 2014:28), with regards to information relating to the prescriber, the patient, and the drug?

2.7.3 Hypothesis

The hypothesis of the proposed research study, which it sets out to prove, is that most doctors do not adhere to the Medicines and Related Substance Act 101 of 1965 (Medicines and Related Substance Act101 of 1965, Regulations as amended,2014:28) when it comes to prescribing, with missing information outnumbering other types of errors.

2.7.4 Aim

The aim of the proposed research study is to identify the pattern of prescribing practice at RCWMCH.

2.7.5 Objectives

The objectives of the current research study are as follows:

- to describe the type of prescribing errors and frequency thereof,
- to describe the prescribing error frequency per different classes of drugs,
- to identify potential drug-drug interactions (DDIs),
- to identify potential**) drug-disease interactions (**DDiS),
- to describe off-label (OL) prescribing, and
- to identify some of the determinants of prescribing errors

2.7.6 Expected outcomes

- Increase in awareness of prescribing in accordance with legal requirements as per medicines and Related Substance Act 101 of 1965
- Importance of rational medicine use in a paediatric hospital
- Importance of medication error reporting
- The need to continuously educate prescribers about the writing style and decision-making process of prescribing
- Standardisation of the prescription charts

Chapter 3

Materials and Method

3.1 Study design, site, and population

The prospective, cross-sectional study took place at Red Cross War Memorial Children's Hospital (RCWMCH) in Cape Town, in wards B1 (28 beds) and B2 (25 beds) (general medical wards) as well as in two specialty wards, that is, the Paediatric Intensive Care Unit (PICU) (20 beds) and ward G1 (oncology) (17 beds). The study involved doctors working in these wards over the period 1 July 2012 to 31 December 2012.

3.2 Inclusion criteria and exclusion criteria

Only in-patient prescriptions generated in the four above mentioned wards and drug items current at the time of prescribing were included in the study. Prescriptions from prescribers (that is, interns, senior house officers (SHOs), registrars, and consultants) affiliated to the RCWMCH were evaluated in the study.

Prescriptions generated in the out-patient department (for acute and chronic conditions) and in the trauma surgical, cardiac, renal, and liver transplant wards as well as prescriptions written by a referring doctor from another hospital were excluded from the study.

3.3 Sample size

Incomplete information formed the basis of the most recurring type of prescribing errors, presumably occurring one and half times more frequently than all the other types of errors combined. Convenience sampling was used during routine working hours. The sample size estimation was accomplished by assuming that incomplete information accounted for 60% (0.6) of all prescribing errors, with other types of prescribing errors assumed at 40% (0.4).

The average of the two proportions was calculated and equaled 0.5. The standardized or effect size was calculated based on a standard statistical formula, with the answer equaling 0.4. The sample size was then calculated for a significant level of 5% and 80% power. The sample size obtained from this calculation equaled 98. Thus, a total sample size of 196 prescriptions for the two groups, namely, junior and senior prescribers, was needed. I thus took 200 prescriptions as the sample size (Hicks, 2009).

3.4. Parameters assessed

The following parameters were assessed during the study: (1) prescribing errors, (2) potential drug interactions (DDIs), (3) potential drug-disease interactions (DDiS), and (4) off-label (OL) prescribing. Information related to parameters 1–4 were transferred into Excel and further analyzed using STATA 11, and (5). Weight-for-age (WAZ) nutritional status was also assessed. Mass of all the patients were converted into weight-for-age z-score (WAZ), using WHO (de Onis et al.,2006) child growth standards, measured via STATA 12**.**

The first datasheet (see Appendix A) included biographical information, that is, the study number, folder number, time of assessment of prescription chart, date of birth, gender of the patient, and body weight. Clinical information, that is, ward location, current date, primary diagnosis, and co-morbid conditions were also included. Drugs were identified by numeric codes, with the drug items identified by the respective number(s) on the data sheet.

3.5 Definitions and nomenclature used

A list of definitions and terms used in this thesis is provided here, presenting the meanings of each as understood and used throughout this study.

3.5.1 Prescribing error

For the purpose of this study, the definition of a prescribing error included failure to comply with the legal requirements for writing a prescription, that is, as per the definition used in the Medicines and Related Substance Act 101 of 1965(Medicines and Related Substance Act, 101 of 1965, Regulations as amended, 2014:28). A prescription is a medico-legal document and requires being written up correctly; any deviation from this required format was recorded in this study as an error on the datasheet. The required medico-legal format means a prescription has to be written in legible print, stating the following: (a) name and signature of the prescriber, (b) name, gender, and admission number of the patient, (c) date of issue of the prescription, (d) the approved or proprietary name of the medicine, (e) the dosage form, (f) the strength of the dosage form and the quantity of the medicine to be administered, (g) instructions for the administration, (h) frequency, and (i) period of use. The study adhered to these requirements with regard to the prescriptions it considered.

Any prescribing error noted was classified on the datasheet according to the type of error, including errors pertaining to (1) incomplete or insufficient information, (2) legibility, (3) clarity, (4) use of abbreviations, (5) wrong name, (6) dose too high, (7) dose to low, (8) allergy, (9) wrong time, (10) wrong route, (11) wrong frequency, (12) wrong unit, (13) drug duplication, (14) alteration, (15) contra-indication, and (16) other. Thus, an expanded definition of prescribing error with regard to the selection of the drug for the patient, the dose, the strength, the route, the quantity, the indication, and the contraindications, were also included for the purpose of the study. Below, I clarify some of the descriptions in the list of errors.

3.5.2 Wrong name

For some prescriptions, the prescriber indicated the wrong name of the medication, that is, a trade or brand name for a drug, for example, bactrim (a brand name) was written down and not the generic name, for example, co-trimoxazole.

3.5.3 Legibility

Some prescriptions were not written in legible print and were difficult to decipher and posed problems in terms of readability.

3.5.4 Clarity

Clarity was identified as a problem when no clear prescribing instructions were provided by the prescriber. For instance, an occurrence of non-clarity with regard to route of administration was recorded as a prescribing error. An example of this included a prescription for paracetamol, in which the prescriber indicated “po” (per oral) and “pr” (per rectum) as “po/pr” in the section for route of administration, thus not providing a clear instruction to the administering nurse.

In some cases, alterations of prescriptions were observed, that is, a prescription for a drug item was changed by a prescriber (for example, a dose) prior to the administration of the drug, with the prescriber failing to draw a clear line through the altered prescription and omitting to write his or her name and signature next to the alteration on the prescription. In other cases, the prescriber changed the prescription (for example, to a different drug item or frequency of administration) after the initial drug item prescribed was already administered. These were also recorded as a type of prescribing error.

In other cases, the type of errors under other type of errors, included prescriptions written by unauthorized prescribers (for example, restricted drug items) and prescriptions

including inappropriate drug items, that is, not the correct or best drug for the condition being treated.

3.5.5 Allergy

An allergy for a drug item was also included as a type of error, that is, in cases where a patient developed an adverse drug reaction on first exposure to the drug.

3.5.6 Contra-indication

Another type of error included contra-indications to a drug, for example, when the drug should not be used, as in one particular case when a drug should not have been prescribed due to a pre-existing condition.

3.5.7 Potential drug-drug interactions

Drugs with the potential to interact were listed by their respective number(s) on the datasheet. The interaction type included: (1) increase in absorption, (2) decrease in absorption, (3) increase in drug distribution, (4) decrease in drug distribution, (5) increase in metabolism, (6) decrease in metabolism, (7) increase in excretion, (8) decrease in excretion, and (9) other (that is, potential pharmacodynamic interactions). A brief description of the potential DDI was given and the interacting drug(s) listed using the numeric codes.

3.5.8 Potential drug-disease interactions

A drug item with the potential to exacerbate an existing disease was indicated on the datasheet according to numeric code; the type of DDiS included potential clinical outcomes, that is, (1) cardiotoxicity, (2) nephrotoxicity, (3) hepatotoxicity, (4) ototoxicity, (5) blood disorders, (6) change in glucose levels, and (7) any other. A brief description of the potential DDiS were also given.

3.5.9 Off-label prescribing

All off-label (OL) drug items were indicated by the relevant drug item number on the datasheet, the type of OL was described in terms of: (1) age, (2) formulation, (3) dose, (4) frequency, (5) route, (6) duration of treatment, and (7) other (such as a drug being prescribed for a condition for which it was not approved).

The second datasheet (see Appendix B in this thesis) included information about the possible determinants of prescribing errors, including the level of experience of the prescriber, the day of the week, age of the patient, and location. Drug characteristics, such as drug formulations (that is, intravenous, intramuscular, oral, suppository, inhalation devices, and topical application) and the class of the drug (that is, gastrointestinal tract, blood system, cardiovascular, hormonal therapy, anti-infective agents, cancer therapy , musculo-skeletal system, nervous system, respiratory tract, and other (topical therapy)), the number of drugs prescribed, and the formulary status of drug (that is, formulary versus non-formulary drug) were also indicated on the datasheet (see Appendix B), to further identify the possible determinants of prescribing errors. These variables were all numerically coded (see Appendix B). For statistical analysis purposes, the variables were collapsed and numerically coded as follows:

- Junior doctors (that is, interns and senior health officers (SHO) (1), versus senior doctors (that is, registrars and consultants) (2),
- Weekday (1) versus weekend (2),
- All patients aged below 12 months (1), versus 13–60 months (2),versus patients aged over 60 months (3),
- Speciality wards (G1 and PICU) (1) versus general medical wards (B1and B2) (2),
- Oral formulation (1) versus other formulations (that is, intravenous, intramuscular, suppository, inhalation, and topical) (2),

- Antibiotics (1) versus vitamins and minerals (2) versus other (that is, gastrointestinal, blood system, cardiovascular, hormonal, antifungal, antiviral, oncology, musculoskeletal, nervous system, and respiratory system) (3),

3.5.10 Nutritional status

The nutritional status for male and female patients for the various defined age categories in the different locations (wards) were assessed using the weight-for-age (WAZ) z-score classification. The classification is based on WHO growth standards (de Onis et.al, 2012), with classifications recorded as: overweight (WAZ >+2.00), normal weight (-2.00<WAZ<+2.0), moderate underweight (-3.00<WAZ<-2.01), and severe underweight (WAZ<-3).

3.6 Data collection

A datasheet (see Appendix A) containing both biographical and clinical information about the patient and a datasheet indicating possible risk factor(s) variables (see Appendix B) were used to collect the relevant information by a pharmacist during daily routine ward rounds in two general medical wards (B1 and B2) and two speciality wards (PICU and G1) at RCWMCH. Data were collected from the respective patient(s) folders and from the prescription charts at their bedside(s).

3.7 Methods of statistical analysis

STATA Version 11 was used for the statistical analysis of this descriptive study. Data was entered into an Excel spreadsheet and then imported into STATA. Data analysis was performed by a biostatistician. Normality of numeric data was assessed, using the Shapiro-Wilks test. The mean ± range or the median ± interquartile range and the odds-ratio (OR)

were calculated, as indicated. Where required, 95% Confidence Interval (CI) and means were estimated. Categorical data were reported as proportions.

Univariate analyses and multivariate logistic regression were used to identify determinants (predictors) for prescribing errors. For these analyses, odds ratios, p-values, and confidence intervals (CI) were calculated. Variables were assessed for inclusion in the regression analysis based on the results of the univariate analysis. These variables included: level of experience of the prescribing doctor, class of drug, ward location, drug formulation, formulary/non-formulary drugs, age of the patient, time of the week when the prescription was boarded, and number of drugs prescribed per patient. Variables on univariate analysis with a p-value of less than 0.25 were selected for inclusion in the logistic regression model. The model was then re-rerun with only significant variables included. No major changes in the regression parameters were noted.

3.8 Timeframe

The study was conducted over a period of 6 months, with data collection taking place from July 2012 to December 2012. In this period, a total of 200 prescriptions were reviewed. Each prescription was assessed once only during routine daily ward rounds by a pharmacist.

3.9 Ethics considerations

Prior to conducting the study, approval was requested from and approved by the following institutions:

1) the University of the Western Cape (UWC) ethics committee, Reference number: 12/5/6,
2) the University of Cape Town (UCT) Faculty of Health Sciences Human Research Ethics Committee, reference number: HREC.REF:315/2012, and
3) the RCWMCH Research Committee, reference number R001/12.

The study was conducted according to the ethics requirements stipulated by the NDoH and the international Declaration of Helsinki. The information collected was kept confidential and saved in a safe file, which can only be accessed by the researcher. Patient confidentiality and privacy was maintained at all times.

Chapter 4

Results

4.1 Sample size and characteristics

The total number of patients in the study sample was 200. Each patient's prescription chart was reviewed once only over a six month period (July 2012–December 2012). The prescription chart comprised altogether 1 282 drug items for study over this period. The study took place in four different wards at the RCWMCH, namely, PICU, G1, B1, and B2.

4.1.1 Age distribution

The 200 patients involved in the study had the following age distribution: 0–30 days (19 patients), 31 days–12 months (58 patients), 13–24 months (27 patients), 25–60 months (35 patients), 61–120 months (35 patients), and those aged above 120 months (26 patients). The median age was 22 months, the 25th quartile was 4.45 months, and the 75th quartile was 78.25months.

4.1.2 Presenting conditions

During this study, the following conditions with occurrence were as follow: acute gastroenteritis (AGE) (19), acute lymphoblastic leukemia (ALL) (13), acute myeloid leukemia (AML) (5), acute promyelocytic leukemia (APL) (1), acute respiratory distress syndrome (ARDS) (5), asthma (6), burns (1), bilateral knee and right ankle effusion (1), bilateral myositis (1), bronchiolitis (1), Burkett lymphoma (2), congestive cardiac failure (CCF) (11), cellulites (1), gastro-oesophageal reflux disorder (GORD) (17), hepatitis (2), HIV positive (31), Haemophagocytic lymphohistocytosis (HLH) (1), Hodgkin's lymphoma (1), hypothyroidism (1), haemoptysis (1), herpetic stomatitis (1), hypocalcemia (1),

hypokalemia (2), idiopathic thrombocytopenic purpura (ITP) (1), lower respiratory tract infection (LRTI) (23), myocardial infarction (MI) (1), myocarditis (1), meningitis (1), necrotic enterocolitis (2), neutropenic fever (NF) (8), otitis media (OM) (4), oral thrush (1), patent ductus arteriosis ligation (2), pneumocystic jiroveci pneumonia (PJP) (4), primary brain tumour (1), pneumonia (14), sickle cell anaemia (2), sepsis (23), seizures (6), septic shock (1), systemic fungal infection (1), tuberculosis (TB) (20), tetralogy of fallot (TOF) (1), thrombo-embolism (1), tinea capitis (1), upper respiratory tract infection (URTI) (6), urinary tract infection (UTI) (1),ventricular septal defect (VSD) (3), haematuria (1), and pulmonary artresia(1).

Table 1, following, depicts the age range of patients in the sample and shows occurrence of the corresponding conditions that were most prevalent (that is, four and more conditions).

Table 1: Age range of the patient(s) with the occurrence of the corresponding conditions

Condition	Age range (in months)	Occurrence of condition
Acute gastroenteritis (AGE)	0.5–120	19
Acute lymphoblastic leukemia (ALL)	5–60	13
Acute respiratory distress syndrome (ARDS)	2–116	5
Asthma	0.5–9	6
Congestive cardiac failure (CCF)	0.16–156	11
Eczema	1–131	10
Epilepsy	11–148	6
Failure to thrive (FTT)	0.6–143	34
Gastro-oesophageal reflux disorder (GORD)	2.3–156	17
HIV infection	0.5–176	31
Lower respiratory tract infection (LRTI)	0.5–163	23
Neutropenic fever (NF)	13–120	8
Otitis media (OM)	0.5–163	4
Pneumocystic jiroveci pneumonia (PJP)	0.5–23	4
Pneumonia	0.4–148	14
Sepsis	0.5–151	23
Seizures	0.5–60	6
Tuberculosis (TB)	0.5–176	20
Upper respiratory tract infection (URTI)	0.9–87	6
Total	—	**260**

Table 2, following, indicates the number of patients with the corresponding number of conditions, the total number of drugs prescribed, and the mean and median number of drugs prescribed per patient. As the number of conditions presented increased from one to three, the mean and median number of drugs increased. Similarly, the mean and median number of drugs prescribed for patients presenting with four to five conditions also increased correspondingly. One patient with six and another with seven conditions had a mean and median of 12 and 10 drugs prescribed, respectively.

Table 2: Total, mean, and median number of drugs prescribed for the 200 patients in the study sample

No. of conditions presented	No. of patients*	Total no. of drugs prescribed	Mean no. of drugs prescribed per patient	Median no. of drugs prescribed per patient
1	57	223	3.9	3
2	76	484	6.4	6
3	46	391	8.5	9
4	15	123	8.2	8
5	4	39	9.8	8.5
6	1	12	12	12
7	1	10	10	10
28	**200**	**1 282**	—	—

***These patients presented with a combination of various conditions, for example, one patient presented with seven conditions. Totals are presented in the final row.**

Table 3, following, indicates the number of scripts, as well as the numbers for minimum, maximum, and mean number of conditions presented**.** Prescriptions with five, six, and seven drugs prescribed had a maximum of four and a median of two conditions.

Prescriptions with the higher number of drugs prescribed, interestingly, had a lower maximum and a lower and /or same median number of conditions as prescriptions with lesser numbers of drugs prescribed; for example, prescriptions with 13 drugs prescribed had a maximum and median of three conditions and prescriptions with 16 drugs prescribed had a maximum of three and a median of two conditions.

Table 3: Number of conditions and scripts with corresponding number of drugs prescribed

No. of drugs prescribed	No. of scripts	Minimum no. of conditions	Maximum no. of conditions	Median no. of conditions
1	3	1	1	1
2	14	1	2	1
3	28	1	3	1
4	22	1	4	2
5	22	1	4	2
6	18	1	4	2
7	31	1	4	2
8	12	1	5	2
9	12	2	5	3
10	12	1	4	3
11	8	2	7	3
12	11	2	6	2
>12	7	7	11	—

4.1.3 Nutritional status

Out of the 200 patients studied, 122 (61.0%) had a normal body weight, 40 (20%) were severely underweight, 25 (12.5%) were moderately underweight, and 13 (6.5%) were overweight. Table 4, following, indicates the number of patients in the categories of nutritional status and age.

Table 4: Nutritional status for male and female patients in the various defined age categories

Nutritional Status Indicators	Gender	Age Category						Total	Percentage (%)
		*1.1	1.2	1.3	2	3	4		
Overweight (WAZ>+2.00)	M	1	1	0	1	1	0	13	6.5
	F	2	3	3	1	0	0		
Normal weight (-2.00<WAZ<+2.00)	M	5	16	6	9	15	5	122	61.0
	F	4	12	7	15	14	14		
Moderate underweight (-3.00<WAZ<-2.01)	M	1	4	4	0	1	4	25	12.5
	F	3	4	1	2	0	1		
Severe underweight (WAZ<-3)	M	1	12	3	3	3	0	40	20.0
	F	2	6	3	4	1	2		
Total		**19**	**58**	**27**	**35**	**35**	**26**	**200**	**100**

***1.1 = 0–30 days; 1.2 = 31 days–12 months; 1.3 = 13–24 months; 2 = 25–60 months; 3 = 61–120months; 4 = >120 months**

Table 5, below, shows the nutritional status for male and female patients per ward.

Table 5: Nutritional status for male and female patients in different locations (wards)

Nutritional Status Indicators	Gender	Location				Total	Percentage (%)
		PICU	G1	B1	B2		
Overweight (WAZ>+2.00)	M	1	1	0	2	13	6.5
	F	0	2	3	4		
Normal weight (-2.00<WAZ<+2.00)	M	8	10	25	13	122	61.0
	F	16	14	13	23		
Moderate underweight (-3.00<WAZ<-2.01)	M	2	2	5	5	25	12.5
	F	2	1	5	3		
Severe underweight (WAZ<-3)	M	2	0	12	8	40	20.0
	F	6	0	5	7		
Total	**—**	**37**	**30**	**68**	**65**	**200**	**100**
Percentage (%)	**—**	**18.5**	**15**	**34**	**32.5**	**100**	**—**

Table 6, following, shows the conditions, nutritional status, and treatment regimen for severely underweight patients.

Table 6: Conditions, nutritional status, and treatment regimen in severely underweight patients

Patient	Condition	*WAZ (z-score)	Name of drug
1	Chronic gastroenteritis (CGE) Pneumonia Down's syndrome	-3.06	Multivitamin Cholestyramine Gentamycin Amoxycillin Zinc Folic acid Formoterol
2	Septic shock Acute renal failure Microcytic anaemia HIV- infection Tuberculosis (TB)	-3.29	Folic acid Paracetamol Pyrazinamide Ethambutol Rifampicin + isoniazid Multivitamin Ampicillin Diazepam Clonidine Pyridoxine Cotrimoxazole Nystatin Acetazolamide Prednisone
3	Pneumonia Gastro oesophageal reflux disorder (GORD)	-3.04	Omeprazole Cotrimoxazole Vidaylin Vitamin D Prednisone Formoterol solution Normal saline
4	Pneumonia	-5.97	Zinc Folic acid Phenobarbitone
5	Gastro Oesophageal Reflux Disorder (GORD)	-7.76	Vidaylin Vitamin D Omeprazole
6	Necrotising enterocolitis Anaemia Hypoglycemia Hypokalemia Laparotomy	-5.4	Meropenem Fluconazole Nystatin Hydrocortisone Zidovudine Paracetamol

			Vancomycin Cimetidine
7	Lower respiratory tract infection (LRTI) Pneumonia Failure to thrive (FFT) Gastro oesophageal reflux disorder (GORD) Normocytic anaemia	-7.35	Ciprofloxacin Normal saline Paracetamol Omeprazole Folate Multivitamin Zinc Salbutamol Morphine
8	Pneumonia	-16.58	Paracetamol Multivitamin Diazepam Piptazobactam Amikacin
9	Hypothyroidism Pneumonia	-6.62	Prednisone Ferrous Gluconate Multivitamin Co-trimoxazole Eltroxin Duocal Azithromycin Folate
10	Acute gastro enteritis (AGE) Hepatotoxicity HIV- infection	-3.16	Abacavir Lopenavir+Ritonavir Lamivudine Ritonavir Rifampicin & Isoniazid Ofloxacin Co-trimoxazole Omeprazole Multivitamin Zinc Hydrocortisone Ethambutol Paracetamol Tilidine hydrochloride
11	Tuberculosis (TB)	-4.48	Paracetamol Acetazolamide Multivitamin Zinc Rifampicin+Isoniazid Pyrazinamide Ethionamide

			Prednisone Phosphate Furosemide
12	Failure to thrive (FFT) Chronic Lung Disease (CLD) Haemolytic anaemia	-13.69	Sorbitol Multivitamin Omeprazole Folic acid Zinc Paracetamol Ferrous gluconate
13	Pneumocystis jerovici pneumonia (PJP)	-5.99	18% sodium chloride Co-trimoxazole Phosphate
14	Gastro Oesophageal Reflux Disorder (GORD) Congestive Cardiac Failure (CCF)	-5.53	Spironolactone Furosemide Vidaylin Vitamin D Nevirapine Omeprazole Co-trimoxazole
15	HIV- infection Microcytic anaemia Pancreatitis Pyelonephritis	-4.27	Tilidine HCL Cimetidine Paracetamol Cefotaxime
16	HIV- infection Eczema	-5	Multivitamin Folic acid Zinc Vitamin D Clotrimazole Aqueous Cream Lopenavir+Ritonavir Lamivudine Abacavir Co-trimoxazole Emulsifying ointment
17	Gastro Oesophageal Reflux Disorder (GORD) Dystonia Failure to thrive (FFT)	-12.79	Multivitamin Paracetamol Zinc
18	Tuberculosis (TB) Fever	-5.84	Paracetamol Multivitamin Rifampicin+Isoniazid Pyrazinamide Ethionamide Zinc

			Prednisone Hyoscine-N-Butylbromide Folic acid
19	Seizures Tuberculosis (TB)	-3.26	Rifampacin + Isoniazid Sodium Valproate Hydrocortisone Pyrazinamide Ethionamide Prednisone Paracetamol
20	HIV- infection Lower respiratory tract infection (LRTI)	-3.1	Multivitamin Zinc Folic acid Lamivudine Abacavir Lopenavir+Ritonavir Nystatin Omeprazole Cefuroxime
21	Necrosis	-4.896	Meropenem Zidovudine Nystatin Fluconazole
22	Cerebral palsy (CP) Lower respiratory tract infection (LRTI)	-4.09	Penicillin G Gentamycin Zidovudine Nystatin Paracetamol Multivitamin
23	Tuberculosis (TB) Fever Failure to thrive (FFT)	-3.23	Prednisone Rifampicin+Isoniazid Pyrizanimide Ethionamide Multivitamin Zinc Acetazolamide Furosemide Paracetamol Folic acid Sodium chloride
24	Tuberculosis (TB) Sepsis	-5.13	Pyrazinamide Rifampicin+Isoniazid Ethambutol Zinc Cefuroxime

			Clonidine
25	Herpetic Stomatitis Asthma	-5.18	Allopurinol Cotrimoxazole Prednisone Sodium chloride Paracetamol Atrovent:berotec:saline Ceftriaxone Acyclovir
26	Primary brain tumour Coartation of aorta	-3.69	Rifampicin + isoniazid Pyrazinamide Ethionamide Prednisone Paracetamol Zinc Acyclovir
27	Acute gastro enteritis (AGE)	-3.87	Zinc Multivitamin Potassium Chloride Cholestyramine Gentamycin Ampicillin
28	Congestive Cardiac Failure (CCF) Failure to thrive (FFT)	-3.85	Multivitamin Folic acid Spironolactone Sodium chloride Fluorometholone
29	Lower respiratory tract infection (LRTI)	-4.1	Amoxycillin Propranolol
30	Upper respiratory tract infection (URTI) Failure to thrive (FFT)	-3.38	Multivitamin Zinc Amoxycillin Amoxicyllin+clavulinic acid
31	Upper respiratory tract infection (URTI) Eye infection	-4.01	Oxymetazoline Zinc Multivitamin Folic acid Fluorometholone
32	Pneumocystis jerovici pneumonia (PJP)	-3.72	Cotrimoxazole
33	Failure to thrive (FFT)	-5.1	Multivitamin vitamin D Folic acid
34	Otitis media (OM)	-3.1	Paracetamol Cefuroxime

35	HIV- infection	-3.01	Lamivudine Stavudine Efavirenz Cotrimoxazole Multivitamin
36	Pneumocystis jerovici pneumonia (PJP) Lower respiratory tract infection (LRTI)	-6.57	Heparin(low molecular weight) Prednisone Cotrimoxazole Paracetamol
37	Failure to thrive (FFT)	-3.49	vitamin D Folic acid
38	Oral candiadiasis Fever	-4.93	Paracetamol Nystatin Fluconazole
39	Failure to thrive (FFT)	-7.11	Vidaylin Caffeine citrate Ferrous lactate Folic acid
40	Hypertension Staphyllococci skin infection	-5.11	Multivitamin Zinc Amlodipine Flucloxacillin Clonidine

***WAZ = weight-for-age z-score (nutritional status indicator)**

As mentioned earlier, WHO (de Onis et al., 2012) defines a WAZ score greater than -3 as indicating a severe underweight for age. A total of 40 patients (20% of the study population) were severely underweight, as indicated by the weight-for-age (WAZ) z-score in the Table 6 above. Z-cores allows clinical tracking of patients whose anthropometric classification lies beyond the measurable limits of the percentile range, as happens in the case of severely undernourished children (de Onis et.al, 2011).

4.2. Prescribing patterns

4.2.1 Prescriber category

From a sample of 200 prescriptions, 24 prescriptions were written by an intern, 47 prescriptions by a senior health officer (SHO), 109 prescriptions by a registrar, and 20 by a consultant. For the number of drug items prescribed by the respective prescriber, see Table 7, which indicates the level of experience of doctor and the corresponding number of drug items prescribed.

Table 7: Number of drug items prescribed per prescriber category

Level of experience of prescriber	No. of drug items prescribed
Intern	114
SHO	291
Registrar	753
Consultant	124
Total	**1 282**

4.2.2 Drug distribution

A total of 1 282 drug items were prescribed collectively by all the prescribers in the sample. Table 8indicates the number of prescription charts (middle row) with the corresponding number of drug items prescribed (top row).

Table 8: Number of prescription charts classified according to the number of drugs prescribed per prescription chart

No. of drugs prescribed (A)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Prescription charts (B)	3	14	28	22	22	18	31	12	12	12	8	11	2	3	0	2
Total no. of drugs (A) x (B)	3	28	84	88	110	108	217	96	108	120	88	132	26	42	0	32

Total (B) = 200; Total [(A) × (B)] = 1 282

4.2.3 Ward distribution

The total and mean numbers of drugs prescribed per location (ward) and the corresponding number of patients treated in the respective ward is illustrated in Table 9.

In the sample, 30 of the 200 (15%) patients had 156 (12%) of the total number (1 282) of drugs prescribed in G1. In PICU, 37 patients (18.5%) had 272 (21.7%) of the total number of drugs prescribed. In the two medical wards, namely, B1, 68 patients (34 %) had 470 (36.7%) drugs prescribed, while in B2, 65 patients (32.5%) had 384 (30%) drugs prescribed.

Table 9: Distribution of drug items as per number of patients in the four different wards

Ward	No. of patients	No. of drugs prescribed	Mean no. of drugs prescribed
PICU	37	272	7.35
G1	30	156	5.20
B1	68	470	6.93
B2	65	384	5.89
Total	**200**	**1 282**	**6.34**

Table 10, below, shows the distribution of drug items prescribed by the various prescribers, with each shown as a category of prescriber.

Table 10: Distribution of drug items prescribed per location as per prescriber category

Level of experience of doctor	No. of drug items prescribed	PICU	G1	B1	B2
Intern	114	0	0	57	57
SHO	291	8	0	147	136
Registrar	753	215	109	254	175
Consultant	124	49	47	12	16
Total	**1 282**	**272**	**156**	**470**	**384**

Among the prescribers, the registrars were responsible for prescribing the most number of drug items in all four wards, as reflected in Table 7 above. Interns did not take responsibility for prescribing in the two specialty wards, namely, PICU and G1, as no interns are assigned to these wards at the RCWMCH. SHO's took responsibility for prescribing in PICU but not in ward G1.

4.2.4 Distribution of drug items: Week day versus weekend

The study compared distribution of drugs in terms of week day versus weekend and genral medical versus specialty wards. Table 11 below shows the result of this comparison.

Table 11: Comparison of drug distribution: Week versus weekend in general medical wards versus specialty wards

Location	Week		Weekend		Total
	No.	%	No.	%	
Speciality wards (PICU and G1)	355	35	70	27	425
General medical wards (B1 and B2)	662	65	190	73	852
Total	**1 017**	**100**	**260**	**100**	**1 277***
Percentage (%)	**80**		**20**		**100**

***Five prescription items did not have a physical date for the starting date of prescribed item, thus no date/day for the item in question was allocated; hence a sample size of 1 277 drug items (and not 1 282) for week versus weekend comparison with regards to drug distribution.**

4.2.5 Distribution of drug items according to age of patient

Table 12, below, reflects the number of patients in the respective wards and the total and mean numbers of drugs prescribed according to patient age. Approximately 25% of the total number of drugs was prescribed for the 0–30 days age group, and approximately 10% of the total number of drugs prescribed for the older children, that is, children aged 10 months and over. The 13–24 months, 25–60 months, and 61–120 month categories showed a similar

pattern with regard to drug distribution, that is, 16%, 17.5%, and approximately 19%, respectively, of all drugs prescribed.

Table 12: Distribution of drug items according to patient age

Age of patient*	Total no. of patients	No. of drugs prescribed		No. of patients in ward			
		Total	Mean	PICU	G1	B1	B2
1.1	44	317	7.20	8	1	15	20
1.2	30	164	5.47	6	1	15	8
1.3	27	210	7.78	7	1	10	9
2	37	225	6.08	4	7	9	17
3	37	243	6.57	5	13	10	9
4	25	123	4.92	7	7	9	2
—	**200**	**1 282**	**6.3**	**37**	**30**	**68**	**65**

***1.1 = 0–30 days; 1.2 = 31 days–12 months; 1.3 = 13–24 months; 2 = 25–60 months; 3 = 6–120 months; 4 = >120 months**

Table 13, following, shows the distribution of drug items prescribed according to formulation.

Table 13: Distribution of drug items according to formulation

Formulation	Drug items prescribed	
	No.	%
Intravenous	151	11.77
Intramuscular	4	0.31
Oral	991	77.30
Suppository	0	0
Inhalation	21	1.63
Topical	64	4.99
Other	51	4.00
Total	**1 282**	**100**

Table 14, shows the distribution of drugs prescribed according to the class of drugs.

Table 14: Distribution of drug items according to class of drugs

Class of drug	Drug items prescribed	
	No.	%
Antibiotics	256	20.00
Antifungals	56	4.37
Antivirals	121	9.43
Other	438	34.16
Nervous system	155	12.09
Cardiovascular	78	6.08
Hormonal	60	4.68
Gastrointestinal	44	3.43
Respiratory system	35	2.73
Oncology	19	1.48
Musculo-skeletal	14	1.09
Blood system	6	0.47
Total	**1 282**	**100**

4.3 Prescribing errors

4.3.1 Frequency and type of errors

The total number of drugs prescribed for the 200 prescriptions reviewed equalled 1 282. Incomplete information was the most common type of error found (65.6%), followed by the wrong drug name, and use of abbreviations in place of generic names. Under other type of prescribing errors, errors such as inappropriate drug and unauthorised prescriber recurred. All other errors occurred at a frequency of less than 5%. Prescribed information (that is, drug name, strength, dose, route, frequency, formulation, and period), including the prescribers name and signature not easy to read on the prescriptions reviewed were problematic in terms of legibility, with the prescription(s) for the drug item(s) thus regarded as a prescribing error. A prescription in which instructions were not clearly stated, that is, in terms of strength, dose, route, frequency, formulation, and period was regarded as a clarity type of prescription error. An example of this is paracetamol having been prescribed as both per oral (po) and per rectum (pr) in the section for route of administration, indicated on that particular prescription as “po/pr”. In the case of a patient with a documented allergy for a drug item being inadvertently prescribed that drug, this was regarded as constituting a prescribing error.

Table 15, following, shows the frequency of prescribing errors found in the sample studied. The type of error identified and its frequency is provided. Incomplete information was observed as the most frequent type of error in most cases, followed by wrong name and use of abbreviations instead of generic name of drug. Allergy and contra-indication to a medicine were the least occurring type of error, as observed in this study. Prescribing errors involving the dose(s), including both high and low doses, occurred infrequently and prescribing errors with regards to the route of administration, frequency and the unit of strength of the medicine, occurred less frequently

Table 15: Frequency of prescribing errors

Type of error	Frequency of error per drug item		95% CI
	No. of errors	N (%)	
Incomplete information	841	65.6	62.9–68.2
Wrong name*	216	16.8	14.8–19.0
Abbreviations	146	11.3	9.7–13.2
Legibility*	57	4.4	3.4–5.7
Clarity*	42	3.3	2.4–4.4
Alteration*	32	2.5	1.7–3.5
High dose	16	1.2	0.7–2.0
Low dose	15	1.1	0.6–1.9
Other*	10	0.8	0.4–1.4
Wrong route	8	0.6	0.3–1.2
Duplication	5	0.4	0.2–1.1
Wrong frequency	6	0.5	0.2–1.0
Wrong unit	4	0.3	0.1–0.8
Allergy*	3	0.2	0.0–0.7
Contra-indication	1	0.1	0.0–0.4
Total	**1 402**	**109**	—

***Refer to Chapter 3 on Materials and Methods of this thesis for definitions of these terms.**

Any drug item can have one or more prescribing errors and the same pertained to those reviewed in this study. The total number of prescribing errors in the entire sample was 1 402. The overall error rate for prescribing errors was 1.09 (that is, the overall error rate = 1.09, thus the frequency is 109% in Table 15 above). This is illustrated by the formula Y = X/N, where Y is the overall prescribing error rate, X the total number of prescribing errors (1 402), and N the total number of prescribed drug items (1 282).

4.3.2. Error frequency: Different classes of drugs

Table 16, following, shows the frequency of prescription errors for drug items prescribed by different classes of drugs.

Table 16: Error frequency for prescribed drug items by different classes of drugs

Class of drug	Total no.s of prescribed drug items	No. of drug items with one or more prescribing error	% Any error 95 CI
Antibiotics	256	192	75.0 (69.3–80.2)
Antifungals	56	40	71.4 (57.8–82.7)
Antivirals	121	82	67.8 (58.7–76.0)
Other (vitamins and minerals)	438	305	69.6 (65.0–73.9)
Nervous System	155	118	76.1 (68.6–82.6)
Cardiovascular	78	61	78.2 (67.4–86.8)
Hormonal	60	46	76.7 (64.0–86.6)
Gastro-intestinal (GI)	44	38	86.4 (72.6–94.8)
Respiratory system	35	21	60.0 (42.1–76.1)
Oncology	19	11	57.9 (33.5–79.7)
Musculo-skeletal	14	11	78.6 (49.2–95.3)
Blood system	6	4	66.7 (22.3–97.7)
Total	**1 282**	**929**	**—**

There were 929 drug items with any type of error. The number of drug items without any type of prescribing errors was 353.This equates to 72.5% of all prescribed drugs with at least one prescribing error.

Antibiotics were prescribed for conditions such as pneumonia, urinary tract infections (UTI), meningitis, sepsis, TB, and HIV-related conditions. Antifungals were prescribed mostly for HIV-related conditions such as severe thrush. Antivirals were commonly prescribed for CMV infections or herpes. Vitamins and minerals were prescribed as part of the WHO's 10 steps for treating malnutrition (WHO, 1999). The routine prescription of zinc for diarrhoea and pneumonia is well known. Analgesics, sedatives, and anti-epileptics were prescribed for their relevant conditions (that is, fever, epilepsy, pain, anxiety, and post-operative treatment, respectively). Children with heart disease, congenital or acquired, were treated with anti-failure medication as needed. Prednisone is often prescribed for its anti-inflammatory properties, for example, in asthma, TB, and meningitis. Proton pump inhibitors, for example,

omeprazole and cimetidine were commonly prescribed in patients with suspected or proven gastro-oesophageal reflux disorder (GORD). Nebulising agents like atrovent, salbutamol, and hypertonic saline were prescribed for asthma and bronchiolitis. Oncology drugs were mostly prescribed by haem-oncologists. Musculo-skeletal agents like ibuprofen and aspirin were prescribed for pain and inflammation. Blood system medication was mostly prescribed to known haemophiliacs and oncology patients.

4.3.3. Error frequency: Location/ward

Table 17, below, shows the frequency for prescription errors by location or ward, with numbers for drug items prescribed and drug items with one or more prescribing errors recorded.

Table 17: Error frequency for prescribed drug items by location/ward

Location/ward	Total no. of prescribed drug items	No. of drug items with one or more prescribing errors	% Any error 95 CI
PICU: specialty ward	272	209	76.8 (72.2–82.5)
G1: Oncology ward	156	140	89.7 (83.2–93.6)
B1: Medical ward	470	342	72.7 (68.3–76.6)
B2: Medical ward	384	238	61.9 (56.8–66.7)
Total	**1 282**	**929**	**—**

G1 (the oncology ward) had a higher percentage of drugs with prescribing errors, compared to the other wards. There were significantly fewer drug items with prescribing errors in B2, the medical ward, compared to the other wards.

4.3.4 Error frequency by prescriber category

Consultants had significantly more prescribing errors than all the other prescribers. Senior doctors (registrars and consultants) committed significantly more prescribing errors than did junior doctors (interns and SHO's), that is, 78.3% of all drug items prescribed by senior doctors had at least one error versus 59.8% by junior doctors, hence the risk ratio of 1.3 (95% confidence interval: 1.2-1.4), $p<0.0001$. Table 18, below, shows the error frequency for prescribed drug items by level of experience of prescribing doctor.

Table 18: Error frequency for prescribed drug items by level of experience of doctor

Qualification of prescribers	Total no. of prescribed drug items	No. of drug items with one or more prescribing error	% Any error 95% CI
Intern	114	58	50.9 (41.3–60.4)
SHO	291	184	63.2 (57.4–68.8)
Registrar	753	579	76.9 (73.7–79.9)
Consultant	124	108	87.1 (79.9–92.4)
Total	**1 282**	**929**	—

4.3.5 Error frequency: Weekday versus weekend

No significant difference for occurrence of prescribing errors was found for weekday and weekend. A missing date was classified as missing information (that is, for prescriptions with no starting date indicated for a newly generated prescription) and observed as a type of prescribing error. Table 19, below, shows the error frequency for prescribed drugs in terms of weekday versus weekend.

Table 19: Error frequency for prescribed drug items: Weekday versus weekend

Day of prescription	Total no. of prescribed drug items	No. of drug items with one or more prescribing error	% Any error 95 CI
Weekday	1 017	752	73.9 (71.1–76.7)
Weekend	260	172	66.1 (60.0–71.9)
No day recorded (no physical starting date written in by prescriber, i.e., missing information, a type of prescribing error)	5	5	100
Total	**1 282**	**929**	**—**

4.3.6 Error frequency: Age of patient

The study looked at frequency of prescribing errors in terms of patient age. Table 20, following, shows this in terms of child patient age ranging from 0–30 days up to 61–120 months as well as the figures for drug items prescribed and prescribing error.

Table 20: Error frequency for prescribed drug items by age of patient

Age of patient	Total no. of prescribed drug items	No. of drug items with one or more prescribing error	% Any error
0–30 days (neonates)	317	212	66.9
31 days–12 months (infants)	164	155	94.5
13–24 months (toddlers)	210	153	72.9
25–60 months (young children)	225	125	55.6
61–120 months	243	141	58.0
>120 months	123	143	—
Total	**1 282**	**929**	**—**

The percentage of prescribing errors was highest in the infant group (94.5%), even though only 12.8% drug items were prescribed in this age group, in comparison to the 24.7% drug items prescribed for neonates. The percentage of prescribing errors observed for neonates was 66.9%

4.3.7 Error frequency: Formulation type

The confidence interval for percentage of errors for oral and intravenous formulation was narrow, in comparison to the confidence interval for percentage of errors for intra-muscular, inhalation, topical, and other formulations. A low number of drug items were prescribed in the intra-muscular, inhalation, topical, and other formulation group, compared to oral and the intravenous formulations group. Table 21, following, shows the error frequency for prescribed drug items by formulation, as found in the study.

Table 21: Error frequency for prescribed drug items by formulation

Formulation	Total no. of prescribed drug items	No. of drug items with one or more prescribing error	% Any error 95 CI
IV	151	127	84.1 (77.3–89.5)
IM	4	0	0 (0–60.2)
Oral	991	717	72.4 (69.5–75.1)
Inhalation	21	13	61.9 (38.4–81.9)
Topical	64	41	64.0 (51.1–75.7)
Other	51	31	60.8 (46.1–74.2)
Total	**1 282**	**929**	—

4.3.8 Error frequency: Range of drug items prescribed per prescription chart

No significant difference was found with regards to the range(s) of drug items per prescription chart. Table 22 shows the result for the search for error frequency for ranges of prescribed drugs per prescription.

Table 22: Error frequency for range(s) of prescribed drug items per prescription

No. of drug items	Total no. of prescription charts	No. of charts with one or more prescribing error	% Any error 95 CI
1 to 4	67	43	64.2 (51.5–75.5)
5 to 10	107	78	72.9 (63.4–81.0)
>10	26	19	73.0 (52.2–88.4)
Total	**200**	**140**	—

4.4. Potential drug-drug interactions

As discussed earlier in chapters one and two of this thesis, drug-drug interaction (DDIs) are a concern as regards prescribing errors, especially for child patients, due to the latter's undeveloped or immature organ systems which places them at greater risk for DDI errors where prescribing is concerned. In this study, the potential for pharmacodynamic drug-drug interactions (DDIs) were regarded as more likely to occur than pharmacokinetic drug-drug interactions (DDIs). Table 23 shows the overall potential for pharmacodynamic drug interactions (DDIs).

Table 23: Potential pharmacodynamic drug-drug interactions

Interaction type	N (%)	95% CI
Pharmacodynamic	20 (1.6)	2.4
(see list below)	—	—

Table 24, following, describes the potential pharmacodynamic drug-drug interactions (DDIs) not necessarily recorded by the prescriber, but present. The combination drugs are separated as A and B categories in the table. The potential adverse reaction or event was listed in a separate column, with the studies that provided the information for the possible adverse effects also tabled.

Table 24: Description of potential pharmacodynamic drug-drug interactions (DDIs) (as indicated in Table 23 but not necessarily recorded by the prescriber, however, potentially present)

Drug A	Drug B	Potential adverse event	Reference(s)
Chloroquine	Co-trimoxazole	Increased risk of potentially fatal skin reactions	Uneke and Ogbonna, 2009
Furosemide	Captopril	Additive hypotensive effect	Kopecky, Thomas and McAfee, 1987
Ethionamide	Isoniazid	Additive neurological effect	Schaaf et al., 2009
Acetazolamide (used for raised intracranial pressure and metabolic alkylosis)	Furosemide	Diuretic effect augmented	Libenson et.al., 1999
Acetazolamide	Prednisone	Development of hypokalemia	Widmer et al., 1995
Furosemide	Prednisone	Development of hypokalemia	Widmer et al., 1995
Diazepam	Phenobarbitone	Additive CNS depressant effect	Brockmeyer et al., 1985
Diazepam	Sodium Valproate	Additive CNS depressant effect	Dhillon and Richens, 1982
Clonidine (used as part of sedation protocol)	Diazepam	Increased hypotensive effect	BNF, 2011
Clonidine	Furosemide	Increased hypotensive effect	Williams et al., 2004
Amikacin	Furosemide	Increased risk of ototoxicity	Smith and Lietman, 1983
Aspirin	Warfarin	Increased risk of bleeding	*Medical Research Council's General Practice Research Framework*, 1998
Aspirin	Enoxaparin	Increased risk of bleeding	Kavanagh et al., 2004
Furosemide	Digoxin	Increased cardiac toxicity risk	Tsutsumi et al., 1979
Spironolactone	Potassium chloride	Increased risk of hyperkalemia	Greenblatt and Koch-Weser, 1973
Furosemide	Ibuprofen	Increased risk of nephrotoxicity	Huerta et al., 2005
Ibuprofen	Spironolactone	Increased risk of hyperkalemia	Hunt et al., 2009
Captopril	Spironolactone	Increased risk of hyperkalemia	Berry et al., 2001
Gentamycin	Benzyl penicillin	Gentamycin inactivated by Benzyl penicillin	SAMF, 2012

[*]**BNF = British National Formulary**
[**]**SAMF = South African Medicines Formulary**

Table 25, below, shows the potential pharmacokinetic (PK) drug-drug interactions (DDIs) of the sample studied.

Table 25: Potential pharmacokinetic (PK) drug-drug interactions (DDIs)

Pharmacokinetic drug interactions	Frequency of PK interactions		95% CI
	No. of PK DDI's	%	
Increase in distribution	15	1.2	0.6–1.9
Decrease in distribution	14	1.1	0.6–1.8
Decrease in metabolism	8	0.6	0.27–1.2
Decrease in absorption	7	0.6	0.2–1.1
Increase in metabolism	3	0.2	0.05–0.68
Increase in excretion	1	0.1	0.02–0.4
Decrease in excretion	1	0.1	0.02–0.4
Increase in absorption	0	0.0	0.0–0.0

Table 26, below, shows the potential PK drug-drug interactions (DDIs), not necessarily recorded by prescribers in the study but potentially present.

Table 26: Description of potential PK drug interactions (DDIs) (as indicated in Table 25 but not necessarily recorded by prescriber, however, potentially present)

Drug A	Drug B	Potential pharmacokinetic interaction	Reference(s)
Omeprazole	Warfarin	Elimination of warfarin prolonged by omeprazole, i.e., decrease in excretion of warfarin	Garcia et al., 1994
Prednisone	Isoniazid	Prednisone reduces plasma concentration of Isoniazid, i.e., decrease in drug distribution	Sarma et al., 1980
Rifampicin	Prednisone	Rifampicin accelerates metabolism of prednisone	Buffington et al., 1976
Sodium Valproate	Phenobarbitone	Valproate increases plasma concentration of phenobarbitone, i.e., increase in drug distribution	Hurst et al., 1997; Bernus et al., 1994
Phenobarbitone	Sodium Valproate	Phenobarbitone reduces plasma concentration of phenobarbitone, i.e., decrease in drug distribution	Hurst et al., 1997; Bernus et al.,

			1994
Ritonavir	Prednisone	Ritonavir increases plasma concentration of Prednisone, i.e., increase in drug distribution	Busse et al., 2008
Prednisone	Lopinavir/Ritonavir (Kaletra)	Prednisone reduces Kaletra levels, i.e., decrease in drug distribution	Busse et al., 2008
Lamivudine	Trimethoprim	Plasma concentration of Lamivudine increased by Trimethoprim, i.e., increase in drug distribution	Sabo etal., 2000
Isoniazid	Paracetamol	Isoniazid inhibits metabolism of paracetamol	Chien et al., 1997
Prednisone	Isoniazid	Prednisone reduces plasma concentration of Isoniazid, i.e., decrease in drug distribution	Sarma et al., 1980
Isoniazid	Prednisone	Isoniazid metabolism increased by Prednisone	Sarma et al., 1980
Co-trimoxazole	Rifampicin	Plasma levels of Co-trimoxazole reduced by Rifampicin, i.e., decrease in drug distribution	Ribera et al., 2001; Bhatia et al., 1991
Omeprazole	Diazepam	Omeprazole inhibits the metabolism of diazepam	Zomorodi& Houston, 1996
Phenobarbitone	Clonazepam	Phenobarbitone induces metabolism of clonazepam	Khoo et al., 1980
Zinc	Ciprofloxacin	Zinc reduces absorption of Ciprofloxacin	Polk, 1989
Sodium Valproate	Phenobarbitone	Valproate increases plasma concentration of phenobarbitone, i.e., increase in drug distribution	Hurst et al., 1997; Bernus et al., 1994
Phenobarbitone	Sodium Valproate	Phenobarbitone reduces plasma concentration of sodium valproate, i.e., decrease in drug distribution	Hurst et al., 1997; Bernus et al., 1994
Phenobarbitone	Neviripine NVP	Phenobarbitone may decrease NVP levels, i.e., decrease in drug distribution	L'homme et al., 2006
Co-trimoxazole	Phenobarbitone	Cotrimoxazole may inhibit Phenobarbitone metabolism	SAMF, 2012
Rifampicin	Co-trimoxazole	Rifampicin induces metabolism of Co-trimoxazole	Ribera et al., 2001; Bhatia et al., 1991
Trimethoprim (TMP) (as co-trimoxazole)	Lamivudine (3TC)	TMP inhibits metabolism of 3TC	Sabo et al., 2000
Cimetidine	Diazepam	Cimetidine inhibits metabolism of diazepam	Lockniskar et al., 1986; Klotz &Reimann, 1981

Ferrous Gluconate	Thyroxine	Absorption of thyroxine reduced by oral iron (ferrousgluconate)	Campbell et al., 1992
Zinc	Ciprofloxacin	Zinc reduces absorption of ciprofloxacin	Polk et al., 1989
Morphine	Ciprofloxacin	Morphine induces metabolism of Ciprofloxacin	Morran et al., 1989
Cimetidine	Carbamazepine	Cimetidine decreases metabolism of Carbamezepine	MacPhee et al., 1984
Folate	Phenobarbitone (PB)	Folate induces metabolism of phenobarbitone, plasma concentration of PB reduced	BNF, 2011
Fluconazole	Ritonavir	Fluconazole inhibits metabolism of Ritonavir	Peytavin et al., 2003
Trimethoprim (TMP) (as co-trimoxazole)	Lamivudine (3TC)	TMP increases plasma concentration of 3 TC, i.e., increase in drug distribution	Sabo et al., 2000
Abacavir (ABC)	Lamivudine (3TC)	ABC decreases absorption of 3TC	Wang et al., 1999
Fluconazole	Zidovudine (AZT)	Fluconazole increases plasma concentration of AZT. Increase in drug distribution	Sahai et al., 1994
Sprironolactone	Digoxin	Spironolactone inhibits metabolism of digoxin	Steimer, Muller &Eber, 2002
Calcium compounds	Zinc sulphate	Absorption of Zinc sulphate reduced by Calcium compounds	Argiratos et al., 1994
Phenobarbitone	Neviripine NVP	Phenobarbitone decreases NVP levels, i.e., decrease in drug distribution	L'homme et al., 2006
Phenobarbitone	Sodium Valproate	Phenobarbitone reduces plasma concentration of sodium valproate, i.e., decrease in drug distribution	Hurst et al., 1997; Bernus et al., 1994
Sodium Valproate	Phenobarbitone	Valproate increases plasma concentration of phenobarbitone, i.e., increase in drug distribution.	Hurst et al., 1997; Bernus et al., 1994
Co-trimoxazole	Rifampicin	Plasma levels of Co-trimoxazole reduced by Rifampicin, i.e., decrease in drug distribution	Ribera et al., 2001; Bhatia et al., 1991
Prednisone	Isoniazid	Prednisone reduces plasma concentration of Isoniazid, i.e., decrease in drug distribution	Sarma et al., 1980
Lamivudine	Trimethoprim (as Co-trimoxazole)	Plasma concentration of Lamivudine increased by Trimethoprim, i.e., increase in drug distribution	Sabo et al., 2000
Sodium Valproate	Phenobarbitone	Valproate increases plasma concentration of phenobarbitone, i.e., increase in drug distribution.	Hurst et al., 1997; Bernus et al., 1994
Co-trimoxazole	Rifampicin	Plasma levels of Co-trimoxazole reduced by	Ribera et al.,

		Rifampicin, i.e., decrease in drug distribution	2001; Bhatia et al., 1991
Prednisone	Isoniazid	Prednisone reduces plasma concentration of Isoniazid, i.e., decrease in drug distribution	Sarma et al., 1980
Sodium Valproate	Phenobarbitone	Valproate increases plasma concentration of phenobarbitone, i.e., increase in drug distribution	Hurst et al., 1997; Bernus et al., 1994
Lamivudine	Trimethoprim (as Co-trimoxazole)	Plasma concentration of Lamivudine increased by Trimethoprim, i.e., increase in drug distribution	Sabo et al., 2000
Trimethoprim (TMP) (as co-trimoxazole)	Lamivudine (3TC)	TMP increases plasma concentration of 3 TC, i.e., increase in drug distribution	Sabo et al., 2000
Ritonavir	Prednisone	Ritonavir increases plasma concentration of Prednisone, i.e., increase in drug distribution	Busse et al., 2008
Sodium Valproate	Phenobarbitone	Valproate increases plasma concentration of phenobarbitone, i.e., increase in drug distribution	Hurst et al., 1997; Bernus et al., 1994
Ritonavir	Prednisone	Ritonavir increases plasma concentration of Prednisone	Busse et al., 2008
Ritonavir	Prednisone	Ritonavir increases plasma concentration of Prednisone, i.e., increase in drug distribution	Busse et al., 2008

***SAMF = South African Medicines Formulary**
****BNF = British National Formulary**

4.5 Drug-disease interactions

Potential drug-disease interactions (DDiS) were potentially present in the study sample, but not necessarily recorded by the prescriber. Table 27, following, shows potential DDiS.

Table 27: Potential drug-disease interactions (new terminology, to be added)(DDiS)

Drug-induced diseases (DDiS)	No.	(%)	95%CI
Hepatotoxicity	16	1.3	0.7–2.0
Nephrotoxicity	9	0.7	0.3–1.3
Other	7	0.6	0.22–1.12
Blood disorders	4	0.3	0.09–0.80
Change in glucose levels	2	0.2	0.02–0.60
Ototoxicity	1	0.1	0.02–0.43

Table 28, below, provides a description of potential DDiS tabulated earlier.

Table 28: Description of the potential DDiS as indicated in Table 27

Drug	Disease	Potential DdiS	Reference(s)
Aspirin	Sepsis*	Symptoms of infection (sepsis) may be masked by aspirin	Habib et al., 2013; Amann&Peskar, 2002
Isoniazid	Drug-induced hepatitis (causative agent = Azathioprine)	potential exacerbation of hepatotoxicity, patient already has high liver enzymes and drug-induced hepatitis	Possuelo et al., 2008
Paracetamol	Drug-induced hepatitis (causative agent = Azathioprine)	potential exacerbation of hepatotoxicity, patient already has high liver enzymes and drug-induced hepatitis	Rivera-Penera et al., 1997
Chloroquine	Drug-induced hepatitis (causative agent = Azathioprine)	potential exacerbation of hepatotoxicity, patient already has high liver enzymes and drug-induced hepatitis	Mottaghi&Karimzade, 2005
Chloroquine	Systemic Lupus Erythromatosus (SLE)	Increased risk of blood disorders, patient has SLE	Ruiz-Irastorza et al., 2010
Cotrimoxazole	HaemophagocyticLymphohistiocytosis (HLH) and Hepatic Impairment (HI)	Cotrimoxazole increases induction of liver enzymes and to be used cautiously in serious haematological disorders	Ransohoff and Jacobs , 1981; Abi Mansur et al., 1981; Yao et al., 1997; Altraif et al., 1994
Clonazepam	Hepatic Encaphalopathy (HE)	Clonazepam is contraindicated in HE	Mullen et al., 1996
Phenobarbitone	Hepatic Encaphalopathy (HE)	Phenobarbitone is contraindicated in HE	Aiges et al., 1980
Co-trimoxazole	Haematological Disorder (HD) (anaemia)	Cotrimoxazole to be used cautiously in anaemia patient	Yao et al., 1997
Co-trimoxazole	Hepatic Impairment (HI) (increase in liver enzymes)	Cotrimoxazole to be used cautiously in patient with HI	Ransohoff&Jacobs, 1981; Abi Mansur et al., 1981; Yao et al., 1997; Altraif et al., 1994
Phenobarbitone	Hepatic Impairment (HI)	Phenobarbitone use is contraindicated in patient with HI	Aiges et al., 1980
Dexamethasone	Chronic Gastro-enterirtis* (CGE)	Exacerbation of gastro-intestinal tract (g.i.t) symptoms (diarrhoea)	SAMF, 2012
Cotrimoxazole	Chronic Gastro-enterirtis*(CGE)	Exacerbation of g.i.t	Sheikh et al., 2009

		symptoms (diarrhoea)	
Ethambutol	Acute renal failure (ARF)	Ethambutol to be used cautiously in patients with ARF	Garcia-Martin et al., 1996
Pyrazinamide	Acute renal failure (ARF)	Pyrazinamide to be used cautiously in patients with ARF	Sanwikarja et al., 1999
Acetazolamide	Acute renal failure (ARF)	Acetazolamide is contra-indicated in renal impairment	Higgenbottom, Ogg& Saxton, 1978
Diazepam	Acute renal failure (ARF)	Diazepam is cautioned in renal impairment	SAMF, 2012
Co-trimoxazole	Acute renal failure (ARF)	Co-trimoxazole is contra-indicated in renal impairment	Windecker et al., 2000; Kraemer et al., 1982
Fluconazole	Renal impairment	Fluconazole is contra-indicated in renal impairment	SAMF, 2012
Co-trimoxazole	Haematological disorders (HD)	Co-trimoxazole to be used cautiously in HD	Heimpel&Raghavachar, 1987
Paracetamol	Haematological disorders (HD)	Paracetamol to be used cautiously in HD	Aster et al., 2009
Amoxycillin	Chronic gastro-enteritis (CGE)	Amoxycillin can exacerbate CGE	Elliot, 2007
Cimetidine	Refractory seizures*	Cimetidine can exacerbate seizures (side effects of Cimetidine includes seizures)	Macphee et al., 1984
Acyclovir	Chronic Gastro-enterirtis* (CGE)	Acyclovir may aggravate diarrhoea	SAMF, 2012
Ertepenem	Renal impairment	Ertepenem may aggravate renal impairment	SAMF, 2012
Oseltamivir	Conjunctivitis*	Conjunctivitis is a side effect of Oseltamivir and patient already has conjunctivitis	SAMF, 2012
Paracetamol	Haemolytic Anaemia	Side effects of Paracetamol includes thrombocytopenia and neutropenia. Paracetamol use can further aggravate the condition	Aster et al., 2009
Omeprazole	Haemolytic Anaemia	Side effects of Omeprazole includes pancytopenia, thrombocytopenia, leucopenia, agranulocytosis, and haemolytic anaemia. Omeprazole can aggravate the condition	Landray et.al, 1998
Cimetidine	Pancreatitis*	Cimetidine exacerbates pancreatitis	Eland et.al, 2000; Nott and De Sousa , 1989
Cimetidine	Renal impairment	Cimetidine to be used cautiously in renal patients	Rudnick et al., 1982

Ertepenem	Renal impairment	Ertepenem may aggravate renal impairment	SAMF, 2012
Cotrimoxazole	Hepatic Impairment (HI) (increase in liver enzymes)	Cotrimoxazole to be used cautiously in patient with HI	Ransohoff&Jacobs, 1981; Abi Mansur et al., 1981; Yao et al., 1997, Altraif et al., 1994
Phenobarbitone	Hepatic Impairment (HI)	Phenobarbitone use is contraindicated in patient with HI	Aiges et al., 1980
Paracetamol	Haematological Disorders (HD)	Paracetamol to be used cautiously in HD	Aster et al., 2009
Diazepam	Hepatic Encephalopathy (HE)	Diazepam is contraindicated in HE	Hermann et al., 1983
Clonazepam	Drug induced Hepatic Encephalopathy (HE)	Diazepam is contraindicated in HE	Mullen et al., 1996
Omeprazole	Jaundice	Omeprazole can aggravate jaundice	Jochem et al., 1992
Paracetamol	Increased liver enzymes	Paracetamol to be used cautiously in patient with raised liver enzymes	Rivera-Penera et al., 1997
Prednisone	Hyperglycemia	Prednisone can further increase glucose levels	Ferris & Kahn , 2012
Gentamycin	Hearing loss	Gentamycin can cause ototoxicity	SAMF, 2012
Prednisone	Hyperglycemia	Prednisone can further increase glucose levels	Ferris & Kahn, 2012

***other DDiS**

4.6 Off–label prescribing

A relatively higher number of OL prescribing with regards to age of patients was observed, as may be observed in Table 29, below, which also indicates other, formulation, route, and dose errors in OL prescriptions.

Table 29: Off-label prescribing

Type of OL prescribing	No.	%	95% CI
Age	24	1.9	1.2–2.8
Other (a drug prescribed for a condition for which it was not approved)	16	1.3	0.72–2.0
Formulation	8	0.6	0.3–1.2
Route	5	0.3	0.13–0.90
Dose	4	0.3	0.09–0.80

Table 30, following, provides a description of OL prescribing in the study sample, as indicated earlier in Table 28.

Table 30: Description of Off-label (OL) prescribing as indicated in Table 29

Type of OL (in terms of age, formulation, route, dose, and other)	Drug	Description of OL
Age	Ethambutol	Ethambutol not recommended for children aged under 8 years
Other (Chloroquine prescribed for a condition completely different from those for which the drug was approved)	Chloroquine	Chloroquine prescribed for Idiopathic Pulmonary Hemosiderosis (IPH)
Other (Clonidine prescribed for a condition completely different from those for which the drug was approved)	Clonidine	Clonidine prescribed as part of sedation protocol
Route	Gentamycin	Parenteral Gentamycin prescribed as oral, as part of bowel "cocktail"
Other (Clonidine prescribed for a condition completely different from those for which the drug was approved)	Cholestyramine	Cholestyramine, a bile acid sequestrant, prescribed as part of bowel "cocktail"
Age	Cholestyramine	Not recommended for children aged under 2 years. Patient is one month old
Formulation	Omeprazole	Omeprazole oral tablet changed to oral solution
Age	Oseltamivir	Not registered for children aged under 1 year
Other (Clonidine prescribed for a condition completely different from those for which the drug was approved)	Gabapentin	Used for neuropathic pain
Other (Amitriptylline prescribed for a condition completely different from those for which the drug was approved)	Amitriptyline	Used as an adjuvant to pain relief in chronic pain syndrome
Other (Clonidine prescribed for a condition completely different from those for which the drug was	Clonidine	Clonidine prescribed as part of sedation protocol

approved)		
Dose	Clonidine	Paediatric dose not established for children aged under 12 years
Age	Omeprazole	Omeprazole registered for short term use (3 months) for GORD in children aged older than 1 year
Formulation	Omeprazole	Omeprazole tablet formulated into solution formulation
Route	Omeprazole	Oral formulation prescribed as via naso-gastric tube (NGT)
Route	Co-trimoxazole	Oral formulation prescribed as via NGT
Route	Prednisone	Oral formulation prescribed as via NGT
Age	Omeprazole	Not registered for children aged under 1 year
Formulation	Omeprazole	Omeprazole tablet formulated into solution formulation
Age	Montelukast	Safety and efficacy not established in children aged under 2 years
Age	Tilidine HCl	Tilidine HCl should not be prescribed and administered in infants aged under 1 year
Other (Mesna prescribed for a condition completely different from that for which the drug was approved)	Mesna	Mesna, a purine analogue usually prescribed as an inhalation, to reduce sputum to prevent urothelial toxicity
Other (Clonidine prescribed for a condition completely different from those for which the drug was approved)	Clonidine	Clonidine prescribed as part of sedation protocol
Dose	Clonidine	Paediatric dose not established for children aged under 12 years
Dose	Clonidine	Paediatric dose not established for children aged under 12 years
Age	Ciprofloxacin	Not licensed for use in neonates
Other (Gabapentin prescribed for a condition completely different from that for which the drug was approved)	Gabapentin	Prescribed for neuropathic pain (unregistered indication)
Other (Unregistered in South Africa)	Phenobarbitone IV	Phenobarbitone IV unregistered
Dose	Clonidine	Paediatric dose not established for children aged under 12 years
Age	Oseltamivir	Not recommended for children aged under 1 year
Age	Prostaglandin	Not recommended in children
Other (Prostaglandin prescribed for a	Prostaglandin	Prescribed as part of Pulmonary Hypertension regimen

condition completely different from that for which the drug was approved)		
Other (Clonidine prescribed for a condition completely different from that for which the drug was approved)	Clonidine	Prescribed as part of sedation protocol
Age	Clonidine	Not registered for use in children aged under 12 years
Age	Gabapentin	Not registered for use in children aged under 12 years
Other (Gabapentin prescribed for a condition completely different from that for which the drug was approved)	Gabapentin	Prescribed for neuropathic pain (unregistered indication)
Age	Meropenem	Not recommended for children aged under 1 month
Age	Cholestyramine	Use not recommended for children aged under 2 years
Formulation	Gentamycin	Parenteral formulation prescribed as oral dose as part of bowel "cocktail"
Age	Cholestyramine	Not indicated for children aged under 2 years
Age	Oseltamivir	Not for use in children aged less than 1 year
Age	Ethambutol	Ethambutol not recommended for children aged under 8 years
Age	Meropenem	Not recommended for children aged under 1 month
Age	Cholestyramine	Use not recommended for children aged under 2 years
Age	Clonidine	Not registered for use in children aged under 12 years
Age	Gabapentin	Not registered for use in children aged under 12 years
Age	Oseltamivir	Not recommended for children aged under 1 year
Age	Prostaglandin	Not recommended in children
Other (Gabapentin prescribed for a condition completely different from that for which the drug was approved)	Gabapentin	Prescribed for neuropathic pain (unregistered indication)
Formulation	Omeprazole	Omeprazole tablet formulated into solution
Formulation	Gentamycin	Parenteral formulation prescribed as oral dose as part of bowel "cocktail"

Formulation	Omeprazole	Omeprazole tablet formulated into solution
Route	Omeprazole	Oral formulation prescribed as via naso-gastric tube (NGT)

4.7 Determinants of or risk factors for prescribing errors

To identify risk factors associated with prescription errors, the following variables were examined: doctor category, class of drug, ward location, drug formulation, formulary, patient age category, day of the week when drug items were prescribed, and the number of drug items prescribed per prescription chart.

Table 31, following, shows the risk factors or determinants associated with a prescribing error. The determinants of the risk factors of prescribing errors were not necessarily mutually exclusive and the determinants reflected factors involved in the prescribing practice in a teaching hospital, for example, the RCWMCH, where the study was conducted.

It can be said that junior prescribers, to some extent, mimic their senior counterparts; thus, the recurring type of prescribing errors frequently observed during the current study, namely, missing information. Secondly, the senior doctors who were more involved than their junior counterparts in prescribing in the specialty wards were more prone to make mistakes in these wards.

The only other interesting determinant of risk factor, relatively easy to observe, was occurrence of more errors during the busier times in the hospital, that is, during weekdays.

Table 31: Risk factors associated with ANY prescribing error

Factor	Total N 1 282	Any error n	% Any error	Univariate analysis		Multivariate analysis	
				OR 95% CI	p value	OR 95% CI	P value
Level of experience							
Junior	405	242	59.75	Referent	—	Referent	—
Senior	877	687	78.34	2.435 (1.886–3.144)	<0.001	1.954 (1.463–2.608)	<0.001
Class of drug							
Antibiotics	271	206	76.01	Referent	—	Referent	—
Vitamins and minerals	438	305	69.63	0.724 (0.512–1.022)	0.066	—	—
Other	573	418	72.95	0.851 (0.609–1.189)	0.344	—	—
Ward location							
Specialty	426	349	81.92	Referent	—	Referent	—
General	856	580	67.76	0.463 (0.349–0.617)	<0.001	0.653 (0.473–0.901)	0.010
Formulation							
Oral	991	717	72.35	Referent	—	Referent	—
Other	291	212	72.85	1.026 (0.765–1.375)	0.866	—	—
Formulary							
Yes	1282	929	72.5	Referent	—	Referent	—
No	0	0	0*	Cannot be estimated	Cannot be estimated	—	—
Age of patient (in months (mo))							
0–12 months	506	367	72.53	Referent	—	Referent (0–12 months combined with > 60 months)	—
13–60 months	404	278	68.81	0.835 (0.627–1.114)	0.220	0.767 (0.587–1.001)	0.051
>60 months	372	284	76.34	1.222 (0.898–1.664)	0.202	Referent (see above)	—
Day							
Weekday	1 017	752	73.9	Referent	—	Referent	—
Weekend	260	172	66.1	0.671 (0.503–0.895)	0.007	0.710 (0.527–0.955)	0.024
Missing dates on prescription (no day	5	5	100	—	—	—	—

could be allocated for five prescribed drug items)							
No. of drugs items prescribed							
1–5 drug items	89	59	66.29	Referent	—	Referent	—
>5 drug items	111	84	75.68	1.582 (0.853–2.933)	0.145	—	—

Univariate and multivariate logistic regression was used to identify risk factors associated with a prescribing error. The odds ratio (OR) indicates the odds of the category making an error compared to that of the referent category. For the multivariate analysis, no prior information was given. There were no adjustments or controls. All variables with a p-value less than 0.25 in the univariate analysis were considered. The model was run and insignificant variables removed. Attention was also given to changes in the model. No major changes were noted.

The final model showed senior doctors (registrars and consultants) to be almost twice as likely to make a mistake, compared to the juniors (interns and SHO's). Prescriptions written up in the general medical wards (B1 and B2) had less errors compared to those written up in the specialty wards (that is, PICU and G1). Prescribing errors were generally, less likely to occur over weekends compared to weekdays. These were the only significant variables found in the study sample.Although children aged 13 to 60 months experienced a reduced error risk, this did not quite reach statistical significance.

Chapter 5

Discussion

Key points based on the outcomes of the study objectives, will be discussed in this chapter. The findings of the study at RCWMCH will be compared to the findings of the literature reviewed.Patient characteristics in terms of age and nutritional status of the patient and the drug treatment regimen prescribed for them, will be briefly included The types of prescribing errors encountered in the study, the potential drug-drug interactions (DDIs), drug-disease interactions (DDiS), and off-label (OL) prescribing will be discussed. In addition important observations for each of these within the context of the study objectives will be mentioned. Determinants of prescribing errors will be discussed, based on the results as observed in the study. Limitations of the study conducted, will be mentioned in terms of prescription chart used, the reporting (or under-reporting) of drug interactions, drug-disease interactions and off-label prescribing and lack of investigators.

The main objectives of the study were as follows: (1) to describe the types of prescribing errors and error frequency, (2) to describe the prescribing error frequency per different classes of drugs, (3) to identify potential drug interactions (DDIs), (4) to identify potential drug-disease interactions (DDiS, (5) to describe off-label (OL) prescribing, and 6) to identify risks or determinants for prescribing errors. The study was conducted in two medical wards and two speciality wards, prescribing practice of doctors from different specialities and from different levels of experience considered for the purpose of searching for the objectives listed. The methodological features of this study design accurately described the prescribing practice, also allowing for critical appraisal and analysis of the prescribing practice. The statistical analysis of the data allowed for identification of the related risk factors associated with prescribing errors.

5.1 Patients characteristics

In the sample in the present study, 104 patients were aged below 24 months (52%), compared to a 255 study sample (included both adults and children) in which 52% were children, in a study conducted by Grimwood and his colleagues, focusing on antimicrobial prescribing errors, with age(s) ranging from 0.2 months to 144 months (Grimwood,Cook & Abbott, 1983). In the)study at RCWMCH, 65% of the patients in the sample were either moderate or severely underweight, compared to 41.2% underweight children aged between 60 to 180 months in a study carried out in India (Srivasta et al., 2012). Only 15.5% of the patients in the study sample were HIV-infected, compared to the 100% HIV infection rate among patients in a retrospective study conducted by Norah in South Africa (Norah, 2011).

Treatment protocols for children who were underweight for age, included zinc, folate, and multivitamins. This reflects adherence at the RCWMCH to the 10 steps recommended by WHO (World Health Organisation, 1999) in the treatment of malnutrition. Where necessary and as the need arose, elemental iron and other trace elements were prescribed.Vitamin A were also administered to the children and they were de-wormed when indicated, a practice often done in the short stay ward. These drugs were not always included in the "real time" study review of the prescription charts since they had already been prescribed and administered as stat (at once) doses .Nutritional medicines (zinc,folate & multivitamins) were prescribed before arrival to the ward (in some cases only). In a few cases it was prescribed as stat doses in short stay ward (excluded in study), in most cases the nutritional medicines were prescribed within the respective wards**.**

Antibiotics and other disease-specific treatments were prescribed on an individual basis. A similar study in India in 2011on 41.2% underweight children also showed anaemia as the most common condition in the underweight group (Srivasta et al., 2012); as for the

underweight group in the study at RCWMCH, drug treatment regimen included drugs such as zinc, folate, and vitamins. Although vitamin A disorders amongst the underweight group was not very common (3.4% of the sample) in the India study, the children were still treated with it where it was deemed necessary.

5.2 Prescribing errors

The study showed that prescribing practice in terms of prescribing errors was easily identifiable seeing there were no significant differences in the types of prescribing errors made by senior and junior doctors. There was, however, a significant difference in the frequency of prescribing errors made by senior and junior doctors, that is, senior doctors made more prescribing errors than did junior doctors.

A total of 929 prescribing errors (72.5%) was found in the study, with incomplete information (65.6%) observed as the most common type of error. In comparison to a study in Wales over a period of 24 months with a sample size of 682 patients (Wilson et.al, 1998), prescribing errors accounted for 68%, of which incomplete information (36%) presented as amongst the most common type of errors.

Incomplete information, the leading type of prescribing error by far (see Table 15 in Chapter 4 of this thesis on page 77, shows that prescribers were not following prescribing STGs (guidelines) stipulated in the Medicines and related substances Act 101, 1965 (Medicines and Related Substance Act 101 of 1965, Regulations as amended, 2014: 28) as well as those provided by the RCWMCH. A possible prescribing practice that could have contributed to this situation is the format of the prescription chart used in wards B1, B2, and G1, which was different to the one used in the PICU ward (see Appendix C and D) for format of the prescription charts), that is, in effect, no standardisation of prescription charts used at the hospital. Even though only 12.8% (164 of a total of 1 282 in the overall sample)

accounted for drug items prescribed for infants, 155 of the 164 drugs prescribed had one or more prescribing errors (94%), that is, most of the prescribing errors occurred in this age category.

The nature of the prescribing errors is seen to have centred on the writing style of the prescriber, incomplete information, wrong drug names, and use of abbreviations; all of these featured as the most prominent types of prescribing errors. Prescribing errors due to the decision-making of the prescriber were low and included alteration of a dose and or frequency, dose too high, and dose too low. For other type of errors (such as inappropriate drug, unnecessary drug therapy, and unauthorised prescriber), the occurrence was low.

There were 929 prescribing errors out of a total of 1 282 drugs prescribed (72.5%) in the study sample, with 200 prescriptions reviewed in all. In a retrospective study carried out by Kozer et al. (2002) in the ED of a hospital in Canada, it was found that trainees (junior doctors) were most likely to make prescribing errors; however, in contrast, in the study based at the RCWMCH, it was found that the registrars (senior doctors) were responsible for most of the recorded prescribing errors. The registrars took most of the responsibility for initiating and completing prescription charts, thus increasing the chances for prescribing errors being made.

If one compares, for example, one of the main concerns relating to prescribing errors, that is, incomplete prescription (or missing information), then the study done at the University Hospital in Wales (Wilson, 1998), showed that incomplete information was among the highest types of prescribing errors. Similarly, as mentioned earlier, for the study at the RCWMCH, incomplete prescription (missing information) was the most recurring type of prescribing error, followed by use of wrong name for the prescribed drug and use of abbreviations.

The error frequency for drugs by different classes of drugs was high for most of the categories. The study at RCWMCH, compared with some of the findings in similar studies done previously, showed that a rational approach to instil good prescribing should be planned, implemented, and monitored. In this regard, for example, in a study undertaken at a tertiary teaching hospital in New York from 1 July 1994 to 30 June 1995 (Lesar, 1997), as with the study at RCWMCH, results showed antimicrobials to be one of the classes of drugs most commonly involved in prescribing errors. In the study, antibiotics was the second class of drugs most commonly prescribed, at times irrationally, during clinical intervention and when an unauthorised prescriber (effectively, this being another type of prescribing error) prescribed restricted antibiotics. The irrational prescribing of antibiotics has the potential to increase resistance in a patient; thus intervention through antibiotic stewardship that includes a pharmacist as part of the prescribing team during ward rounds, will improve future practice of this very significant class of drugs at the RCWMCH.

Most drugs were prescribed in the general medical wards, as observed in the results of the study presented in Chapter 4 (Table 9 on page 72) of this thesis. Interestingly, ward G1, a speciality ward, had a higher error rate (1.43) compared to the PICU ward (also a specialty ward) and the two general medical wards involved in the study. Similarly, in a study conducted at a tertiary care teaching hospital in New York from 1 July 2000 to 4 January 2002 medication errors were observed in the neonatal, PICU, and general paediatric wards (Lesar, 2002). It was observed that tenfold prescribing errors occurred in the paediatric/neonatal ICU (Lesar, 2002). In G1, the oncology ward, important information missing from the prescription chart, contributed towards the high prescribing error rate. Another similarity between the study and another carried out by Kozer and colleagues in 2000 in Canada related to weekdays versus weekends for occurrence rate of prescribing errors; in both studies there was an increased risk of prescribing errors occurring during

weekdays, an indication that the volume of prescriptions generated during weekdays is greater than that over weekends. The univariate analysis of the study carried out by Kozer et al. (2000) also revealed that it is the younger age group that was associated with a greater number of prescribing errors compared to older children. Similarly, in the study, the younger age group was at greater risk for prescribing errors. A wrong prescribed dose, based on small body weight and surface area, also resulted in more prescribing errors in the younger age group (1.03–12 months), as observed in the results presented in Chapter 4 (Table 20 on page 82 of this study).

5.3 Potential drug interactions

Potential drug interactions (DDIs) were minimal, indicating that the doctor might have considered the possibility of a potential interaction, prescribing sensibly, that is, only in the event that of the drug interactions being beneficial. Potential pharmacodynamic drug interactions were more likely to occur than pharmacokinetic drug interactions, even though not necessarily reported in the clinical notes of the patient. Pharmacodynamic interactions were generally more intuitive for those with advanced medical training (as observed in the PICU ward) because the interacting drugs had related actions. An example of the synergistic effect of two drugs prescribed as per PICU sedation protocol is illustrated by the potential interaction between diazepam (CNS depressant) and morphine (opioid analgesic). This potential drug interaction led to pronounced CNS depression, which was a desired outcome as observed in this study.

Another example in the current study of a pharmacodynamic interaction was that between acetazolamide (a carbonic anhydrase inhibitor) used for raised intracranial pressure and furosemide (a loop diuretic). The diuretic effect was augmented, by increased sodium

load delivered to the collecting duct. In addition acetazolamide increased potassium excretion, resulting in hypokalemia, as indicated in the laboratory results (Libenson et.al., 1999). Another example of a pharmacodynamic interaction, observed in my study, was in a renally compromised patient, who received both furosemide (a loop diuretic) and ibuprofen (a non-steroidal anti-inflammatory drug (NSAID). Renal impairment, as observed in the clinical notes, worsened in this particular case. Ibuprofen can cause renal impairment, particularly in patients with hypovolaemia or dehydration and in whom prostaglandins are playing an important role in maintaining renal function. Hence, the concurrent use of furosemide and ibuprofen may increase the nephrotoxicity of NSAIDs . Additive central nervous system (CNS) was observed in two cases; in the first case, the patient received both diazepam (a benzodiazepine) and phenobarbitone. A simple synergistic effect (Brockmeyer et.al., 1985) was observed, as desired by the prescriber. Similarly, in the second case, the patient received both diazepam and sodium valproate. The latter drug has the potential to slightly increase the sedative effect of the former drug (Dhillon&Richens, 1982), a desired outcome, as observed.

An observed daily decrease in the blood was recorded on the vital signs recording chart, indicated a potential hypotensive effect, possibly caused by interacting drugs. Drug interactions between furosemide and captopril showed potential additive hypotensive effect. Laboratory results, as recorded in the clinical notes of the patient, also helped in identifying potential drug interactions. For example, the potential interaction between captopril and spironolactone, observed in two cases in my study, led to a potential increase in potassium levels. Captopril (an ACE inhibitor) reduces plasma levels of aldosterone, which results in the retention of potassium. This would be expected to be additive, with the potassium retaining effects of spironolactone leading to hyperkalaemia (Berry et.al., 2001). Another important potential pharmacodynamic interaction observed in the present study was that

between aspirin and warfarin. A higher than normal international normalised ratio (INR) value, observed in the clinical notes, was indicative of a high warfarin dose. Increased risk of bleeding may occur even in a low dose of aspirin (75mg) when prescribed concurrently with warfarin. In addition, aspirin has a direct irritant effect on the stomach lining and can cause gastrointestinal bleeding; it also decreases platelet aggregation and prolongs bleeding time (Weil et.al, 1995).

In the study, pharmacokinetic drug interaction between ethambutol and pyrazinamide, that is, an additive potential for elevation of serum urate or clinically significant, hyperuricaemia Both drugs were prescribed in the intensive and continuation phase of TB). Another pharmacokinetic drug interaction of note was that between sodium valproate and phenobarbitone, both anti-epileptic drugs, readily prescribed for patients with uncontrolled seizures. In eight cases of pharmacokinetic drug interactions observed during the present study, phenobarbitone plasma concentrations levels were raised. Valproate has the potential of increasing the plasma concentration of phenobarbitone, that is, increases drug distribution (Hurst, 1997). Conversely, plasma concentration of valproate was reduced by phenobarbitone in most cases, as indicated by the laboratory results. In a study undertaken at a teaching hospital in Brazil by Martinbiancho et al. (2007) in 2006, similar potential drug interactions were identified. Examples included the concurrent use of valproic acid and phenobarbitone, increased serum levels of phenobarbitone, and reduced effects of valproic acid. There was a difference in identifying and notifying these potential drug-drug interactions. In the study undertaken at RCWMCH, the pharmacist was solely responsible for identifying the potential interaction and notifying the prescriber during ward rounds, whereas in the study by Martinbiancho et al. (2007) from January 2005 and December 2006, the utilisation of computer programs was the most effective way of identifying potential drug interactions and notifying prescribers.

Two other potential pharmacokinetic drug interactions, that were clinically significant, were those between cimetidine (H2-receptor antagonist) and diazepam (a benzodiazepine) and between omeprazole (a proton pump inhibitor) and diazepam. Both cimetidine and omeprazole have the potential to inhibit the metabolism of diazepam, thus delaying the elimination of diazepam and leading to increased or prolonged effect (Lockniskar&Zomorodi, 1996). Zinc was commonly prescribed as a supplement in patients with nutritional concerns and a potential drug interaction with ciprofloxacin (a quinolone antibiotic) was observed. Both drugs were prescribed for being given at the same time, zinc once daily (at 08h00) and ciprofloxacin twice daily (at 8h00 and 20h00). Since zinc has the potential to reduce the absorption of ciprofloxacin (Polk, 1989), therapeutic outcome was compromised in one patient, though not necessarily reported. Advice was given to administer the two drugs two hours apart. The potential for drugs to interact is real, even though the actual outcome may be difficult to measure. The prescriber should exercise caution to minimise additive harmful effects due to an overlooked drug interaction.

5.4 Drug-disease interactions

The potential for a drug-disease interactions was very low, thus no adverse event was observed during the period in which the study was undertaken. The potential to exacerbate a pre-existing liver disease was relatively more common than other types of potential drug-disease interactions.

In two separate cases where both patients were diagnosed with hepatic encephalopathy, diazepam was prescribed in the one case and clonazepam in the other, even though both drugs are contra-indicated for patients with hepatic encephalopathy (Mullen et al., 1996). The laboratory reports of both showed increased levels of liver enzymes. In two

other cases, both patients were diagnosed with hyperglycemia, with prednisone prescribed as part of a treatment regimen for TB. Prednisone increased the glucose levels in both patients. Documented evidence by Ferris (2012) shows that prednisone has the potential to increase glucose levels by inhibiting a number of steps in the insulin signalling network. Thus, the disease state of the patient should be carefully considered before potentially harmful drugs are prescribed to compromised patients.

5.5 Adverse Drug Reactions:

Adverse drug reactions (ADR's) are not intended and occur at normal doses of medicines. The identification of ADR's is dependant upon health professionals being alert and reporting any such event. It can be difficult to identify a true ADR and it rests with the all healthcare professionals to suspect for the occurrence of an ADR, particularly in infants and children.In one particular case in the study, the patient was diagnosed with drug induced hepatitis,a known adverse drug reaction of azathioprine. Isoniazid was given prophylactically to the same patient, the latter which caused an increase in liver enzymes, that is, an increased risk of drug interaction leading to the worsening of hepatotoxicity (Possuelo et al., 2008). This patient was also prescribed paracetamol, thus further increasing the risk of hepatotoxicity (Rivera-Penera et al., 1997).The patient was also prescribed chloroquine, compounding the risk of hepatotoxicity (Mottaghi&Karemzade, 2005). The patient's liver enzymes were significantly raised, as noted in the laboratory results. Adverse drug reactions were under reported by healthcare professionals, no ADR's were reported during the study period. In addition, it was not included as an objective of the study at RCWMCH.

5.6 Off-label prescribing

In the present study, off- label prescribing was not considered a bad practice. In particular, when benefits outweighed risks, very high doses were prescribed and where drugs were not readily available in paediatric formulation, adult formulations were prescribed and modified according to the prescriber's instructions.

The frequency of off-label prescribing in my study was less than 2% for any type of off-label prescribing. Age was the most common factor regarding OL prescribing, with other factors infrequently being a causal factor for OL prescribing. In a study carried out by Conroy, McIntyre &Choonara (1999) in the United Kingdom, it was observed that off-label prescribing in terms of age, that is, outside the licensed age range, was a common practice. Similarly, in this study conducted at RCWMCH ,age was the common reason for off-label prescribing. Another similarity between the present study and that of Conroy and his colleagues (1999) was the use of morphine in neonates. Morphine is not recommended for use in neonates, but was readily prescribed when deemed necessary. For certain drugs (for example, Ethambutol), the manufacturer does not recommend use in children aged below eight years, except in certain conditions, for example, in patients with extra-pulmonary TB. However, Ethambutol is readily prescribed (off -label), as observed in the present study at RCWMCH. Clonidine (an antihypertensive agent) is also readily prescribed for children, including neonates, although safety has not been established for children aged below 12 years. Clonidine was found to be prescribed as part of pain and sedation protocol, a practice also commonly observed at RCWMCH in the study. Another drug readily prescribed in children aged as young as one month as part of a "bowel cocktail" is cholestyramine (a bile acid sequestrant). Cholestyramine is not recommended for children aged below six years. Parenteral gentamycin was also readily prescribed as part of the "bowel cocktail", with the route of administration oral. In the present study, drugs such as gabapentin (an anti-epileptic)

and amiptriptyline (a tricyclic anti-depressant) were prescribed as part of pain management regimen, as approved by the pain management team at RCWMCH. For paediatric formulation, adult drug formulations were modified as per prescriber instructions, for example, omeprazole MUPS (multiple unit pellet system) tablets were crushed and made into a solution for easier administration. In some cases, especially in neonates, a drug such as gentamycin was not prescribed as recommended by the manufacturer, that is, a dose higher than the recommended dose of 2.5mg–3mg/kg/dose to be given twice daily for neonates was prescribed in some cases.

Off-label prescribing, as observed in the present study, was a much less common than expected, with hardly any recording or monitoring of this practice occurring. Monitoring and recording of OL prescription is important to improve knowledge of this widely acceptable practice amongst prescribers at RCWMCH. The above-mentioned study by Conroy et al. (1999) showed OL prescribing to be a common practice in Europe. Not all OL prescribed drugs can be harmful; in fact, experienced prescribers (in both Conroy and the present study) show confidence in their practice when the need to prescribe an OL drug arises. At the same time, other prescribers, especially junior doctors at RCWMCH, must be well informed in order to make the best possible decision with regard to OL prescribing, while at the same time adhering to good prescribing practice, currently, not happening due to the prevailing trend over the years.

The potential and occurrence for drug interactions (DDIs) (see Tables 23 and 25 in Chapter 4, pages 84 and 86) and drug-disease interactions (DDiS) (see Table 27 in Chapter 4 (on page 90) and off-label (OL) prescribing (see Table 29 in Chapter 4 of this thesis, page 93)were lower than expected. Under-reporting by prescribers regarding outcome of such interactions and drug induced diseases as well as the occurrence of OL prescribing as an accepted norm by most, if not all, prescribers could have been a contributing factor to the low

numbers observed in the present study as far as DDIs, DDiS and OL prescribing is concerned.

5.7 Determinants of risk factors for prescribing errors

Senior doctors, especially registrars, were found in the study to be responsible for most of the prescribing in all the wards. Senior doctors are thus almost twice as likely to prescribe in error than are junior doctors (see Table 18 in Chapter 4 of this thesis, page 80).The trend of prescribing practice, reflected by the recurrence of prescribing errors, showed that junior doctors, guided by their senior counterparts in the wards, to some extent, "copied" the prescribing style of the latter. Prescribing guidelines as per an internal memo at RCWMCH (see Appendix I) were not adhered to by most of the prescribers. Also, a surprise finding was that more prescribing errors occurred in the specialty wards than in the general medical wards (see Table 17 in Chapter 4 of this thesis, page 79), considering that therapeutic intervention in the specialty ward requires more intense prescribing and decision-making by prescribers. In the context of the dynamic environment in the specialty wards, the risk of prescribing errors,cannot be under-estimated.

Prescribing errors occurred more during weekdays than over weekends. In a study by Lesar, Briceland& Stein (1997) in New York , factors associated with prescribing errors, that is, determinants, included the patient's age, with the very young also indicated as a risk factor. Other factors considered in the study by Lesar, Briceland& Stein (1997), included the following: inadequate knowledge of drug therapy; impaired renal function; drug allergy; the need for calculation of drug doses and specialised dosage formulation; and the nomenclature used in prescribing. These factors were not considered in the present study at RCWMCH but may well prove to be of great interest and significance regarding factors for consideration in future studies on prescribing errors

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5.8 Limitations of the study

5.8.1 Prescription chart design

The layout of the prescription charts in three wards, namely, B1, B2, and G1 at RCWMCH, as observed during this study, differed from the one used by prescribers in the PICU at the same hospital. The chart used in PICU had a section for the calculation of the amount of drug to be administered, thus enabling the prescriber to perform and show the calculation for the required dose, as well as providing clear instructions for the administering nurse regarding the correct amount of drug to be administered. The prescription chart used in wards B1, B2, and G1 were incomplete (that is, it contained no such section for showing the calculation of dose as in the chart used in PICU), thus placing the prescribers from these three wards at a distinct disadvantage. Moreover, the principal investigator was deprived of this relevant information, not shown by the prescriber due to lack of the relevant section (for dose calculation) on the prescription chart, thus directly or indirectly affecting relevant data, as evident in the results of the present study.

5.8.2 Under-reporting and lack of documentation of drug interactions, drug-disease interactions and off-label prescribing

Often, symptoms due to an underlying subtle drug interaction (DDI) or drug-disease interactions (DDiS) might have been misinterpreted as a new condition and treated with more drugs, thus the occurrence of a potential drug interaction and/or drug induced disease is

downplayed . Thus, only in very few cases, as per the clinical notes, could drug interactions and drug induced diseases be reported, affecting the outcome of the data collection in this study. In order for potential drug interactions and drug induced diseases to be reported, it would be an advantage to have potential drug interactions and drug induced diseases listed on a database for prescribers to access the information in the wards at the time of prescribing potential interacting drugs. This reporting method of clinically significant drug interactions and drug induced disease will be practical to implement. In the case of off label prescribing, no mention is made that certain drugs were used as off label. OL was, in fact, more the norm than the exception, with prescribers almost regarding it their exclusive right to prescribe off label drugs. A database listing all the drugs used off-label will assist in keeping a check on these drugs. In the event of an untoward reaction, knowledge of off label drugs will be an advantage to all future prescribers at RCWMCH.

5.8.3 Lack of investigators

Unlike the study carried out by Lesar et al. (2002) in New York, which involved many investigators in the project and errors being detected by an automated computer system, the study at RCWMCH involved one principal investigator, with errors manually detected and discussed with the prescriber and/or the doctor on duty during ward rounds. The collection of the relevant data and recording of all the information regarding prescribing errors and so forth was the sole activity of the principal investigator.

Chapter 6

Conclusions and Recommendations

6.1 Conclusions

With an overall prescribing error rate of 72.5%, the study at RCWMCH, demonstrated that prescribing errors posed a risk in the medicine management chain. The different types of prescribing errors were likely to occur due to the writing style of the prescriber. This pertains to prescribing errors such as incomplete prescription (missing information); use of wrong drug approved name; use of abbreviations; legibility concerns; and lack of clarity, among others. This clearly demonstrated the lack of adherence by the prescribers to the Medicines and Related Substances Act 101 of 1965 (Medicines and Related Substance Act 101 of 1965, Regulations as amended, 2014: 28) that defines and stipulates the legal requirements for a correct prescription. Currently, due to limited research studies on prescribing practice undertaken among child patients, there exists no benchmark that can be used as a guideline to correct prescribing, especially in South Africa. The need to monitor and measure prescribing as an important tool of medicine management is of vital importance. An incomplete prescription constitutes an illegal medico-legal document and a problematic practice by prescribers in general, and should, in particular, be addressed at the RCWMCH, the site of this study. As per the requirement for correct prescribing (Medicines and Controlled Substance Act 101 of 1965 (Medicines and Related Substance Act 101 of 1965, Regulations as amended, 2014: 28) prescribers should exercise more responsibility in prescribing practise by writing complete prescriptions, that is, all relevant information about the drug in terms of the correct name, dose, frequency, duration, route of administration, and quantity to be administered. Training on prescribing guidelines should be implemented to improve

prescribing practice by providing the necessary skills to health care practitioners about the writing and handling of prescriptions.

The present study showed no big difference in the prescribing error frequency per different classes of drugs, an indication that any drug was at risk for a prescribing error. Abbreviations, the third most frequent type of error, were mostly used for vitamins and minerals, the class of drugs prescribed the most, but with one of the lowest frequency of error, as observed in this study. In some cases, the wrong name, that is, the trade or brand name was used for drugs, for example, antibiotics, a class of drug frequently prescribed in most medical cases, with antibiotics therefore having a relatively higher frequency of prescribing errors compared to other classes of drugs. Dosing errors, as observed in this study, contributed to a low frequency of error, including the mistaken placing of an extra zero or naught (0) in some of the calculations, for example, for benzyl penicillin, making the potential for a tenfold error real.

The presence of potential drug interactions (DDIs) and drug-disease interactions (DDiS) was not easily identifiable, mostly under-reported, and difficult to predict. Interpretation of laboratory results assisted in identifying the outcome of drug interactions, for example, an increase in potassium levels was observed in some cases. The recording of blood pressure on the vital sign chart also served as a guideline in cases where drug interactions caused additive hypotensive effects. Drug-disease interactions were less likely to be reported in the clinical notes than were drug interactions, with concerns often raised in the form of a question by the prescriber. For example, Azathioprine as a causative agent for drug induced hepatitis? A recommendation to address this would be the use of computer database programs in the wards to help identify and monitor drug interactions and drug-disease interactions.Prescribers will then be alerted to potential drug interactions and drug-disease

interactions assisting prescribers in making better clinical decisions pertaining to drug therapy and disease state of the patient.

Off-label (OL) prescribing, viewed as an acceptable practice by most prescribers, is also under-reported. Age was certainly not a major deterrent when one considers the relatively high number of off label prescribing in the paediatric population in this study. The procurement of pharmaceuticals also has an indirect influence on off-label prescribing practice at paediatric hospitals such as RCWMCH. The standard treatment guidelines (STGs) for paediatrics, the code list of the Provincial Government of the Western Cape (PGWC), tenders by the National Department of Health (NDoH), the Pharmacy and Therapeutics Committee and the procurement policies of the PGWC all provide guidelines for the procurement of pharmaceuticals. These exogenous factors influence off-label prescribing and pose a challenge to both senior and junior prescribers, who in many instances in this study, were found to have no awareness even of any challenges in the procurement of pharmaceuticals. Not all medicines on the PGWC code list are on the NDoH tenders; NDoH tenders are renewed every two years and often medicines on the PGWC code list are removed from the tender. In addition, paediatric formulations of medicines are often not on NDoH tenders but incorporated in the STGs. Thus, off-label prescribing should be monitored and recorded more closely, especially in the very young age group, in order to minimise the risks associated with off-label prescribing.

The determinants of prescribing errors included: (a) senior doctors who were responsible for writing up more prescriptions and consequently responsible for more prescribing errors, (b) prescriptions generated in the speciality wards where doctors generally worked under greater pressure due to the dynamic environment in these wards, (c) weekdays, during which most prescriptions were written up, thus the greater frequency of errors.

A pilot study to assess the benefit of electronic prescribing (e-prescribing) will assist in determining whether a shift towards e-prescribing might help to minimise prescribing errors. The need for a ward/clinical pharmacist to be part of the healthcare team daily ward rounds in all the wards can be of great benefit with respect to pharmacovigilance. The present study showed that many prescribing errors could have been avoided if a pharmacist was present during the clinical ward rounds. Thus, a study to measure the impact of a clinical pharmacist on prescribing practices, especially at a ward level in South African hospitals would be interesting. A study on the clinical intervention by pharmacists will also assist in analysing the different types of interventions, namely, (a) indications describing unnecessary medicine therapy, untreated condition, inappropriate drug, and therapeutic duplication, (b) effectiveness describing inappropriate dosage, and/or frequency or duration, and (c) safety describing adverse drug reaction, adverse drug event, and drug food interaction.

Another important observation made in the course of the present study was misunderstanding shown by the administering nurse regarding an order as instructed on the prescription chart. An example illustrating this was the clarity of prescriptions reading "po/per" (per oral or per rectum) for paracetamol. An instruction such as this left the administering nurse with a certain degree of uncertainty as to the formulation to be administered to the patient. A study on administration of medicines as part of medicine management use would also make for an interesting research project aimed at showing the clinical significance of potential administration errors due to incorrect prescribing instructions and misinterpretations.

6.2 Recommendations

In order to minimise the risk of prescribing errors, potential drug interactions (DDIs), potential drug-disease interactions (DDiS), and off-label (OL) prescribing, the following recommendations should be considered:

- Educating all prescribers via tutorials or training workshops on a regular basis will be beneficial in the future and translate into better patient health outcomes in alignment with two of the health objectives of the National Drug Policy (NDP), that is, (a) ensuring good prescribing practices and (b) promoting the rational use of medicines by prescribers through provision of necessary training, education, and information;

- There should be standardisation of the triaging system from the point of entry when a patient is admitted to a ward where a new prescription chart is generated right up to the point of the patient being discharged;

- Standardisation of prescription charts in all the wards at RCWMCH to allow for provision of complete information required,as per the prescribing guidelines described in the Medicines and Related Substances Act 101 of 1965 (Medicines and Related Substance act 101 of 1965, Regulations as amended, 2014: 28) including a section showing the amount of drug to be administered by the administering nurse;

- Prescriptions with abbreviations and wrong names should be referred for rectification by the prescriber on duty and calculations checked by a pharmacist on ward rounds prior to the drug being administered to the patient;

- The use of computer database programs in wards to help identify and monitor drug interactions (DDIs) and drug-disease interactions (DDiS). Prescribers will then be alerted to potential drug interactions and drug-disease interactions, which will assist

them in making informed clinical decisions with regard to drug therapy and disease state of the patient;

- Implementation of optimal alignment of the various policies (see the earlier section on conclusions in this chapter) affecting rational prescribing in children with regard to off-label (OL) prescribing;

- Reporting of prescribing errors should be the responsibility of all healthcare professionals involved in the medication management system in order to measure and improve the practice of prescribing;

- The undertaking of further research to optimise the prescribing chart and to determine the effect of an improved prescription chart on prescribing practice. In addition, the frequency of known drug interactions (DDIs), drug-disease interactions (DDiS) and, consequently, adverse drug reactions (ADRs) require further study, especially in a hospital setting such as the RCWMCH where patients are known to have co-morbid conditions and are subjected to poly-pharmacy practice;

- There is also a need to include a pharmacist as part of the multidisciplinary healthcare team, especially with regard to pharmacovigilance. Pharmacists could act in an advisory capacity at ward level with regards to rational prescribing. Their involvement in generating correct prescriptions will minimise risk to patient health outcomes. The pharmacist's role in drug utilisation review cannot be underestimated in this regard.

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Appendix A

Data collection sheet 1

Title : Prescribing practice at a Tertiary level paediatric hospital in South Africa

Biographical information				
Study number				
Folder number				
Time of assessment of prescription chart in relation to admission date	Day 3-5	Day 7-10		
Date of birth (dd/mm/yyyy)				
Gender	Female	Male		
Date of admission (dd/mm/yyyy)				
Mass (kg)	Length (cm)	BSA (m^2)		
Clinical Information				
Ward location	B1	B2	ICU	G1
Current date (dd/mm/yy)				
Primary Diagnosis				
Co-morbid conditions				

Current Drugs Prescribed

Drug no.	Name of drug	Class of drug	Job title of Dr.	Strength	Formulation	Dose	Route	Frequency	Duration	Quantity	Formulary status	Day of the week

PRESCRIBING ERROR

Drug no.	Description of error	Type of error

Potential Drug – Drug Interaction (DDI)

Drug no.	Description of potential DDI	Type of DDI

Potential Drug – induced diseases		
Drug No.	Description of DDisI	Type of DDisI
Off – Label Prescribing (OL)		
Drug no.	Description of OL	Type of OL

Class of drug

(1) Gastrointestinal; (2)Blood System; (3)Cardiovascular;

(4)Hormonal; (5) Anti-Infective agent; (6) Oncology;

(7)Musculo-skeletal; (8) Nervous system;

(9) respiratory System; (10)other

Classification of prescribing errors

(1)Incomplete information; (2) Legibility; (3) Clarity;

(4) Abbreviations; (5) Wrong drug approved name;

(6) Dose too high; (7) Dose too low; (8) Allergy;

(9) Wrong time; (10) Wrong route; (11) Wrong frequency;

(12) Wrong unit; (13) Duplication (14) Alteration;

(15) Contraindication; (16) Other

Classification of potential drug-drug interaction

(1)Increase in absorption; (2) Decrease in absorption;

(3) Increase in drug distribution; (4) Decrease in drug distribution;
(5) Increase in metabolism; (6) Decrease in metabolism;

(7) Increase in excretion; (8) Decrease in excretion; (9) Other

Classification of potential drug-disease interaction

(1)Cardiotoxicity; (2) Nephrotoxicity; (3) Hepatotoxicity; (4) Ototoxicity;

(5) Blood disorders; (6) Change in glucose levels; (7) Other

Classification of off-label prescribing

(1)Age; (2) Formulation; (3) Dose; (4) Frequency; (5) Route;

(6) Duration; (7) Other

Appendix B

Data collection sheet 2

Possible determinants/predictors of prescribing errors

1. Level of qualification of prescriber

Intern	1
SHO	2
Registrar	3
Consultant	4

2. Day of the week item prescribed

Monday	1
Tuesday	2
Wednesday	3
Thursday	4
Friday	5
Saturday	6
Sunday	7

3. Age of the patient (in years)

0-2	1
3-5	2
6-10	3
>10	4

4. Location (ward)

PICU	1
G1 (Oncology)	2
B1 (Medical)	3
B2 (Medical)	4

5. Drug formulation

IV	1
IM	2
Oral	3
Suppository	4
Inhalation	5
Tppical	6
Other	7

6. Class of drug

Gastrointestinal tract	1
Blood system	2
Cardiovascular	3
Hormonal	4
Anti-Infective agent	5
Oncology	6
Musculo-skeletal	7
Nervous system	8
Respiratory system	9
Other	10

7. No. of drugs prescribed

1-4	1
5-10	2
>10	3

8. Formulary status of drug

Formulary	1

Appendix C

RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL

DRX 437

Ward: _____

Dept: _____

Admitted: _____

COMPLETE BY HAND WHEN LABEL NOT AVAILABLE

Name: _____ Age: _____

Folder No: _____ Birth: _____ Race: _____ Sex: _____

Date	DOCTOR'S ORDERS	Signature

PREMED AND ONCE ONLY DOSES

Date	Drug	Dose	Route	Time	Signature	Pharm	Time Given	Signature

Patient's Name: ______________________

Folder No.: ______________________

Weight: ______________________

THE WORDS "OR GE" (GENERIC EQUIVALENT) IF NOT DELETED BY THE PRESCRIBER, WILL INDICATE THAT THE APPROVED GENERIC EQUIVALENT MAY BE SUPPLIED.

REGULAR PRESCRIPTION

N.B. MEDICAL STAFF

CAPITAL LETTERS AND APPROVED NAMES ARE USED FOR DRUGS.
WHEN STOPPING MEDICATION DRAW A LINE DOWN THE DATE COLUMN AND SIGN.
SIGNATURE AND NAME IN BLOCK LETTERS ESSENTIAL.

ORAL MEDICATIONS

			DATE / TIME
DRUG APPROVED NAME OR GE	DOSE	ROUTE	
FREQUENCY	DATE	PERIOD	
DRS SIGNATURE AND NAME	PHARMACY		
DRUG APPROVED NAME OR GE	DOSE	ROUTE	
FREQUENCY	DATE	PERIOD	
DRS SIGNATURE AND NAME	PHARMACY		
DRUG APPROVED NAME OR GE	DOSE	ROUTE	
FREQUENCY	DATE	PERIOD	
DRS SIGNATURE AND NAME	PHARMACY		
DRUG APPROVED NAME OR GE	DOSE	ROUTE	
FREQUENCY	DATE	PERIOD	
DRS SIGNATURE AND NAME	PHARMACY		
DRUG APPROVED NAME OR GE	DOSE	ROUTE	
FREQUENCY	DATE	PERIOD	
DRS SIGNATURE AND NAME	PHARMACY		
DRUG APPROVED NAME OR GE	DOSE	ROUTE	
FREQUENCY	DATE	PERIOD	
DRS SIGNATURE AND NAME	PHARMACY		

DRX 437

TO BE GIVEN AT STANDARD MEDICINE ROUNDS

Weight:

IM/IV INJECTIONS

			DATE														
			TIME	CHECK	GIVEN	CHECK	GIVEN	CHECK	GIVEN	CHECK	GIVEN	CHECK	GIVEN	CHECK	GIVEN	CHECK	GIVEN
DRUG APPROVED NAME OR GE	DOSE	ROUTE															
FREQUENCY	DATE	PERIOD															
DRS SIGNATURE AND NAME	PHARMACY																
DRUG APPROVED NAME OR GE	DOSE	ROUTE															
FREQUENCY	DATE	PERIOD															
DRS SIGNATURE AND NAME	PHARMACY																
DRUG APPROVED NAME OR GE	DOSE	ROUTE															
FREQUENCY	DATE	PERIOD															
DRS SIGNATURE AND NAME	PHARMACY																
DRUG APPROVED NAME OR GE	DOSE	ROUTE															
FREQUENCY	DATE	PERIOD															
DRS SIGNATURE AND NAME	PHARMACY																
DRUG APPROVED NAME OR GE	DOSE	ROUTE															
FREQUENCY	DATE	PERIOD															
DRS SIGNATURE AND NAME	PHARMACY																
DRUG APPROVED NAME OR GE	DOSE	ROUTE															
FREQUENCY	DATE	PERIOD															
DRS SIGNATURE AND NAME	PHARMACY																

"AS REQUIRED" AND NON-MEDICINE ROUND PRESCRIPTIONS

DATE CARD COMMENCES		DAY ☞														
			Time	Given by	Time	Given by	Time	Given by	Time	Given by	Time	Given by	Time	Given by	Time	Given by
DRUG APPROVED NAME OR GE	DOSE	ROUTE														
SPECIAL INSTRUCTIONS	DATE	PERIOD														
DRS SIGNATURE AND NAME	PHARMACY															
DRUG APPROVED NAME OR GE	DOSE	ROUTE														
SPECIAL INSTRUCTIONS	DATE	PERIOD														
DRS SIGNATURE AND NAME	PHARMACY															
DRUG APPROVED NAME OR GE	DOSE	ROUTE														
SPECIAL INSTRUCTIONS	DATE	PERIOD														
DRS SIGNATURE AND NAME	PHARMACY															
DRUG APPROVED NAME OR GE	DOSE	ROUTE														
SPECIAL INSTRUCTIONS	DATE	PERIOD														
DRS SIGNATURE AND NAME	PHARMACY															
DRUG APPROVED NAME OR GE	DOSE	ROUTE														
SPECIAL INSTRUCTIONS	DATE	PERIOD														
DRS SIGNATURE AND NAME	PHARMACY															
DRUG APPROVED NAME OR GE	DOSE	ROUTE														
SPECIAL INSTRUCTIONS	DATE	PERIOD														
DRS SIGNATURE AND NAME	PHARMACY															

Appendix D

Paediatric Intensive Care Drug Chart

Name:
Date of Birth:
Folder Number:

Weight:

Allergies:

Once Only Doses

Date	Drug	Dose	Route	Time	Doctor	Checked	Given	Time

Date ▶								
Time ▼								

Drug Name	Dose	Frequency	Route
Print: Drs name	Drs Signature	Start date	End date
Calculation	Srs Signature	Checked	Dose: ml
Pharmacy Notes and Signature			Quantity
Drug Name	Dose	Frequency	Route
Print: Drs name	Drs Signature	Start date	End date
Calculation	Srs Signature	Checked	Dose: ml
Pharmacy Notes and Signature			Quantity
Drug Name	Dose	Frequency	Route
Print: Drs name	Drs Signature	Start date	End date
Calculation	Srs Signature	Checked	Dose: ml
Pharmacy Notes and Signature			Quantity
Drug Name	Dose	Frequency	Route
Print: Drs name	Drs Signature	Start date	End date
Calculation	Srs Signature	Checked	Dose: ml
Pharmacy Notes and Signature			Quantity
Drug Name	Dose	Frequency	Route
Print: Drs name	Drs Signature	Start date	End date
Calculation	Srs Signature	Checked	Dose: ml
Pharmacy Notes and Signature			Quantity

Name:
Folder Number:
Date of birth:

Weight: **Allergies:**

Date	Drug	Dose	Heparin	Solution	Total ml	Concentration and Dosage Range	Doctor	Calculation	Checked	Given
Date	Drug	Dose	Heparin	Solution	Total ml	Concentration and Dosage Range	Doctor	Calculation	Checked	Given
Date	Drug	Dose	Heparin	Solution	Total ml	Concentration and Dosage Range	Doctor	Calculation	Checked	Given
Date	Drug	Dose	Heparin	Solution	Total ml	Concentration and Dosage Range	Doctor	Calculation	Checked	Given
Date	Drug	Dose	Heparin	Solution	Total ml	Concentration and Dosage Range	Doctor	Calculation	Checked	Given
Date	Drug	Dose	Heparin	Solution	Total ml	Concentration and Dosage Range	Doctor	Calculation	Checked	Given
Date	Drug	Dose	Heparin	Solution	Total ml	Concentration and Dosage Range	Doctor	Calculation	Checked	Given
Date	Drug	Dose	Heparin	Solution	Total ml	Concentration and Dosage Range	Doctor	Calculation	Checked	Given
Date	Drug	Dose	Heparin	Solution	Total ml	Concentration and Dosage Range	Doctor	Calculation	Checked	Given
Date	Drug	Dose	Heparin	Solution	Total ml	Concentration and Dosage Range	Doctor	Calculation	Checked	Given
Date	Drug	Dose	Heparin	Solution	Total ml	Concentration and Dosage Range	Doctor	Calculation	Checked	Given

Appendix E

UNIVERSITY of the
WESTERN CAPE

OFFICE OF THE DEAN
DEPARTMENT OF RESEARCH DEVELOPMENT

15 June 2012

To Whom It May Concern

I hereby certify that the Senate Research Committee of the University of the Western Cape has approved the methodology and ethics of the following research project by:
Prof P Mugabo (School of Pharmacy)

Research Project:	Prescribing practice at a tertiary paediatric hospital in South Africa.
Registration no:	12/5/6

Ms Patricia Josias
Research Ethics Committee Officer
University of the Western Cape

Private Bag X17, Bellville 7535, South Africa
T: +27 21 959 2988/2948 . F: +27 21 959 3170
E: pjosias@uwc.ac.za
www.uwc.ac.za

Appendix F

UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences
Human Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Ms S Ariefdien - Tel: [021]4066492 • Fax: [021]4066411
email: sumayah.ariefdien@uct.ac.za

26 June 2012

HREC REF: 315/2012

Prof Brian Eley,
Paediatrics
Red Cross War Memorial Children's Hospital

Dear Prof Eley, SCAH # 646/12

PROJECT TITLE: PRESCRIBING PRACTICE AT A TERTIARY LEVEL PAEDIATRIC HOSPITAL IN SOUTH AFRICA

Thank you for submitting your new study to the Faculty of Health Sciences Human Research Ethics Committee

It is a pleasure to inform you that the Ethics Committee has formally approved the above-mentioned study.

Approval is granted until 28 July 2013

Please submit an annual progress report (FHS016) if the research continues beyond the expiry date. Please submit a brief summary of findings if you complete the study within the approval period so that we can close our file (FHS010).

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC. REF in all your correspondence.

Yours sincerely

PROFESSOR MARC BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Appendix G

Mrs SE Roodt
Manager: Nursing
Email: Sandra.Roodt@pgwc.gov.za
Tel: +27 21 658 5187

03 July 2012

Mr H Sablay
5 Duine Rd
Rylands Estate
7764

Dear Mr Sablay

RESEARCH PROJECT: PRESCRIBING PRACTICE AT A TERTIARY LEVEL PAEDIATRIC HOSPITAL IN SOUTH AFRICA

Your request to conduct research dated 29 June 2012 has reference.

It is a pleasure to inform you that your request to conduct above-mentioned research at Red Cross War Memorial Children's Hospital has been formally approved by the Research Committee.

A condition of this approval is that results of this research be made available to Hospital Management. As this results has a particular significance for practices at RCWMCH we will appreciate it that you share this results with Hospital Management as soon as it becomes available.

Yours sincerely,

Mrs SE Roodt
RESEARCH COMMITTEE
R001/12

Appendix H

Western Cape Government
Health

Memo 8/2013

To: ALL CLINICAL AREAS

From: DR TA BLAKE

Date: 01 MARCH 2013

Re: INFLUENZA VACCINATION CAMPAIGN 2013

The Department of Health will be conducting a Flu vaccine campaign in Public Health facilities from **04 March 2013 to 19 April 2013**. The campaign will be conducted here at Red Cross War Memorial Children's Hospital for the stipulated period.

The campaign stock is available from the pharmacy.

The following groups of children will be vaccinated:

- Children at high risk for influenza-related complications because of underlying medical conditions including chronic pulmonary disease, asthma, cardiovascular disease (except hypertension), renal, hepatic, neurologic, haematologic or metabolic disorders (including diabetes mellitus), morbid obesity (BMI >40) and immunosuppression (including HIV-infected persons).
- Pregnant women – irrespective of stage of pregnancy.
- Children aged 6 months to 59 months.
- Children aged 6 months to 18 years on long-term aspirin therapy.

Trivalent inactivated influenza vaccine should not be administered to:

- People who have previously had a severe reaction (such as collapse caused by anaphylaxis), to any of the components which make up the vaccine, including eggs or the antibiotics neomycin or polymyxin.
- People who have had a severe reaction to previous influenza vaccination.
- People who developed "Guillain Barre Syndrome" within 6 weeks of getting the influenza vaccine.
- Children under 6 months of age.

Immunisation Plan for patients

Ward/area	Responsible person
Wards	Professional nurses in wards
S11	Professional nurses in the area
S12 and passage	Professional nurses in the area
IDC clinics	Professional nurses in the area
Speciality clinics	Professional nurses in the area
General OPD	Agency nurse (Mon-Fri: 8:30 – 15:30) at the station

Appendix I

Western Cape Government
Health

Memo 41/2013

To: All Clinicians

From: Dr Blake

Date: 12 November 2013

Re: PRESCRIPTION WRITING

Written prescriptions must be **written indelibly, clearly and legibly.** Preferably print (block letters) the name of the medicine prescribed to prevent misreading or misinterpretation. **No abbreviations allowed.**

The format must comply with the legal requirements that are summarised below:

- Name, surname, folder number, date of birth, gender, address of patient. (Information available on Patient sticker)
- Body weight
- Date
- Diagnosis/ ICD10 Code corresponding with medications prescribed.
- Approved name of medicine (generic), dosage form, strength and quantity to be supplied.
- When writing a prescription for a Schedule 6 medicine, write the strength and final quantity in both figures and words for a maximum of 30 days. All Schedule 6 prescriptions are not repeatable.
- Instructions for use (dose and frequency of administration)
  No Latin abbreviations allowed e.g. instead of tds write 8 hourly.
- Number and intervals of repeats.
- Prescriber's signature

www.westerncape.gov.za

Appendix J

MEDICINES AND RELATED SUBSTANCES ACT 101 OF 1965
(Gazette No. 1171, Notice No. 1002 dated 7 July 1965. Commencement date: 1 April 1966 [Proc. No. 94, Gazette No. 1413]
GENERAL REGULATIONS MADE IN TERMS OF THE MEDICINES AND RELATED SUBSTANCES ACT 101 OF 1965, AS AMENDED
Government Notice R510 in Government Gazette 24727 dated 10 April 2003. Commencement date: 2 May 2003 (see regulation 50).
As amended by:
Government Notice R1506 in Government Gazette 25593 dated 16 October 2003. Commencement date: 16 October 2003. Correction Notice – Government Notice 1565 in Government Gazette 25622 dated 31 October 2003.
Government Notice R389 in Government Gazette 33177 dated 12 May 2010. Commencement date: 12 May 2010.
Government Notice R766 in Government Gazette 36929 dated 14 October 2013. Commencement date: 14 October 2013.
Government Notice R870 in Government Gazette 37032 dated 15 November 2013. Commencement date: 15 November 2013 (except for the amendments addressing complementary medicines as per regulations 8, 9, 10, 40 and 48 of the General Regulations).
Government Notice R870 in Government Gazette 37032 dated 15 November 2013. Commencement date of the amendments addressing complementary medicines as per regulations 8, 9, 10, 40 and 48 of the General Regulations: 15 February 2014.
28. PARTICULARS WHICH MUST APPEAR ON A PRESCRIPTION OR ORDER FOR A MEDICINE
(1) Every prescription or order for a medicine must be written in legible print, typewritten or computer generated and signed in person by a medical practitioner, dentist, veterinarian or authorised prescriber or in the case of an order, an authorised person, and must at least state the following:
(a) the name, qualification, practice number and address of the prescriber or authorised person placing the order;
(b) the name and address of the patient in the case of a prescription or the name and address of the person to whom the medicines are delivered in the case of a prescription issued by a veterinarian;
(c) the date of issue of the prescription or order;
(d) the approved name or the proprietary name of the medicine;
(e) the dosage form;
(f) the strength of the dosage form and the quantity of the medicine to be supplied: Provided that in the case of Schedule 6 substances the quantity to be supplied shall be expressed in figures as well as in words: Provided further that where the prescriber has failed to express the quantity in figures as well as in words, the medical practitioner, dentist, veterinarian or pharmacist dispensing the medicine may, after obtaining confirmation from the prescriber, insert the words or figures that have been omitted;
(Regulation 28(1)(f) substituted by regulation 17 of Government Notice R870 in Government Gazette 37032 dated 15 November 2013)
(g) in the case of a prescription, instructions for the administration of the dosage, frequency of administration and the withdrawal period in the case of veterinary medicines for food producing animals;
(h) the age and sex of the patient and in the case of veterinary medicine, the animal species; and
(i) the number of times the prescription may be repeated.