Adverse drug reactions in paediatric in-patients in a South African tertiary hospital

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DECLARATION

I, **Memela MacDonald Makiwane**, hereby declare that the work contained in this assignment is my own original work and that it has not previously, neither in its entirety nor in part, been submitted at any university for a degree.

Signature: _____ Date: December 2017

ABBREVIATIONS

- Confidence Interval (CI).
- Drug induced liver injury (DILI).
- High-income countries (HIC).
- Human immunodeficiency virus (HIV).
- Immune reconstitution inflammatory syndrome (IRIS).
- Interquartile range (IQR).
- Low to middle-income countries (LMIC).
- Odds Ratio (OR).
- Rifampicin, isoniazid, pyrazinamide & ethambutol (RHZE).
- Tuberculosis (TB).

DEFINITIONS

- Adverse drug reaction (ADR) – a response to a medicine that is noxious and unintended and occurs at doses normally used for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function.
- Adverse event (AE) – any untoward medical occurrence in a patient, which does not necessarily have a causal relationship with the administered medication.
- Assent – a minor's affirmation of their parent's consent.
- Causality (assessment) – assessing the probability of a causal relationship between the suspected causative medicine(s) and the observed adverse patient medical outcome(s).
- Chart review – Review of medical notes, including prescriptions and laboratory reports.
- Child / paediatric patient – patients up to the age of 16.

- Consent – agreeing to participate in the research study and have ones medical records reviewed, recorded and analysed for study purposes.
- Disability – substantial disruption of a person's ability to conduct normal life functions or disruption in the patient's body function/structure, physical activities and/or quality of life.

- Principal Investigator (PI) – The first author.
- Seriousness – categorisation based on whether the patient's outcome was "fatal, life threatening, necessitates hospitalisation, prolongs existing hospitalisation or results in persistent or significant disability or incapacity."
- Severity – categorisation of the ADR as per Hartwig severity scale (table 2) into mild, moderate and severe.
- Type A ADR – augmented normal pharmacological action(s) of the drug which are dose related, and therefore predictable.

Abstract

Purpose: Paediatric patients have more adverse drug reaction (ADR) rates than adults due to off-label use of medicines and the prevalence data of ADRs in Sub-Saharan African children is limited. The aim was to describe the prevalence and nature of ADRs in paediatric (≤ 16 years old) in-patients at a tertiary hospital in South Africa.

Methods: We conducted a prospective study of paediatric in-patients to identify suspected ADRs. Children had to be admitted for at least 24 hours during the 3-month study period (1 December 2015 to 29 February 2016). The data collected included age, sex, diagnosis and medicines received. We assessed causality using the 10-question Naranjo probability scale and classified severity using the Hartwig severity scale.

Results: We found that 18.4% (52/282) of patients had 61 ADRs. The median age of patients with ADRs was 1.4 years (interquartile range (IQR): 0.5 – 5.3 years). ADR was the reason for admission in a third of the patients (31%; 16/52). Paediatric oncology patients suffered the majority of the ADRs (56.5%; 13/23), followed by HIV-infected patients on antiretroviral therapy (ART) (42.9%; 9/21) and tuberculosis (TB) patients (17.5%; 7/40). HIV-TB co-infected patients also experienced a high 30.8% (4/13) rate of ADRs. The majority of the ADRs were moderate 45.9% (28/61), while 42.6% (26/61) were mild, and 11.5% severe ADRs (7/61). These ADRs range from severe neutropaenia 4.9% (3/61) and drug induced liver injury (DILI) 4.9% (3/61) to mild cutaneous rashes 13.1% (8/61). There were no fatal ADRs, while 13.1% (8/61) ADRs were considered life threatening; 27.9% (17/61) necessitated and/or prolonged hospitalisation and 31.1% (19/61) resulted in persistent or significant disability or incapacity. Thirty eight percent of ADRs (23/61) were predictable. Paediatric oncology patients on chemotherapy were 7 times more likely to have ADR(s) than other patient groups [OR 7.3 (3.0 – 17.9), $p < 0.01$]. More ADRs were associated with chemotherapy 44.3% (27/61) and

antimicrobials 42.6% (26/61), while the other miscellaneous medicine classes were associated with 34.4% (21/61) of the recorded ADRs.

Conclusion: The prevalence of ADRs was 18.4% and in 31% the ADR was the reason for admission. The ADRs in paediatric oncology patients were expected, but of note nearly half the HIV-infected patients (43%) suffered an ADR.

Key words: Adverse drug reactions, prevalence, paediatric, in-patient, tertiary hospital, South Africa.

Introduction

The World Health Organisation (WHO) defines an adverse drug reaction (ADR) as a response to a medicine that is noxious and unintended and occurs at doses normally used for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function.[1] The importance of ADRs has been documented by 4 systematic reviews conducted between 1966 and 2012 in different paediatric therapeutic settings,[2–5] revealing that up to 39% of admissions are precipitated by ADRs often requiring more specialised care. However, the reported prevalence of ADRs varies from country to country in both high income[6] and low to middle income countries.[7–9] Limited and recent data in the sub-Saharan Africa (SSA)[9] suggests a strong association between paediatric ADRs with the treatment of infectious diseases. Approximately 25%[10] of the world's burden of human immunodeficiency virus (HIV)-tuberculosis (TB) co-infection is in South Africa, while the estimated annual risk of TB infection in children in the Western Cape Province ranges between 4% and 7%[11,12] per annum. TB and HIV co-infection necessitates polypharmacy, which poses as an important risk factor for ADRs.[2] Children in this setting may, therefore, have an inadequately documented increased risk of ADRs.

Aims

The primary objective was to determine the prevalence of ADRs in children admitted to Tygerberg hospital, a large tertiary hospital in South Africa. The secondary objectives were to determine the nature of the ADRs, assess causality and compare the prevalence of ADRs in the different patient sub-populations including patients with HIV, TB and/or cancer.

Methods

We conducted a 3-month prospective observational study of paediatric patients admitted to Tygerberg hospital. This study utilised chart reviews alone. We included paediatric (≤16 years) in-patients admitted to Tygerberg hospital for at least 24 hours between 1 December 2015 and 29 February 2016, whose parents gave informed consent (assent where relevant from the child participants).

The principal investigator (PI) conducted comprehensive chart reviews of the records of study participants, who met the above inclusion criteria, on alternate days of the week to identify suspected ADRs on and during admission. These suspected ADRs were investigated, using the Naranjo probability scale, which is a validated causality assessment tool.[13] This scale (table 1) answered 10 questions which were scored and used to categorise the probability of ADR causation into most probable (score ≥ 9), probable (score 5 – 8), possible (score 1 – 4) and doubtful (score ≤ 0). We excluded all (7) of the suspected ADRs that scored ≤ 0 on the Naranjo ADR scale (doubtful ADRs) from our ADR count.

The Hartwig severity scale (table 2) was used to classify ADR severity[14] while the seriousness of the ADR was assessed in accordance with the International Conference on Harmonisation (ICH) and Council for International Organizations of Medical Sciences (CIOMS) definitions based on patient's outcome. Seriousness was categorised based on whether the patient's outcome was "fatal, life threatening, necessitates hospitalisation, prolongs existing hospitalisation or results in persistent or significant disability or incapacity."[6]

Tygerberg hospital is a 1384 bed tertiary hospital with 24% (n=331) paediatric beds.[15] The study was conducted in 4 of the 12 paediatric wards, excluding neonatology, surgical wards and the intensive care units. The four wards were identified and selected in conjunction with the Head of Department of Child Health and Paediatrics. Data collected included demographic

(age, sex) and clinical data, namely diagnosis, reason for admission, suspected ADR(s) and associated medication. In patients with suspected ADR(s), history of previous ADR diagnosis, dose response of the suspected ADR, alternative explanation(s) of the suspected ADRs as well as predisposing factors were recorded and captured on a Microsoft Excel (version 14) spreadsheet (annexure 1).

Ethics

The study was approved by the Stellenbosch Health Research Ethics Committee (Reference S15/08/171). The study was conducted in accordance with the 2013 Declaration of Helsinki, the South African Department of Health's 2004 Guidelines as well as the South African Good Clinical Practice (SA-GCP) Guidelines. Unique patient identification numbers were used to anonymity during data analysis and reporting.

Statistical analysis

The data was analysed, using Stata version 14.2 (Stata Corporation, College Station, TX).[16] Non-normally distributed data were described using medians and ranges. For descriptive analyses of patient characteristics and between patient groups, the chi-squared and Wilcoxon rank-sum (Mann-Whitney) tests were used. We used logistic regression analysis to evaluate covariates for occurrence of ADRs. We included all the study variables in the multivariate analysis and eliminated the non-statistically significantly associated variable via backward elimination. We expressed data as absolute numbers and percentages. We considered p-values < 0.05 to be statistically significant.

Results

A total of 305 patients were admitted for at least 24 hours, of whom 7.5% (23/305) declined consent to participate in the study. Of the 282 consenting patients (median age 1.4 years, range

9 days to 16.3 years, IQR 0.5 – 5.3 years), 18.4% (52/282) experienced at least one ADR. The underlying diagnosis was tuberculosis (TB) in 40, a cancer in 23 patients, 21 were HIV-infected and 13 had HIV-TB co-infection, while 198 had miscellaneous diagnoses. Of the 52 patients who experienced an ADR(s), 13 were paediatric oncology patients, 9 were HIV-infected, 7 had TB, 4 had HIV-TB co-infection, while 23 had miscellaneous diagnoses (figures 1 and 2). ADRs were the primary reason for admission in 30.8% (16/52) patients. There were 61 ADRs for these 52 patients, of whom 47 had only 1 ADR, 3 had 2 ADRs and 2 had 4 ADRs each (Table 3). According to the Naranjo ADR probability scale, the suspected ADRs were classified (table 5) as possible 61% (31), probable 31% (19) and most probable 8% (5).

The majority of ADRs in our study were mild 42.6% (26/61) or moderate 45.9% (28/61), while only 11.5% (7/61) were severe as shown in table 6. More ADRs were associated with chemotherapy 44.3% (27/61) and antimicrobials 42.6% (26/61), while the other miscellaneous medicine classes were associated with 34.4% (21/61) of the recorded ADRs. More than half 55.7% (34/61) of the ADRs were serious, although none was fatal, but 13.1% (8/61) were life threatening, 27.9% (17/61) necessitated or prolonged hospitalisation and 14.8% (9/61) resulted in persistent or significant disability or incapacity. More than a third 37.7% (23/61) of ADRs in our study were type A (dose related).

Serious ADRs included oncology patients with anaemia (n=2) and febrile neutropaenia (n=3); HIV-infected patients with severe diarrhoea (n=1) and rash and vomiting (n=1); TB-infected patients with drug induced liver injury (DILI) (n=2) and immune reconstitution inflammatory syndrome (IRIS) (n=1); patients with TB-HIV co-infections were also admitted with IRIS (n=2); and other diagnoses included acute kidney injury (n=1), ileus (n=1), constipation (n=1) and viral meningitis (n=1).

Life threatening ADRs included an ampicillin associated anaphylaxis in a 13-month old boy admitted for bronchiolitis obliterans. Two TB-infected girls aged 2 and 3 years, respectively, were admitted for DILI related to anti-TB treatment. One 7-year old girl with acquired immunodeficiency syndrome (AIDS) had aplastic anaemia while on co-trimoxazole prophylaxis. Febrile neutropenia after chemotherapy was the reason for admission in 3 patients aged 6, 9 and 10 years old respectively. One neonate (27-day old male), was admitted with an acute kidney injury with metabolic acidosis and hypoglycaemia associated with the use of a topical salicylate preparation (wintergreen ointment) applied to the umbilicus.

The following were considered disabling or persistent serious ADRs: viral meningitis and Cushing's syndrome attributed to prednisone in a 2-year old child on chronic treatment for auto-immune haemolytic anaemia; Cushing's syndrome in a 10-year old treated for leukaemia; 3 oncology patients on the combination of doxorubicin, L-Asparaginase, etoposide, carboplatin and vincristine for acute lymphoblastic leukemia (ALL) treatment had pancytopaenia and 3 patients on anti-TB treatment with DILI.

A higher prevalence 56.5% (13/23) of ADRs occurred in oncology patients on chemotherapy, followed by HIV-infected patients on antiretroviral therapy (ART) 42.9% (9/21). HIV-TB co-infected patients also experienced a high 30.8% (4/13) rate of ADRs. We found that 17.5% (7/40) of patients treated for TB had at least one ADR while the miscellaneous group of the patients had the lowest prevalence 11.6% (23/198) of ADRs. Oncology patients on chemotherapy had a 7-fold increased risk of having an ADR [OR: 7.3 (3.0 – 17.9), $p < 0.0001$)]. Age, sex, HIV status and TB status were not predictive of the possibility of experiencing an ADR (table 8).

Discussion

Our findings are consistent with those of larger studies elsewhere[9,18–22], which suggest that ADRs are a significant cause of morbidity, perhaps requiring increased pharmacovigilance. The high (18.4%) prevalence of ADRs, of which almost a third (31%) were the cause of patient hospitalisation, falls within the ranges seen in both low to middle income countries (LMIC) and high income countries (HIC) such as Ethiopia[9] in SSA and United Kingdom (UK).[18] Eshetie et al[9] reported an ADR rate of 9.2% in an Ethiopian study of 634 admissions, while a larger study of 6,601 admissions in the UK by Thiesen et al[18] revealed a higher prevalence of 17.7%. However, systematic reviews of studies of ADRs in children revealed varied rates of ADRs ranging from 0.6% to 16.8%.[2,3]

In our study, only malignancy was statistically significantly associated with the prevalence of ADRs whereas HIV, TB and others were not. HIV-TB co-infection was also surprisingly not predictive of ADR occurrence even though nearly a third (31%) of patients with co-infection experienced ADRs. This lack of association is likely due to the small study sample size since HIV and TB infections are treated with multiple anti-infective medicines that, similar to cancer treatment protocols, are also known to be associated with high rates of ADRs.[8,19,20] Moreover, polypharmacy as indicated by both HIV and TB treatment, individually, and in co-infection, is likely predictive of ADRs. We could not assess the effect of polypharmacy (≥5 medicines) in our study because information on medicines was only collected for the patients who experienced suspected ADRs. However, only 11.5% (6/52) of patients who experienced ADRs had ≤ 4 medicines prescribed. The majority 88.5% (46/52) of patients who experienced ADRs had polypharmacy.

The majority of the ADRs in our study were associated with chemotherapy and antimicrobials, 44.3% (27/61) and 42.6% (26/61), respectively. All the other drug categories,

combined, were associated with less ADRs, 34.4% (21/61). This is consistent with findings in systematic reviews[2,3] which reported strong associations between antimicrobials, polypharmacy and ADRs. Smyth et al found that 17% of studies showed anti-infective agents were the therapeutic class most frequently associated with ADRs.[2] Moreover, the treatment of childhood malignancies is known to have one of the highest ADR rates due to the complications of intensive multi-drug cancer treatment protocols.[14,21]

Also consistent with the international studies[2,3,6,8,9,14] which assessed a very small proportion of suspected ADRs with a high degree of certainty, most (61%) of the suspected ADRs in our study could only be assessed as possible ADR while 31% were assessed as probable and only a few (8%) were assessed as most probable. Even a large multicentre cohort of 1340 admissions conducted by Rashed et al only assessed 7.9% of identified ADRs as definite while the majority were assessed as possible 26.8% and probable 65.3%.[6] Equally few (7.3%) ADRs were assessed as definite by Thiesen et al.[20] These findings highlight the difficulties of attributing adverse clinical outcomes to the treatment rather than to the disease process. This difficulty increases when multiple medicines are combined in complex treatment regimens as it becomes more difficult to isolate the individual culprit medicine(s). A significant proportion (38%) of ADRs in our study were type A (dose related), which means they were predictable. This highlights the importance of good pharmacovigilance to help anticipate and mitigate the morbidity caused by these ADRs.

Our study contributes to the limited data and documents the prevalence of ADRs in paediatric in-patients in the SSA and South Africa in particular. We believe the strength of our study lies in its prospective nature which enables better identification of ADRs than a retrospective study would. However, notable limitations include the short duration of three months and the resultant small sample size; the study was conducted from a single site. Some ADRs might

have been missed and some ADRs such as nausea in inexpressive, under age children may have been missed. The study also did not analyse the effect of off-label medication use, as well as length of hospital stay on the prevalence of ADRs. The specificity of ADR causality could not be established as we could not determine which components of the different treatment regimens were responsible for the ADR. We therefore listed all medicines plausibly linked to the identified ADR as culprit medicines. A larger sample size with power to investigate more sub-population comparisons and perhaps inclusion of other relevant potentially predictive variables such as off-label medicines should be considered for future studies.

Conclusion

The high prevalence (18.4%) of ADRs and the high proportion (38%) of potentially preventable ADRs give impetus to institute a concerted and sustained drive towards improved pharmacovigilance. These data provide important baseline information that may prove crucial for augmentation of pharmacovigilance programmes at Tygerberg and similar hospitals.

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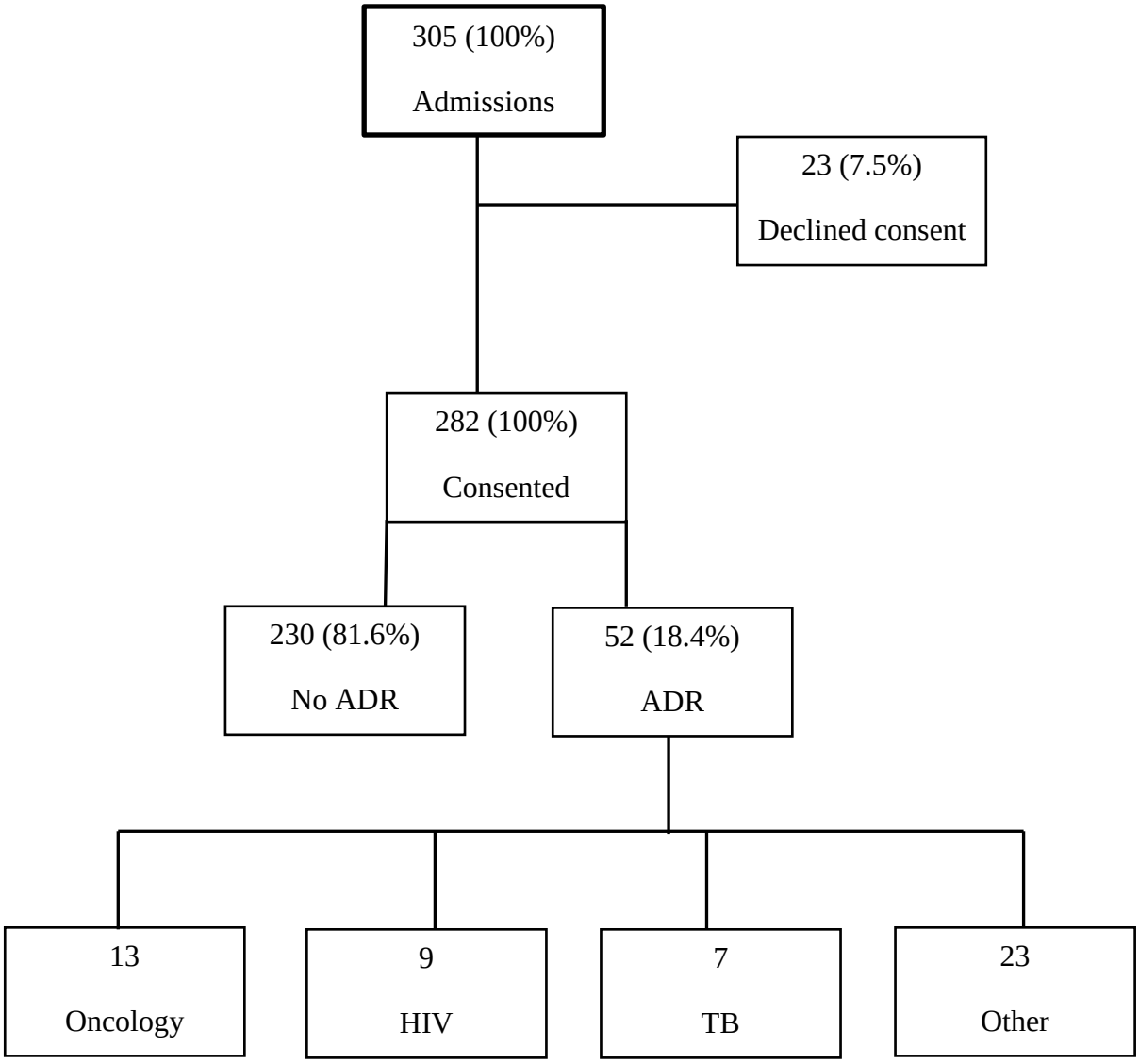
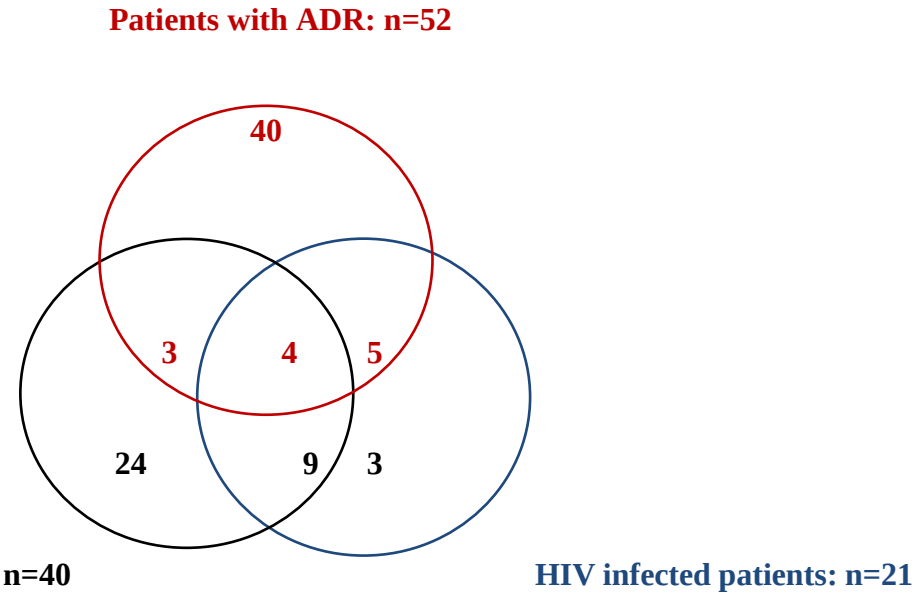
Figure 1: Patients admitted during the study period



ADR: Adverse drug reaction; HIV: Human immunodeficiency virus; TB: Tuberculosis.

Figure 2: Relationship between ADR and the overlap of HIV-TB co-infection



ADR: Adverse drug reaction; HIV: Human immunodeficiency virus; TB: Tuberculosis

Table 1: Naranjo Adverse Drug Reaction (ADR) Probability Scale[13]

Questions	**Yes**	**No**	**Don't know**
Are there previous conclusive reports on the ADR?	+1	0	0
Did the ADR appear after the medicine was administered?	+2	-1	0
Did the ADR improve when the medicine was discontinued?	+1	0	0
Did the ADR appear with rechallenge with medicine?	+2	-1	0
Are there alternative causes of the ADR?	-1	+2	0
Did the reaction appear when placebo was given?	-1	+1	0
Was the medicine detected in blood at toxic levels?	+1	0	0
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0
Did the patient have a similar reaction to the same or similar medicine in any previous exposure?	+1	0	0
Was the ADR confirmed by any objective evidence?	+1	0	0
Each question is rated from -2 to +2. A total score ≥9 points: most probable; 5 to 8: probable; 1 to 4: possible and ≤ 0: doubtful			

ADRs: Adverse Drug Reactions

Table 2: Hartwig severity scale[14]

Severity	Description
Mild	ADRs which are self-limiting, resolve without treatment and do not contribute to prolongation of length of stay.
Moderate	ADRs which require therapeutic intervention and hospitalization prolonged by 1 day but resolved in <24 h or change in drug therapy or specific treatment to prevent a further outcome.
Severe	ADRs which result in disability, prolonged hospital stay or lead to hospitalization, required intensive medical care, life threatening or led to the death of the patient.

ADRs: Adverse Drug Reactions

Table 3: Summary of ADRs and implicated drugs

ADR	Description	Patients (n)	Drug(s) implicated
Gastrointestinal	Vomiting	4	Metronidazole; vincristine; lopinavir/ritonavir.
	Diarrhoea	2	Lopinavir/ritonavir; azathioprine.
	Constipation	8	Ferrous sulphate; baclofen; tilidine; morphine.
	Ileus	1	Tilidine.
Renal impairment and electrolyte disorders	Hyperkalaemia	1	Potassium chloride;
	Hypokalaemia	5	Salbutamol; furosemide; insulin.
	Hypocalcaemia	1	Unknown traditional medicine; oil of wintergreen.
	Hypernatremia	1	Normal saline.
	Hypomagnesaemia	1	Dexamethasone.
	Hypertension	1	Vincristine.
Metabolic and endocrine disorders	Hypoglycaemia,	2	Insulin.
	Metabolic acidosis	1	Oil of wintergreen.
	Cushing's syndrome	2	Prednisone.
Haematological	Pancytopenia	3	Doxorubicin; etoposide; carboplatin; vincristine; L-

	Anaemia	4	Asparaginase. Cotrimoxazole; doxorubicin; etoposide; carboplatin; vincristine.
	Leukopaenia	1	L-Asparaginase; cotrimoxazole.
	Febrile neutropaenia	6	Etoposide, carboplatin doxorubicin; vincristine.
	Tumour lysis syndrome	1	L-Asparaginase; dexamethasone; vincristine; methotrexate.
Infections	Vaginal candidiasis	1	Azithromycin; ceftazidime; amikacin.
	Viral meningitis	1	Azathioprine; prednisone.
Cutaneous rashes and miscellaneous	Rash	8	Cotrimoxazole; isoniazid; abacavir; lopinavir/ritonavir; RHZE ertapenem; ampicillin; efavirenz; cloxacillin.
	DILI	3	RHZE; acyclovir.
	IRIS	2	RHZE; zidovudine; lamivudine.
	Anaphylaxis	1	Ampicillin.

ADR: Adverse drug reaction; DILI: Drug induced liver injury; IRIS: Immune reconstitution inflammatory syndrome; RHZE: rifampicin, isoniazid, pyrazinamide & ethambutol fixed dose combination tablets

Table 4: Prevalence of ADRs per disease subgroup

	Patients with ADR(s)	**Total number patients**	**Prevalence (%)**
Malignancy	13	23	56.5
HIV infected	9	21	42.9
TB infected	7	40	17.5
Others	23	198	11.6

ADR: Adverse drug reaction; HIV: Human immunodeficiency virus; TB: Tuberculosis

Table 5: ADR causality assessment

ADR	**Naranjo score**	**n (%)**
Most probable	≥ 9	5 (8)
Probable	5 - 8	19 (31)
Possible	1 - 4	37 (61)
Total		61 (100)

ADR: Adverse drug reaction

Table 6: ADR severity categories

Severity	**Proportion (%)**
Mild	26/61 (42.6)
Moderate	28/61 (45.9)
Severe	7/61 (11.5)

ADR: Adverse drug reaction

Table 7: Seriousness assessment

Seriousness	**n (%)**
Fatal	0 (0)
Life threatening	8 (13)
Cause/prolong hospitalisation	17 (28)
Persistent/significant disability	9 (15)

Table 8: Factors associated with ADRs

Factor	Univariate logistic regression			Multivariate logistic regression		
	OR	95%CI	P-value	OR	95%CI	P-value
Age	1.00	0.99 – 1.01	0.48	1.00	0.99 – 1.01	0.97
Sex (Male)	0.62	0.34 – 1.14	0.12	0.54	0.28 – 1.03	0.06
HIV status	1.01	0.26 – 3.96	0.18	1.04	0.23 – 4.68	0.96
TB status	0.93	0.39 – 2.23	0.87	0.80	0.28 – 2.28	0.68
Oncology status	7.33	3.01 – 17.89	<0.01	8.71	3.39 – 22.37	<0.01

ADR: Adverse drug reaction; OR: Odds ratio; 95%CI: 95% Confidence interval; p-value: probability value

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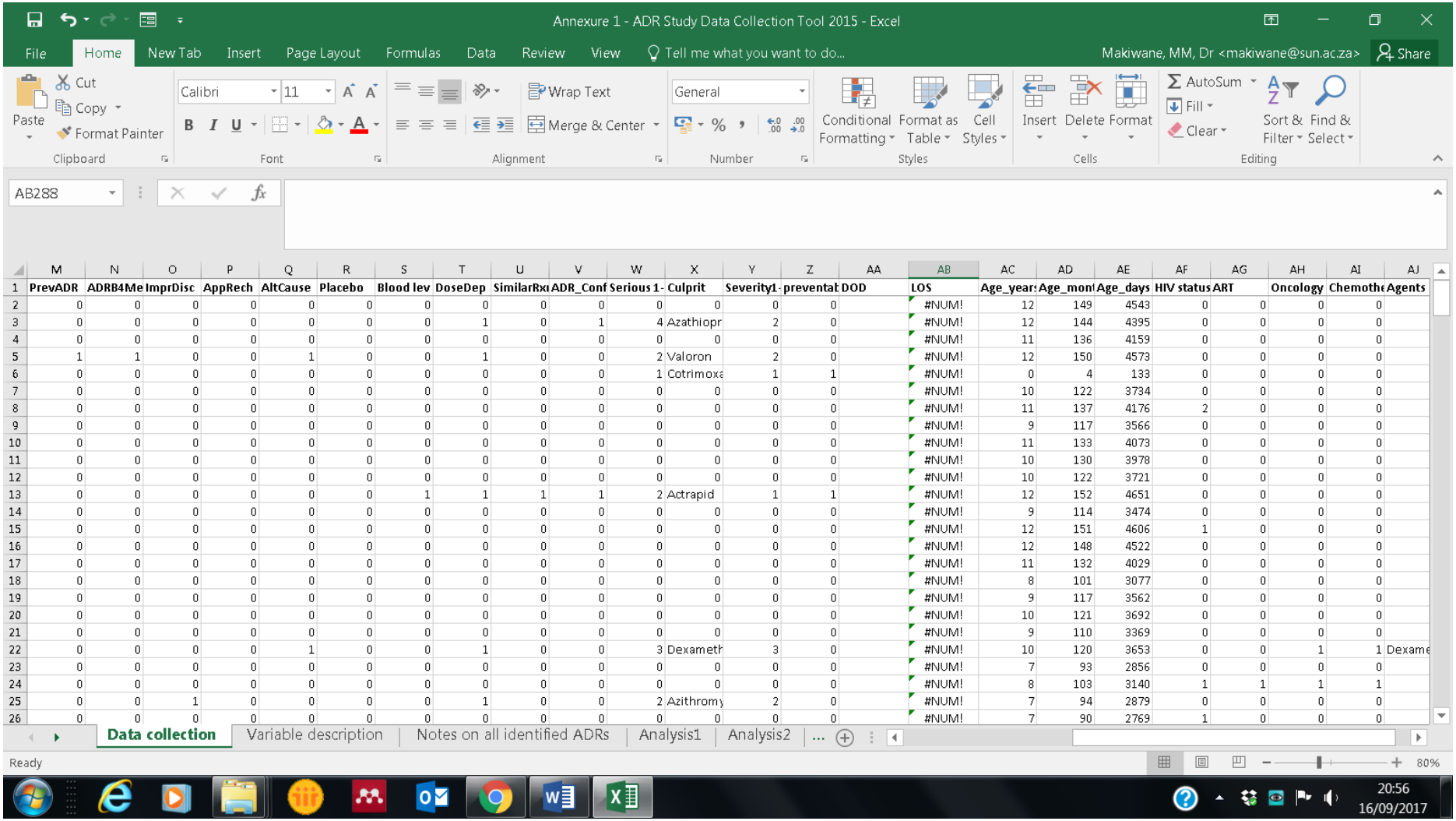
Annexure 1: ADR Study Data Collection Tool 2015 - Excel



	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z	AA	AB	AC	AD	AE	AF	AG	AH	AI	AJ
1	PrevADR	ADRB4Me	ImprDisc	AppRech	AltCause	Placebo	Blood lev	DoseDep	SimilarRx	ADR_Conf	Serious 1-	Culprit	Severity1-	preventat	DOD	LOS	Age_years	Age_mont	Age_days	HIV status	ART	Oncology	Chemothe	Agents
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0		#NUM!	12	149	4543	0	0	0	0	
3	0	0	0	0	0	0	0	1	0	1	4	Azathiopr	2	0		#NUM!	12	144	4395	0	0	0	0	
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0		#NUM!	11	136	4159	0	0	0	0	
5	1	1	0	0	1	0	0	1	0	0	2	Valoron	2	0		#NUM!	12	150	4573	0	0	0	0	
6	0	0	0	0	0	0	0	0	0	0	1	Cotrimoxa	1	1		#NUM!	0	4	133	0	0	0	0	
7	0	0	0	0	0	0	0	0	0	0	0	0	0	0		#NUM!	10	122	3734	0	0	0	0	
8	0	0	0	0	0	0	0	0	0	0	0	0	0	0		#NUM!	11	137	4176	2	0	0	0	
9	0	0	0	0	0	0	0	0	0	0	0	0	0	0		#NUM!	9	117	3566	0	0	0	0	
10	0	0	0	0	0	0	0	0	0	0	0	0	0	0		#NUM!	11	133	4073	0	0	0	0	
11	0	0	0	0	0	0	0	0	0	0	0	0	0	0		#NUM!	10	130	3978	0	0	0	0	
12	0	0	0	0	0	0	0	0	0	0	0	0	0	0		#NUM!	10	122	3721	0	0	0	0	
13	0	0	0	0	0	0	1	1	1	1	2	Actrapid	1	1		#NUM!	12	152	4651	0	0	0	0	
14	0	0	0	0	0	0	0	0	0	0	0	0	0	0		#NUM!	9	114	3474	0	0	0	0	
15	0	0	0	0	0	0	0	0	0	0	0	0	0	0		#NUM!	12	151	4606	1	0	0	0	
16	0	0	0	0	0	0	0	0	0	0	0	0	0	0		#NUM!	12	148	4522	0	0	0	0	
17	0	0	0	0	0	0	0	0	0	0	0	0	0	0		#NUM!	11	132	4029	0	0	0	0	
18	0	0	0	0	0	0	0	0	0	0	0	0	0	0		#NUM!	8	101	3077	0	0	0	0	
19	0	0	0	0	0	0	0	0	0	0	0	0	0	0		#NUM!	9	117	3562	0	0	0	0	
20	0	0	0	0	0	0	0	0	0	0	0	0	0	0		#NUM!	10	121	3692	0	0	0	0	
21	0	0	0	0	0	0	0	0	0	0	0	0	0	0		#NUM!	9	110	3369	0	0	0	0	
22	0	0	0	0	1	0	0	1	0	0	3	Dexameth	3	0		#NUM!	10	120	3653	0	0	1	1	Dexame
23	0	0	0	0	0	0	0	0	0	0	0	0	0	0		#NUM!	7	93	2856	0	0	0	0	
24	0	0	0	0	0	0	0	0	0	0	0	0	0	0		#NUM!	8	103	3140	1	1	1	1	
25	0	0	1	0	0	0	0	1	0	0	2	Azithromy	2	0		#NUM!	7	94	2879	0	0	0	0	
26	0	0	0	0	0	0	0	0	0	0	0	0	0	0		#NUM!	7	90	2769	1	0	0	0	

UNIVERSITY OF STELLENBOSCH
DEPARTMENT OF MEDICINE
DIVISION OF CLINICAL PHARMACOLOGY

Adverse drug reactions in paediatric in-patients in a South African tertiary hospital: A prospective observational study.

Study protocol submitted in partial fulfillment of the degree Master of Medicine (MMED)Clinical Pharmacology

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8/4/2015

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Title: Adverse drug reactions in paediatric in-patients in a South African tertiary hospital: A prospective observational study.

Background and rationale

The World Health Organisation defines an adverse drug reaction (ADR) as a response to a medicine that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function (1). Notably, this definition is not as inclusive as that of adverse events (AEs) which includes all adverse outcomes that occur to patients who take medication without regard to the causal relationship between the medication and the adverse outcome concerned. ADRs (a subset of AEs) are therefore focused on the harmful outcome in the patient whereas adverse drug events include medication errors and intentional overdose which do not necessarily have to result in negative clinical effects (1). Medication errors involve mistakes in the medicine administration process which do not necessarily result in negative clinical effects. This distinction is very important since health care facilities which fail to recognize the difference between medication errors and ADRs may concentrate their efforts on systems that improve the accuracy of medicine administration but that produce only marginal reductions in patient harm (2).

The prevalence of ADRs may be higher than generally reported, considering treatment with medicine is the most common medical intervention. Rieder and colleagues reported that an average of 4 prescriptions per child per annum were written (3), confirming the high frequency of treatment with medication. However, this frequency is much higher in certain populations of children, such as those with chronic diseases and malignancies, who tend to use more prescription medication and hence have a higher risk of ADRs (4–7). The importance of ADRs has been highlighted by four systematic reviews conducted between 1966 and 2012 in different therapeutic settings in children, (4,6,8,9). Even though the reported prevalence of ADRs varies from country to country in the developed world, the consistent finding is that the prevalence of ADRs in hospitalised paediatric patients (9.5%) is at least comparable to that of adult patients (10). ADRs are of significant public health and health economic concern since as many as 2% of paediatric patients were admitted as a direct result of ADRs, leading to additional hospitalisation days and treatment costs (10). Thirty nine per cent of the admissions precipitated by ADRs were due to serious ADRs (6) which often required more specialised care . This signifies considerable morbidity and mortality (4) and highlights the importance of investigating the actual prevalence of ADRs and causes thereof.

An assessment (11) of the impact of ADRs on patients revealed that the majority, 73%, of ADRs had a low impact on patients (i.e. necessitated minor treatment) while only 2% had a severe impact (i.e. caused permanent damage or life threatening to patients). Considering the high prevalence of ADRs, 2% translates to significant numbers. Catastrophic ADRs, defined as those that result in death are rare, 0.1%, while those with moderate impact (i.e. requiring moderate increase in treatment but causing no permanent harm to the patient) occur more commonly, 25%. This assessment also revealed that as much as 55% of ADRs were either

definitely or possibly avoidable. This implies poor management of ADRs in terms of inadequate anticipation and prevention which is probably due to inadequate awareness among clinicians. In countries where the prevalence of ADRs is known such as the Netherlands, ADRs were found to increase the average length of hospital stay by 6.2 days resulting in average additional cost of €2500 (12) per patient.

Smyth and group highlighted the association between certain therapeutic classes of medicines such as opioids and ADRs (8). This finding is also supported by Rashed et al 2012 who correlated the frequent use of high-risk medicines such as morphine with the higher incidence of ADRs in the United Kingdom than other European countries (10). Paediatric oncology has one of the highest ADR rates due to the complications of intensive multidrug treatment protocols of childhood malignancies (3).

Despite the extensive literature in the developed world, including the four systematic reviews discussed above, the developing world, including Sub-Saharan Africa lacks data on paediatric ADRs. However, a recent adult study found the prevalence of ADRs in hospitalised adults to be 14% (13). Considering that children are at higher risk of ADRs partly because of a significantly higher off-label medicines use than in the adult population (14), a higher prevalence of ADRs than 14% is expected in the hospitalised paediatric population of a local hospital. The unavailability of local prevalence data on ADRs in the paediatric population limits our understanding of factors that influence which patients are more likely to develop ADRs than others. The often quoted rates of commonly occurring ADRs are derived from efficacy studies (Yaffe & Aranda, 1992) which are frequently poorly representative of the medicine's target population. Clinical trials for marketing approval are sufficiently large (a few hundreds or thousands of subjects) to evaluate efficacy but inadequate for characterising the frequency of ADRs. These studies typically exclude relevant patients such as those using other medicines than the ones under evaluation. In paediatrics this is further compounded by having fewer numbers of study participants per age group, such as premature neonates and adolescents, when studies get done at all.

Spontaneous reporting of ADRs by healthcare workers remains low (4,6,9,12,15) despite well-established reporting means such as the yellow card system. This is despite a significant proportion (15%) of in-patients who have ADRs with a considerable proportion (6.5%) of those admissions having been precipitated by such ADRs (7,16). Reasons for the under-reporting of ADRs have been documented (17) as varying from a lack of time, competing care priorities, uncertainty about medicine and ADR causal relationship, administrative difficulties as well as lack of awareness of the relevance and importance of reporting ADRs (17).

Data in Sub-Saharan Africa are scanty despite the fact that there are children in this region in various hospitals receiving multiple and usually concurrent medicines, some of which are likely associated with ADRs such as those typically observed in oncology wards (6,9). There are additional challenges in reporting ADRs in children in particular. For instance, young children may be unable to communicate discomfort and therefore depend on observant clinicians or caregivers to recognise changes related to the manifestation of the adverse event. The resultant low detection might partly explain the low reporting rate of ADRs (9).

While the literature shows that ADRs are predominantly related to medication used in chronic diseases of life style including cardiovascular, hypoglycaemics and anti-inflammatory drugs, the predominant causes of ADRs in adults in a Sub-Saharan African hospital was found to be related to medication directed at the treatment of infectious diseases (13). This is probably as a result of the current HIV infection pandemic which fuels opportunistic infectious diseases such as tuberculosis, fungal and bacterial infections within this region. It is therefore reasonable to expect a difference in the prevalence and nature of ADRs in the paediatric populations of Sub-Saharan Africa.

Approximately a quarter (18) of the world's burden of HIV associated TB is in South Africa where the estimated annual risk of TB infection in children in the Western Cape Province ranges between 4% and 7% (18) per annum. TB and HIV co-infection necessitates polypharmacy which which is a risk factor for ADRs (8). However, the prevalence of ADRs in this paediatric population is not documented. This knowledge gap needs to be closed so as to enable healthcare resource planning and delivery. This study intends to document the prevalence, nature and management of paediatric adverse drug events in a tertiary hospital in Cape Town, South Africa.

The current clinical management of adverse drug reactions (5) requires that the following steps be followed:

1. Identification of the possibility of an ADR.
2. Assessment through a thorough medicine history, timing and rationale thereof, examination and exclusion of potential confounders.
3. Analysis of the differential diagnosis and systematic causality assessment.
4. Assistance of the patient with relief of symptoms usually by withdrawal of the potential medication causing an adverse drug event and instituting appropriate symptomatic and supportive treatment.
5. Documentation and management of complications when necessary.
6. Alert the patient, family, other healthcare workers as well as the relevant authorities such as the regulatory and pharmacovigilance units.

This process is both labour intensive and requires significant amounts of time. In order to improve efficiency at identifying ADRs, trigger tools which may assist investigators to conduct focused patient chart reviews have been used by other researchers (2,19–21). Trigger tools are clues or information in patient records which may 'trigger' further investigation to determine the presence or absence of an adverse drug reaction. In the United Kingdom (21) application of the trigger tool reduced patient record review time by an average of more than 90% while other studies reported significantly more yield of adverse reactions than routine spontaneous reporting systems (19,20). Using a trigger tool to identify potential adverse drug reactions therefore appears to allow for more efficient patient record reviews and increase the chances of identifying more ADRs than when none is used. However, these trigger tools need to be modified and tailored to the specific study environment as demonstrated by Rozich et al (2) when they changed the tool to a manual and less expensive one which

could be used in hospitals with no electronically integrated patient record systems. The original trigger tools were expensive and had limited utility since they required substantial information technology capital and the attendant requirement of training (2). Relying on trigger tools to identify ADRs may further limit detection of those ADRs associated with, or presenting differently from, the predefined triggers, thereby potentially limiting the findings to predefined ADRs.

Combining the traditional intensive patient chart reviews with a trigger tool might increase the yield and identify more adverse drug event than either method alone. However, due to resource constraints as well as limited utility of trigger tools (22,23), this study will utilise the gold standard (22,23), chart reviews, alone.

Aim

To describe the prevalence and nature of adverse drug reactions (ADRs) in paediatric inpatients in a South African tertiary hospital.

The primary objective of this study is to:

1. Determine the prevalence of ADRs

The secondary objectives are to:

1. Characterize the nature of the ADRs
2. Characterize the drugs implicated (causality assessment), including possible predisposing factors for ADRs
3. Compare the prevalence of ADRs in different patient subpopulations such as HIV and/or tuberculosis infected and oncology patients

Methods

A 3-month prospective observational study of paediatric patients admitted to general paediatric wards will be conducted. All paediatric in-patients, aged under 18 years, admitted in those wards at Tygerberg hospital for at least 24 hours during the 3-month period will be included.

This study will use a comprehensive and intensive chart review, the gold standard in pharmacoepidemiology (22,23), in order to minimise missing any frequently occurring ADRs. The lead investigator will screen all patient records on alternate days of the week to identify any harmful clinical and laboratory patient outcomes during admission. All suspected ADRs will be discussed weekly with the two senior supervisors (a clinical pharmacologist and a paediatrician). The patient records and laboratory results (where available and appropriate) of the patient(s) with suspected ADRs will be assessed to determine by consensus whether the observed harmful outcome is an ADR. For those adverse events deemed to be ADRs, a simple validated causality assessment tool, the Naranjo probability scale (26) will be applied to assess causality. Due to its simplicity, the Naranjo scale is the most widely used causality assessment method (26) since its introduction in 1981. This scale answers 10 questions which are scored and used to categorise the probability of ADR causation into most probable, probable, possible and doubtful as follows:

Table 1: Naranjo Adverse Drug Reaction (ADR) Probability Scale

Questions	Yes	No	Don't know
Are there previous conclusive reports on the ADR?	+1	0	0
Did the ADR appear before the medicine was administered?	+2	-1	0
Did the ADR improve when the medicine was discontinued?	+1	0	0
Did the ADR appear with rechallenge with medicine?	+2	-1	0
Are there alternative causes of the ADR?	-1	+2	0
Did the reaction appear when placebo was given?	+1	+1	0
Was the medicine detected in blood at toxic levels?	+1	0	0
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0
Did the patient have a similar reaction to the same or similar medicine in any previous exposure?	+1	0	0
Was the ADR confirmed by any objective evidence?	+1	0	0
Each question is rated from -2 to +2. A total score ≥9 points: most probable; 5 to 8: probable; 1 to 4: possible and ≤ 0: doubtful			

The Hartwig severity scale (table 2) will be used to classify ADR severity in terms of being mild, moderate or severe (25) while the seriousness of the ADR will be assessed in accordance with the International Conference on Harmonisation (ICH) and Council for International Organizations of Medical Sciences (CIOMS) definitions (26) based on patient's outcome. Seriousness will therefore be categorised on the basis of whether the patient outcome is "fatal, life threatening, necessitates hospitalisation, prolongs existing hospitalisation or results in persistent or significant disability or incapacity"(26).

Table 2: Hartwig severity scale

Severity	Description
Mild	ADRs which are self-limiting, resolve without treatment and do not contribute to prolongation of length of stay.
Moderate	ADRs which require therapeutic intervention and hospitalization prolonged by 1 day but resolved in <24 h or change in drug therapy or specific treatment to prevent a further outcome.
Severe	ADRs which result in disability, prolonged hospital stay or lead to hospitalization, required intensive medical care, life threatening or led to the death of the patient.

Tygerberg hospital uses a paper-based health record and drug chart system which incorporates an electronic system for laboratory results.

Once an eligible patient completes 24 hours of hospital admission, the lead investigator will review their hospital records to screen for clinical and laboratory indication of the possibility of an ADR (documented as: definite/probable/possible). If present, grading, causality and preventability assessments will be done.

The study will therefore collect data from all eligible in-patient records necessary for determining whether or not an ADR exists in a participant, determining the characteristics of such ADRs including grading, causality and preventability as detailed in Annexure 1 (Excel workbook: ADR Study Data Collection Tool 2015).

During hospital stay, patients will repeatedly be screened and assessed for the development of ADRs on alternate days. The clinicians in charge of patients in the chosen wards will also alert the lead investigator to investigate when ADRs are suspected. Upon discharge, inpatient records will again be reviewed (when necessary, i.e. confirm or exclude ADR) to document presence or absence of ADR.

Ethical considerations

All admissions to the selected paediatric wards will be included in the study. As this is an observational study which will not assign any intervention to the study participants or even alter their current standard of care, the study participants are not likely to be harmed by the study. Ethics approval and a waiver of informed consent will be sought from the Stellenbosch Health Research Ethics Committee before the study commences. Confidentiality will be strictly maintained at the data analysis and reporting level by using unique patient identification numbers rather than patient identification data such as name, national identification number or hospital folder number.

All identified adverse drug reactions will be reported to the treating clinicians who will be encouraged to inform the patients or their caregivers while managing the adverse drug reactions as per their standard protocol.

Envisaged outputs of this study, which will be conducted in accordance with the 2013 Declaration of Helsinki, the South African Department of Health's 2004 Guidelines as well as the South African Good Clinical Practice (SA-GCP) Guidelines are:

1. Publication
2. Conference presentations
3. Masters of Medicine (MMed) degree project

Permission for access to medical records for the purposes of the study will also be sought from the Chief Executive Officer of Tygerberg Hospital prior to the commencement of the study.

Sample size calculation

Considering the proportion of ADRs reported in adult inpatients in a South African study (13) of 14% and the expectation of a higher adverse drug reaction in children based on the higher prevalence of off-label drug use,

we liberally increased the expected proportion to 21% (i.e. a 50% increase on the reported adult prevalence). According to the simplified sample size calculation for a population of undefined size (15), using an accepted margin of error $\alpha = 0.05$, a 95% confidence interval and power of 90%, the sample size required to determine the prevalence of ADRs in paediatric inpatients of Tygerberg hospital would be 255 patients.

Based on the Tygerberg hospital's wards G3 and G10 current combined admissions averaging 110 patients per month, a larger sample which would improve our power for analyses pertinent to secondary objectives is obtainable in the allocated 3 months.

Statistical analysis

Data will be entered on an Excel spread sheet and all patients who complete the study will be included in the analysis. Total days of admission will be documented and prescription episodes will be used to compute the rates of ADRs and their different characteristics of interest such as seriousness and preventability. Categorical data will be expressed as proportions (%), and continuous data as means with standard deviations (SD). Nonparametric data will be summarized using medians and interquartile ranges (IQR) and compared using the Kruskal–Wallis test. Comparisons with the local data on adult ADRs as well as and the international data on in-patient paediatric ADRs will be discussed.

Table 3: Study timeline

Activity	**Year 2015**						**Year 2016**					
	2	4	6	8	10	12	2	4	6	8	10	12
Protocol development and HREC approval												
Data collection												
Data cleaning, analysis and write-up												
Submission to faculty												
Publication												

Study budget

Self-funded R1,000.00.

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Protocol Synopsis

Title: Adverse drug reactions in paediatric in-patients in a South African tertiary hospital: A prospective observational study.

MMed Clinical Pharmacology Candidate: Memela M. Makiwane.

Supervisors: Dr EH Decloedt, Prof B Rosenkranz & Prof M Kruger.

Aim and objectives

To describe the prevalence and nature of adverse drug reactions (ADRs) in paediatric in-patients in a South African tertiary hospital.

The objectives of this study are to:

1. Determine the prevalence of ADRs.
2. Characterize the nature of the ADRs.
3. Characterize the drugs implicated (causality assessment), including possible predisposing factors for ADRs.
4. Compare the prevalence of ADRs in different patient subpopulations such as HIV and/or tuberculosis infected and oncology patients.

Background and rationale

Despite the extensive literature in the developed world, the developing world, including Sub-Saharan Africa lacks data on paediatric ADRs. The unavailability of local prevalence data on ADRs in paediatrics limits our understanding of determinants of ADRs which negatively impacts their management. ADRs are of significant public health and health economics concern since as many as 2% of paediatric patients were admitted as a direct result of an ADRs, leading to additional hospitalisation days and treatment costs (Rashed et al. 2012). Thirty nine per cent of the admissions precipitated by ADRs were due to serious ADRs (Impicciatore et al. 2001) which often required more specialised care . This signifies considerable morbidity and mortality (Aagaard et al. 2010) and highlights the importance of investigating the actual local prevalence of ADRs and causes thereof.

Study design

A 3-month prospective observational study of paediatric patients aged under 18 years, admitted to Tygerberg hospital paediatric wards G3 and G10 for at least 24 hours, within the study period, will be conducted. Comprehensive and intensive chart reviews will be undertaken on alternate days of the week by the lead investigator who will screen all patient records in participating wards to identify harmful clinical and laboratory patient outcomes at and during admission. Identified ADRs will be graded for severity. Causality, preventability and seriousness assessments will be done.

Ethics

A waver of informed consent will be requested from the University of Stellenbosch Research Ethics Committee. De-identified data analysis will be performed. Identified ADRs will be reported to treating clinicians for appropriate management.

Anticipated outcomes and significance

Documentation of the prevalence and determinants of ADRs in paediatric in-patients in South Africa.

UNIVERSITY OF STELLENBOSCH
DEPARTMENT OF MEDICINE
DIVISION OF CLINICAL PHARMACOLOGY

Adverse drug reactions in paediatric in-patients in a South African tertiary hospital: A prospective observational study.

Standard Operating Procedures (SOP)

Memela MacDonald Makiwane
MBChB (UCT); Dip HIV Man (SA); Dip Pharm Med (Stell)

11/6/2015

Supervisors:
Dr EH Decloedt MBChB; BSc Hons (Pharm); FCCP (SA); MMED (Clin Pharm)

Prof B Rosenkranz MD; PhD; FFPM

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Purpose: This procedure provides instruction on the step by step conduct of the study.

Procedure:

1. Consenting:

1.1. The Principal Investigator administers the consent and assent to the parent and the minor participant, respectively, on admission.

1.2. All paediatric admissions, aged under 18 years, admitted in the participating wards are to be invited to participate in the study.

2. Comprehensive and intensive chart review:

2.1. Once a consented patient completes 24 hours of hospital admission, the lead investigator will review their hospital records to screen for clinical and laboratory indication of the possibility of an ADR.

2.2. The Naranjo Adverse Drug Reaction (ADR) Probability Scale will be used to determine probability and present as definite/probable/possible).

2.3. Assess whether the reason (diagnosis) for admission is an ADR

2.4. Assess whether the patient has experienced or is experiencing an ADR during admission.

2.5. If ADR is detected, grading, causality and preventability assessments will be done as follows:

2.6. The Hartwig severity scale will be used to classify ADR severity in terms of being **mild, moderate or severe.**

2.7. Seriousness of the ADR will be assessed in accordance with the International Conference on Harmonisation (ICH) and Council for International Organizations of Medical Sciences (CIOMS) definitions based on patient's outcome as "**fatal, life threatening, necessitates hospitalisation, prolongs existing hospitalisation or results in persistent or significant disability or incapacity**

2.8. The Hartwig severity scale will be used to classify ADR severity in terms of being **mild, moderate or severe.**

2.9. Clinicians in charge of patients in the chosen wards will also alert the lead investigator to investigate when ADRs are suspected.

2.10. Principal Investigator will present weekly findings to at least one supervisor at a meeting to discuss and agree (by consensus) on the classification, grading, causality and preventability assessments of the detected ADRs.

2.11. Upon discharge, inpatient records will again be reviewed (when necessary, i.e. confirm or exclude ADR) to document presence or absence of ADR.

3. Documentation:

3.1. Data will be documented on an excel spread sheet – Protocol Annexure 1

3.2. Data cleaning and analysis to begin in March 2016.

Annexure 2: Parent/guardian/caregiver Information leaflet and Informed Consent Form

Title: Adverse drug reactions in paediatric in-patients in a South African tertiary hospital: A prospective observational study.

Reference number: S15/08/171.

Study Doctor: Dr Memela M Makiwane MB.ChB (UCT), Dip HIV Man (SA), PGDip Pharm Med (Stell).

Address: 7060 Clinical Building, Faculty of Medicine and Health Sciences, Stellenbosch University.

Contact number: 021 938 9335

Introduction: You are being asked to take part in this research study because we want to determine how often adverse drug reactions (ADRs) happen to children admitted to Tygerberg Hospital. We also want to determine if your child has suffered an adverse drug reaction and, if so, how ill this made your child. An **adverse drug reaction** is any unwanted, uncomfortable, or dangerous effect that a patient may suffer from after taking a medicine (drug). For example, a patient with an infection may have an adverse drug reaction such as a rash after receiving an antibiotic.

This study has been approved by the **Health Research Ethics Committee at Stellenbosch University** and will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

What is this research study all about?

We want to know how often adverse drug reactions (ADRs) occur in children admitted to Tygerberg Hospital. We also want to know if your child has suffered an adverse drug reaction and, if so, how ill this made your child. We also want to know what causes these adverse drug reactions.

Why have you been invited to participate?

We are inviting all children who need to be admitted to selected children's wards of Tygerberg Hospital during the study period to take part in the study.

What will your responsibilities be?

The study doctor will check your child's hospital records and results of his/her tests to see if s/he got ill because of an adverse drug reaction, got an adverse drug reaction while in hospital or not. You will not be required to do any activity for the study.

Will you benefit from taking part in this research?

The study doctor will inform you whether your child has suffered an adverse drug reaction, if that is so, and why that has happened.

Are there any risks involved in your taking part in this research?

There are no risks for you or your child. This research is only looking at what normally happens to children on treatment in hospitals.

If you do not agree to take part, what alternatives do you have?

You are free to refuse taking part in the study and your child will still receive the same treatment required for the illness for which s/he is admitted.

Who will have access to your medical records?

Only the doctors treating your child and the study doctor will know s/he is in the study. When the research is finished, other doctors will be told about what was found but no one else will know that your child was in the study. That is because no one's name will be included when telling other doctors about what was found by the research.

What will happen in the unlikely event of some form of injury occurring as a direct result of your taking part in this research study?

It is very unlikely that any injury could result from taking part in the study since the study only observes what normally happens to children admitted and treated in hospital.

Will you be paid to take part in this study and are there any costs involved?

No, your child and you will not be paid to take part in the study.

Is there anything else that you should know or do?

You can contact the Health Research Ethics Committee at 021 938 9207 if you have any concerns or complaints that have not been adequately addressed by your study doctor.

Declaration by parent/guardian/caregiver:

By signing below, I ……..……..agree for my dependent to take part in this research study.

I declare that:

- I have read or had read to me this information and consent form and it is written in a language I understand.
- I have had a chance to ask questions and all my questions have been adequately answered.
- I understand that taking part in this study is **voluntary** and I have not been pressurised to take part.
- I may choose to leave the study at any time and will not be penalised or prejudiced in any way.

Signed at (*place*) ..... on (*date*) ……..…….. 2015.

..... …..

Signature of parent/guardian/caregiver

Declaration by investigator

I *(name)* …….. declare that:

- I explained the information in this document to …….
- I encouraged him/her to ask questions and took adequate time to answer them.
- I am satisfied that s/he adequately understands all aspects of the research, as discussed above

Signed at (*place*) ..... on (*date*)…….. 2015.

.....	.....
Signature of investigator	**Signature of witness**

Bylaag 2: Inligtingsblaadjie en oorwoëtoestemmingsvorm vir ouer/voog/versorger

Titel: Nadelige middelreaksies by pediatriese hospitaalpasiënte in ’n Suid-Afrikaanse tersiêre hospitaal: ’n Voornemende waarnemingstudie

Verwysingsnommer: S15/08/171

Studiedokter: Dr. Memela M Makiwane MB,ChB (UK), Dip MIV/Vigs-best (SA), NGDip Farm Gen (Stell)

Adres: Kliniese Gebou 7060, Fakulteit Geneeskunde en Gesondheidswetenskappe, Universiteit Stellenbosch

Kontaknommer: 021 938 9335

Inleiding: Jy word gevra om aan hierdie navorsingstudie deel te neem omdat ons wil bepaal hoe dikwels nadelige middelreaksies plaasvind by kinders wat in Tygerberg-hospitaal opgeneem word. Ons wil ook bepaal of jou kind ’n nadelige middelreaksie ervaar het en, indien wel, hoe siek dit jou kind gemaak het. ’n **Nadelige middelreaksie** is enige ongewenste, ongerieflike of gevaarlike effek wat ’n pasiënt kan ervaar nadat ’n middel (medikasie) geneem is. ’n Persoon met ’n infeksie kan byvoorbeeld ’n nadelige middelreaksie, soos ’n uitslag, ondervind nadat ’n antibiotikum toegedien is.

Die studie is deur die **Gesondheidsnavorsingsetiekkomitee van die Universiteit Stellenbosch** goedgekeur en sal uitgevoer word in ooreenstemming met die etiekriglyne en -beginsels van die internasionale Verklaring van Helsinki, Suid-Afrikaanse riglyne vir goeie kliniese praktyk en die Mediese Navorsingsraad se etiekriglyne vir navorsing.

Waaroor gaan hierdie navorsingstudie?

Ons wil weet hoe gereeld nadelige middelreaksies plaasvind by kinders wat in Tygerberg-hospitaal opgeneem word. Ons wil ook bepaal of jou kind ’n nadelige middelreaksie ervaar het en, indien wel, hoe siek dit jou kind gemaak het. Ons wil ook weet wat hierdie nadelige middelreaksies veroorsaak.

Hoekom is jy genooi om deel te neem?

Ons nooi alle kinders wat by gekose kindersale van Tygerberg-hospitaal tydens die studietydperk opgeneem moet word om aan die studie deel te neem.

Wat sal jou verantwoordelikhede wees?

Die studiedokter sal jou kind se hospitaalrekords en uitslae van sy/haar toetse nagaan om te bepaal of hy/sy siek geword het as gevolg van ’n nadelige middelreaksie en of jy ’n nadelige middelreaksie ervaar het terwyl jy in die hospitaal was. Daar sal nie van jou verwag word om enige aktiwiteit vir die studie uit te voer nie.

Sal jy voordeel trek uit deelname aan hierdie navorsing?

Die studiedokter sal jou in kennis stel as jou kind ’n nadelige middelreaksie ervaar het, en indien wel, waarom dit gebeur het.

Is daar enige risiko's verbonde aan jou deelname aan hierdie navorsing?

Daar is geen risiko's vir jou of jou kind nie. Hierdie navorsing behels bloot 'n ondersoek na wat gewoonlik met kinders gebeur met behandeling in hospitale.

Wat sal gebeur as jy nie instem om deel te neem nie?

Jy kan weier om aan die studie deel te neem, en jou kind sal steeds dieselfde behandeling ontvang wat nodig is vir die siekte waarvoor hy/sy opgeneem is.

Sal enige iemand toegang tot jou kind se mediese rekords hê?

Net die dokters wat jou kind behandel en die studiedokter sal weet dat hy/sy aan die studie deelneem. Wanneer die navorsing voltooi is, sal ons ander dokters inlig oor wat ons bevind het, maar hulle sal nie weet dat jou kind aan die studie deelgeneem het nie. Dit is omdat niemand se naam gebruik sal word wanneer ons ander dokters van die bevindinge van die navorsing vertel nie.

Wat sal gebeur in die onwaarskynlike geval dat 'n vorm van besering voorkom as 'n direkte gevolg van deelname aan hierdie navorsingstudie?

Dit is hoogs onwaarskynlik dat enige besering sal plaasvind as gevolg van deelname aan die studie, aangesien die studie slegs waarneming behels van wat normaalweg met kinders gebeur wat in 'n hospitaal opgeneem en behandel word.

Sal jy betaal word om aan die studie deel te neem en is daar enige koste daarby betrokke?

Nee, jy en jou kind sal nie betaal word om aan die studie deel te neem nie en dit sal jou ook niks kos nie.

Is daar enigiets anders wat jy moet weet of doen?

Jy kan die Gesondheidsnavorsingsetiekkomitee skakel by 021 938 9207 as jy enige bekommernisse of klagtes het wat nie voldoende deur jou studiedokter hanteer is nie.

Verklaring deur ouer/voog/versorger:

Deur hier onder te onderteken, stem ek, ……., in dat my afhanklike aan hierdie navorsingstudie mag deelneem.

Ek verklaar dat:

- Ek hierdie inligting en toestemmingsvorm gelees het of dat dit vir my voorgelees is en dat dit geskryf is in 'n taal wat ek verstaan.
- Ek kans gekry het om vrae te vra en dat al my vrae bevredigend beantwoord is.
- Ek verstaan dat my deelname aan hierdie studie **vrywillig** is en dat ek nie onder druk geplaas is om deel te neem nie.
- Ek verstaan dat ek kan besluit om die studie op enige tyd te verlaat en dat ek op geen manier gepenaliseer of benadeel sal word nie.

Onderteken by (*plek*) ..... op (*datum*) ..... 2015.

....

Handtekening van ouer/voog/versorger

Verklaring deur ondersoeker / dokter

Ek *(naam)*, ..., verklaar dat:

- Ek die inligting in hierdie dokumente aan ..... verduidelik het.
- Ek hom/haar aangemoedig het om vrae te vra en genoeg tyd gebruik het om dit te beantwoord.
- Ek tevrede is dat hy/sy alle aspekte van die navorsing, soos hier bo bespreek, voldoende verstaan.

Onderteken by (*plek*) ..... op (*datum*)..... 2015.

....

Verklaring deur ondersoeker / dokter **Handtekening van getuie**

Isihlomelo sesi-2: Iphetshana elineeNkcukacha zoMzali / zomgcini womntwana / zomnonopheli neFomu yesiVumelwano.

Isihloko: Iingxaki zokungamelani namachiza kubantwana abazizigulane ezilaliswe kwisibhedlele esikumgangatho ophezulu eMzantsi Afrika: Uphononongo oluqwalasela okunokwenzeka.

Inombolo yesalathisi: S15/08/171.

Ugqirha woPhononongo: uGqr. Memela M Makiwane MB.ChB (UCT), Dip HIV Man (SA), PGDip Pharm Med (Stell).

Idilesi: 7060 Clinical Building, Icandelo leNzululwazi ngezaMayeza nezeMpilo, kwiYunivesithi yaseStellenbosch.

Inombolo yoqhagamshelwano: 021 938 9335

Intshayelelo: Uyacelwa ukuba uthathe inxaxheba kolu phononongo lophando kuba sifuna ukufumanisa iingxaki zokungamelani namachiza (ADRs) kubantwana abalaliswa kwiSibhedlele saseTygerberg. Sifuna nokufumanisa ukuba ingaba umntwana wakho ukhe wanengxaki yokungamelani namachiza kwaye, ukuba kunjalo, kumenze wagula njani umntwana wakho. **Iingxaki zokungamelani namachiza** zizo naziphi na iimpembelelo ezingafunekiyo, zokwenza ungakhululeki okanye ubesengozini xa usebenzise amayeza (ichiza). Umzekelo, isigulane esiye sosuleleka singanayo ingxaki yokungamelani namachiza nto leyo efana nerhashalala emva kokusebenzisa amayeza alwa ukosuleleka yintsholongwane.

Olu phononongo luvunywe **yiKomiti ejongene nokuziPhatha kuPhando lwezeMpilo kwiYunivesithi yaseStellenbosch** kwaye luza kwenziwa ngokwemigaqo nemithetho-siseko yeSibhengezo sikazwelonke saseHelsinki, iMigaqo yaseMzantsi Afrika kwiZenzo eziLungileyo kwezeMpilo neMigaqo yokuziPhatha kweBhunga loPhando kwezeMpilo (MRC).

Lumalunga nantoni olu phononongo?

Sifuna ukwazi ukuba zibakho kangakanani na iingxaki zokungamelani namachiza (i-ADR) kubantwana abalaliswe kwiSibhedlele saseTygerberg. Sifuna nokwazi ukuba ingaba umntwana wakho ebekhe wanayo na ingxaki yokungamelani namachiza kwaye, ukuba kunjalo, kumenze wagula njani umntwana wakho. Sifuna nokwazi ukuba yintoni eyenze le ngxaki yokungamelani namachiza.

Kutheni umenyiwe ukuba uthathe inxaxheba?

Simeme bonke abantwana abazakulaliswa kumawadi abantwana akhethiweyo kwiSibhedlele saseTygerberg ngexesha kusenziwa uphononongo ukuba bathathe inxaxheba kolu phononongo.

Luza kuba yintoni uxanduva lwakho?

Ugqirha owenza uphononongo uza kujonga iingxelo zomntwana zasesibhedlele neziphumo zovavanyo lwakhe ukujonga ukuba uguliswe kuba enengxaki yokungamelani namachiza, ubenengxaki yokungamelani namachiza ngeli xesha asesibhedlele okanye engekho sesibhedlele. Akukho nto kuza kufuneka uyenze kolu phononongo.

Ingaba uza kuxhamla ngokuthatha kwakho inxaxheba kolu phando?

Ugqirha owenza uphononongo uza kukwazisa ukuba umntwana wakho unengxaki yokungamelani namachiza, ukuba kunjalo, yintoni eyenze oko.

Ingaba bukhona ubungozi obubandakanyekayo xa uthatha inxaxheba kolu phando?

Akukho bungozi obuza kubakho kuwe okanye kumntwana wakho. Olu phando lujonga ukuba yintoni eqhelekileyo eyenzekayo kubantwana abafumana unyango kwizibhedlele.

Ukuba awufuni kuthatha inxaxheba, zeziphi ezinye izinto ezinokwenziwa?

Ukhululekile ukuba ungala ukuthatha inxaxheba kuphononongo kwaye umntwana wakho uhleli eza kulufumana unyango olufunekayo kwisigulo anaso alaliselwe sona

Ngubani oza kuzifumana iingxelo zakho zonyango?

Ngoogqirha kuphela abanyanga umntwana wakho nogqirha owenza uphononongo abaza kumazi ukuba ukolu phononongo. Xa lugqityiwe uphando, abanye oogqirha baza kuxelelwa oko kufunyanisiweyo kodwa akukho namnye oza kumazi ukuba umntwana wakho ebekolu phononongo. Oku kwenzeka kuba akukho gama lamntu lifakwayo xa kuchazelwa abanye oogqirha oko kuye kwafunyaniswa luphando.

Kuza kwenzeka ntoni xa kunokubakho umenzakalo owenzeke ngenxa yokuthatha kwakho inxaxheba kolu phando?

Akufane kwenzeke ukuba umntu afumane nawuphi na umenzakalo obangelwa kukuthatha kwakho inxaxheba njengoko uphononongo luqwalasela nje kuphela oko kuqhele ukwenzeka kubantwana abalaliswe esibhedlele.

Ingaba uza kuhlawulwa na ngokuthatha kwakho inxaxheba kolu phononongo kwaye ingaba zikhona na iindleko ezibandakanyekayo?

Hayi, wena nomntwana wakho anizi kuhlawulwa ngokuthatha kwenu inxaxheba kolu phononongo.

Ingaba ikhona na enye into ekufuneka uyazi okanye uyenze?

Ungaqhagamshelana neKomiti ejongene nokuziPhatha kuPhando lwezeMpilo ku-021 938 9207 ukuba kukho nantoni na ekuxhalabisayo okanye nasiphi na isikhalazo esingaqwalaselwanga ngokwaneleyo ngugqirha wakho wophononongo.

Isibhengezo somzali/somgcini womntwana/somnonopheli:

Ngokutyikitya ngezantsi, mna …….. ndiyavuma ukuba lowo uxhomekeke kum angathatha inxaxheba kolu phando.

Ndazisa ukuba:

- Ndizifundile okanye ndizifundelwe ezi nkcukacha nale fomu yesivumelwano kwaye zibhalwe ngolwimi endilwaziyo.

- Ndibe nalo ithuba lokubuza imibuzo kwaye yonke imibuzo yam iphendulwe ngokwanelisayo.
- Ndiyakuqonda ukuba ukuthatha kwam inxaxheba kolu phononongo oko ndikwenza **ngokuzithandela** kwaye andifakwanga xinezelelo lokuba ndithathe inxaxheba.
- Ndingakhetha ukuluyeka uphononongo nanini na kwaye andizi kohlwaywa okanye ndigwetywe nangayiphi na indlela.

Ityikitywe (*indawo*) e..... (*umhla*) nge-..... ngo-2015.

....

Ukutyikitya komzali/komgcini womntwana/komnonopheli

Isibhengezo somphandi / sogqirha omlalisayo

Mna *(igama)* .....ndazisa ukuba:

- Ndizicacisile iinkcukacha ezikolu xwebhu ku.....
- Ndimkhuthazile ukuba abuze imibuzo kwaye ndathatha ixesha elaneleyo ukuyiphendula.
- Ndanelisekile ukuba uyiqonde ngokwaneleyo yonke imiba yophando, njengoko ichaziwe ngentla

Ityikitywe (*indawo*) e..... (*umhla*) nge-..... ngo-2015.

....

Ukutyikitya komphandi/kogqirha omlalisayo **Ukutyikitya kwengqina**

Annexure 3: Participant Information Leaflet and Assent Form

Adverse drug reactions in paediatric in-patients in a South African tertiary hospital: A prospective observational study.

Researcher: Dr Memela M. Makiwane MB.ChB (UCT), Dip HIV Man (SA), PGDip Pharm Med (Stell)

What is RESEARCH*?*

Research is something we do to find new knowledge about the way things (and people) work. We use research projects or studies to help us find out more about disease or illness. Research also helps us to find better ways of helping, or treating children who are sick.

What is this research research all about?

We want to see how often adverse drug reactions (ADRs) happen to children admitted to Tygerberg Hospital. We also want to see if you have had an adverse drug reaction and how ill that made you. An **adverse drug reaction** is any unwanted, uncomfortable, or dangerous effect that may happen to someone after taking a medicine (drug). For example, someone may get a rash after taking medicine.

Who is doing the research?

Dr Memela Makiwane of Tygerberg hospital and Stellenbosch University.

What will happen to me in this study?

If you agree to be in the study, Dr Makiwane will check your hospital records and results of your tests to see if you got ill because of an adverse drug reaction, got an adverse drug reaction while in hospital or not. If Dr Makiwane finds an adverse drug reaction he will tell the doctor(s) who are treating you. You will be part of the study until you leave the hospital to go home unless you change your mind and choose to stop being in the study while you are still in hospital.

Can anything bad happen to me?

No. This research is only looking at what normally happens to children on treatment in hospitals.

Can anything good happen to me?

Yes. You will be told if you had an adverse drug reaction or not.

Will anyone know I am in the study?

Only the doctors treating you and the study doctor will know you are in the study. When the research is finished, other doctors will be told about what was found but no one else will know that you were in the study. That is because no one's name will be included when telling other doctors about what was found in the research.

Who can I talk to about the study?.

Dr Memela Makiwane

Phone: 0219389335

Email: Makiwane@sun.ac.za

What if I do not want to do this?

You can say you do not want to be in the study and no one can force you to be. Even if you say yes today, you can still change your mind and stop being in the study any time just by saying so. That will not get you into any trouble. It will also not make anyone change the way you are being treated in hospital.

Do you understand this research study and are you willing to be in it?

YES	NO

Do you understand that you can pull out of the study at any time?

YES	NO

_____ _____

Name and/or Signature of Child Date

Bylaag 3: Inligtingsblaadjie en instemmingsvorm vir deelnemer

Nadelige middelreaksies by pediatriese hospitaalpasiënte in ’n Suid-Afrikaanse tersiêre hospitaal: ’n Voornemende waarnemingstudie

Navorser: Dr. Memela M Makiwane MB,ChB (UK), Dip MIV/Vigs-best (SA), NGDip Farm Gen (Stell)

Wat is NAVORSING?

Navorsing is iets wat ons doen om nuwe kennis te kry van hoe dinge (en mense) werk. Ons gebruik navorsingsprojekte of -studies om ons te help om meer oor siektes uit te vind. Navorsing help ons ook om beter maniere te vind om siek kinders te help of te behandel.

Waaroor gaan hierdie navorsing?

Ons wil sien hoe dikwels nadelige middelreaksies plaasvind by kinders wat by Tygerberg-hospitaal opgeneem word. Ons wil ook sien of jy ’n nadelige middelreaksie gehad het en hoe siek dit jou gemaak het. ’n **Nadelige middelreaksie** is enige ongewenste, ongerieflike of gevaarlike effek wat iemand kan ervaar nadat ’n middel (medikasie) geneem is. Iemand kan byvoorbeeld ’n uitslag kry nadat hy of sy medisyne gedrink het.

Wie doen die navorsing?

Dr. Memela Makiwane van Tygerberg Hospitaal en die Universiteit Stellenbosch.

Wat sal met my gebeur in die studie?

As jy instem om aan die studie deel te neem, sal dr. Makiwane na jou hospitaalrekords en die uitslae van jou toetse kyk om te sien of jy siek geword het van ’n nadelige middelreaksie of ’n nadelige middelreaksie gehad het terwyl jy in die hospitaal was. As dr. Makiwane ’n nadelige middelreaksie vind, sal hy die dokter of dokters wat jou behandel, daarvan vertel. Jy sal deel wees van die studie totdat jy die hospitaal verlaat of huis toe te gaan, of tensy jy van plan verander en nie meer aan die studie wil deelneem terwyl jy nog in die hospitaal is nie.

Kan enigiets sleg met my gebeur?

Nee. In hierdie navorsing kyk ons net wat gewoonlik met kinders gebeur wanneer hulle in hospitale behandel word.

Kan enigiets goed met my gebeur?

Ja. Ons sal vir jou sê of jy 'n nadelige middelreaksie gehad het of nie.

Sal enigiemand weet ek neem aan die studie deel?

Net die dokters wat jou behandel en die studiedokter sal weet dat jy aan die studie deelneem. Wanneer die navorsing voltooi is, sal ons ander dokters vertel wat ons gevind het, maar hulle sal nie weet dat jy aan die studie deelgeneem het nie. Dit is omdat niemand se naam gebruik sal word wanneer ons ander dokters vertel wat ons in die studie gevind het nie.

Met wie kan ek oor die studie praat?

Dr. Memela Makiwane

Telefoon: 021 938 9335

E-pos: Makiwane@sun.ac.za

Sê nou ek wil nie deelneem nie?

Jy kan sê jy wil nie aan die studie deelneem nie, en niemand kan jou dwing om deel te neem nie. Selfs al sê jy vandag ja, kan jy steeds van plan verander en enige tyd vir ons sê as jy nie meer daaraan wil deelneem nie. Jy sal glad nie in die moeilikheid kom nie. Dit sal ook nie die manier waarop jy in die hospitaal behandel word, verander nie.

Verstaan jy hierdie navorsingstudie en is jy bereid om daaraan deel te neem?

JA	NEE

Verstaan jy dat jy enige tyd kan ophou om aan die studie deel te neem?

JA	NEE

_____ _____

Naam en/of handtekening van kind Datum

Isihlomelo sesi-3: Iphetshana elineenkcukacha lalowo uthatha inxaxheba neFomu yesiVumelwano

Iingxaki zokungamelani namachiza kubantwana abazizigulane ezilaliswe kwisibhedlele esikumgangatho ophezulu eMzantsi Afrika: Uphononongo oluqwalasela okunokwenzeka.

Umphandi: uGqr Memela M. Makiwane MB.ChB (UCT), Dip HIV Man (SA), PGDip Pharm Med (Stell)

Yintoni UPHANDO*?*

Uphando yinto esiyenzayo ukufumana ulwazi olutsha malunga nendlela izinto (nabantu) abasebenza ngayo. Sisebenzisa iiprojekthi zophando okanye uphononongo ukusinceda sazi ngakumbi ngezifo okanye ngezigulo. Uphando lukwasinceda sifumane iindlela ezingcono zokunceda okanye zokunyanga abantwana abagulayo.

Lumalunga nantoni olu phando?

Sifuna ukwazi ukuba zibakho kangakanani na iingxaki zokungamelani namachiza (i-ADR) kubantwana abalaliswe kwiSibhedlele saseTygerberg. Sifuna nokwazi ukuba ingaba wena wakhe wanayo na ingxaki yokungamelani namachiza kwaye kukwenze wagula njani oko. **Iingxaki zokungamelani namachiza** zizo naziphi na iimpembelelo ezingafunekiyo, zokwenza ungakhululeki okanye ubesengozini xa usebenzise amayeza (ichiza). Umzekelo, umntu anganerhashalala emva kokusebenzisa amayeza.

Ngubani owenza uphando?

NguGqr Memela Makiwane wesibhedlele saseTygerberg nakwiYunivesithi yaseStellenbosch.

Kuza kwenzeka ntoni kum kolu phononongo?

Ukuba uyavuma ukuba kolu phononongo, uGqr Makiwane uza kujonga iingxelo zakho zasesibhedlele neziphumo zovavanyo lwakho ajonge ukuba ingaba uguliswe kuba unengxaki yokungamelani namachiza, ufumene ingxaki yokungamelani namayeza ngoku usesibhedlele okanye ungekho sesibhedlele. Ukuba uGqr Makiwane ufumanisa ingxaki yokungamelani namachiza uza kuxelela u(oo)gqirha okunyangayo. Uza kuba yinxalenye yolu phononongo ude uphume esibhedlele ugoduke ngaphandle kokuba utshintsha iingqondo zakho ukhethe ukuyeka ukuba kolu phononongo ngeli xesha usesesibhedlele.

Ingaba ikhona into eza kwenzeka kum?

Hayi. Olu phando lujonga kuphela okuqheleke ukwenzeka kubantwana abafumana unyango esibhedlele.

Ingaba ikhona into entle enokwenzeka kum?

Ewe. Uza kuxelelwa ukuba unengxaki yokungamelani namachiza okanye awunayo.

Ingaba ukhona umntu oza kundazi ukuba ndikolu phononongo?

Ngoogqirha kuphela abakunyangayo nogqirha owenza uphononongo abaza kukwazi ukuba ukolu phononongo. Xa lugqityiwe uphando, abanye oogqirha baza kuxelelwa oko kufunyanisiweyo kodwa akukho namnye oza kukwazi ukuba ukolu phononongo. Oku kwenzeka kuba akukho gama lamntu lifakwayo xa kuchazelwa abanye oogqirha oko kuye kwafunyaniswa luphando.

Ndingathetha nabani ngolu phononongo?.

NoGqr Memela Makiwane

Umnxeba: 0219389335

I-imeyile: Makiwane@sun.ac.za

Ukuba andifuni kuyenza le nto?

Ungatsho ukuba awufuni kuba kolu phononongo kwaye akukho namnye onokukunyanzela. Nokuba ungathi ewe namhlanje, ungayitshintsha ingqondo yakho nanini na ngokuchaza nje. Oko akuzi kukufaka engxakini. Kwaye oko akuzi kwenza nabani na ayitshintshe indlela akunceda ngayo esibhedlele.

Uyaluqonda olu phando kwaye unomdla wokuba kulo na?

EWE	HAYI

Uyazazi ukuba ungaphuma kolu phononongo nanini na?

EWE	HAYI

_____ _____

Igama kunye/okanye nokutyikitya koMntwana **Umhla**

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HEALTH RESEARCH ETHICS COMMITTEE 1 AND 2

INVESTIGATOR'S DECLARATION

(INFORMATION SHOULD BE TYPED)

The principal investigator, supervisor, as well as all sub- & co-investigators must each sign a separate declaration.

SECTION 1: INVESTIGATOR DETAILS and ROLE IN THIS RESEARCH							
Title, First name, Surname: Dr Memela Makiwane		**SU number:** 17315158				***PROJECT ID NUMBER*** *(HREC office use only)*	
Professional Status: Clinical Pharmacology Registrar							
University DIVISION and DEPARTMENT: Clinical Pharmacology, Department of Medicine							
Telephone No: 0219389045		**E-mail address:** makiwane@sun.ac.za					
Role *(mark with x)*	**Principal investigator**	☒	**Co-investigator**	☐	**Sub-investigator**	☐	**Supervisor** ☐

SECTION 2: PROJECT TITLE *(maximum 250 characters for database purposes)*

Adverse drug reactions in paediatric inpatients in a South African tertiary hospital: A prospective observational study.

SECTION 3: CONFLICT OF INTEREST DECLARATION (OBLIGATORY)

I, *(Title, Full name)* Dr Memela M Makiwane declare that:

☒ I have **no financial or non-financial interests**, which may inappropriately influence me in the conduct of this research study; **OR**

☐ I **do have the following financial or other competing interests** with respect to this project, which may present a potential conflict of interest: (Please attach a separate detailed statement)

Signature: ..... **Date:** 2015/08/11

SECTION 4: DECLARATION (OBLIGATORY)

I, *(Title, Full name)* Dr Memela Makiwane declare that:

- **I have read through the submitted version of the research protocol and all supporting documents and am satisfied with their contents**
- I am **suitably qualified and experienced** to perform and/or supervise the above research study.
- I agree to conduct or supervise the described study **personally** in accordance with the relevant, current protocol and will only change the protocol after approval by the **HREC**, except when urgently necessary to protect the safety, rights, or welfare of subjects. In such a case, I am aware that I should notify the HREC without delay.
- I agree to timeously report to the HREC **serious adverse events** that may occur in the course of the investigation.
- I agree to maintain **adequate and accurate records** and to make those records available for inspection by the appropriate authorised agents when and if necessary.
- I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in the Declaration of Helsinki (2013), as well as South African and ICH GCP Guidelines and the Ethical Guidelines of the Department of Health as well as applicable regulations pertaining to health research.
- I agree to comply with all regulatory and monitoring requirements of the HREC.
- I agree that I am conversant with the above **guidelines**.
- I will ensure that every patient (or other involved persons, such as relatives), shall at all times be **treated in a dignified manner and with respect**.
- I will submit all required reports within the stipulated **time frames**.

Signature: ..... **Date:** 2015/08/11

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Approval Notice

Response to Modifications- (New Application)

05-Nov-2015
Makiwane, Memela MM

Ethics Reference #: S15/08/171

Title: **Adverse drug reactions in paediatric in-patients in a South African tertiary hospital: A prospective observational study.**

Dear Dr Memela Makiwane,

The **Response to Modifications -** ***(New Application)*** received on **19-Oct-2015**, was reviewed by members of **Health Research Ethics Committee 1** via Expedited review procedures on **04-Nov-2015** and was approved.
Please note the following information about your approved research protocol:

Protocol Approval Period: **04-Nov-2015 -04-Nov-2016**

Please remember to use your **protocol number** (**S15/08/171**) on any documents or correspondence with the HREC concerning your research protocol.

Please note that the HREC has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

After Ethical Review:
Please note a template of the progress report is obtainable on www.sun.ac.za/rds and should be submitted to the Committee before the year has expired. The Committee will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit.
Translation of the consent document to the language applicable to the study participants should be submitted.

Federal Wide Assurance Number: 00001372
Institutional Review Board (IRB) Number: IRB0005239

The Health Research Ethics Committee complies with the SA National Health Act No.61 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 Part 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes 2004 (Department of Health).

Provincial and City of Cape Town Approval

Please note that for research at a primary or secondary healthcare facility permission must still be obtained from the relevant authorities (Western Cape Department of Health and/or City Health) to conduct the research as stated in the protocol. Contact persons are Ms Claudette Abrahams at Western Cape Department of Health (healthres@pgwc.gov.za Tel: +27 21 483 9907) and Dr Helene Visser at City Health (Helene.Visser@capetown.gov.za Tel: +27 21 400 3981). Research that will be conducted at any tertiary academic institution requires approval from the relevant hospital manager. Ethics approval is required BEFORE approval can be obtained from these health authorities.

We wish you the best as you conduct your research.
For standard HREC forms and documents please visit: www.sun.ac.za/rds

If you have any questions or need further assistance, please contact the HREC office at 0219389657.

Included Documents:
Protocol Synopsis
CV M Kruger
Declaration B Rosenkranz
Declaration M Kruger

20150929 MOD Consent
Declaration E Decloedt
20151019 MOD2 Application form
Application form
CV M Makiwane
CV E Decloedt
Protocol
20151019 MOD2 Assent form
Checklist
20151019 MOD2 Parent ICF
20150929 MOD Child assent
20151019 MOD2 Cover letter
20150929 MOD Cover letter
Cover letter
Data collection tool
ADR Study data collection tool
CV B Rosenkranz
Declaration M Makiwane
20150929 MOD Application form
20150929 MOD Protocol

Sincerely,

Franklin Weber
HREC Coordinator
Health Research Ethics Committee 1

Investigator Responsibilities

Protection of Human Research Participants

Some of the responsibilities investigators have when conducting research involving human participants are listed below:

1.Conducting the Research. You are responsible for making sure that the research is conducted according to the HREC approved research protocol. You are also responsible for the actions of all your co-investigators and research staff involved with this research.

2.Participant Enrolment. You may not recruit or enrol participants prior to the HREC approval date or after the expiration date of HREC approval. All recruitment materials for any form of media must be approved by the HREC prior to their use. If you need to recruit more participants than was noted in your HREC approval letter, you must submit an amendment requesting an increase in the number of participants.

3.Informed Consent. You are responsible for obtaining and documenting effective informed consent using **only** the HREC-approved consent documents, and for ensuring that no human participants are involved in research prior to obtaining their informed consent. Please give all participants copies of the signed informed consent documents. Keep the originals in your secured research files for at least fifteen (15) years.

4.Continuing Review. The HREC must review and approve all HREC-approved research protocols at intervals appropriate to the degree of risk but not less than once per year. There is **no grace period.** Prior to the date on which the HREC approval of the research expires, **it is your responsibility to submit the continuing review report in a timely fashion to ensure a lapse in HREC approval does not occur.** If HREC approval of your research lapses, you must stop new participant enrolment, and contact the HREC office immediately.

5.Amendments and Changes. If you wish to amend or change any aspect of your research (such as research design, interventions or procedures, number of participants, participant population, informed consent document, instruments, surveys or recruiting material), you must submit the amendment to the HREC for review using the current Amendment Form. You **may not initiate** any amendments or changes to your research without first obtaining written HREC review and approval. The **only exception** is when it is necessary to eliminate apparent immediate hazards to participants and the HREC should be immediately informed of this necessity.

6.Adverse or Unanticipated Events. Any serious adverse events, participant complaints, and all unanticipated problems that involve risks to participants or others, as well as any research-related injuries, occurring at this institution or at other performance sites must be reported to the HREC within **five (5) days** of discovery of the incident. You must also report any instances of serious or continuing problems, or non-compliance with the HRECs requirements for protecting human research participants. The only exception to this policy is that the death of a research participant must be reported in accordance with the Stellenbosch Universtiy Health Research Ethics Committee Standard Operating Procedures www.sun025.sun.ac.za/portal /page/portal/Health_Sciences/English/Centres%20and%20Institutions/Research_Development_Support/Ethics/Application_package All reportable events should be submitted to the HREC using the Serious Adverse Event Report Form.

7.Research Record Keeping. You must keep the following research-related records, at a minimum, in a secure location for a minimum of fifteen years: the HREC approved research protocol and all amendments; all informed consent documents; recruiting materials; continuing review reports; adverse or unanticipated events; and all correspondence from the HREC

8.Reports to the MCC and Sponsor. When you submit the required annual report to the MCC or you submit required reports to your sponsor, you must provide a copy of that report to the HREC. You may submit the report at the time of continuing HREC review.

9.Provision of Emergency Medical Care. When a physician provides emergency medical care to a participant without prior HREC review and approval, to the extent permitted by law, such activities will not be recognised as research nor will the data obtained by any such activities should it be used in support of research.

10.Final reports. When you have completed (no further participant enrolment, interactions, interventions or data analysis) or stopped work on your research, you must submit a Final Report to the HREC.

11.On-Site Evaluations, MCC Inspections, or Audits. If you are notified that your research will be reviewed or audited by the MCC, the sponsor, any other external agency or any internal group, you must inform the HREC immediately of the impending audit/evaluation.

Western Cape Government
Health

TYGERBERG HOSPITAL
REFERENCE: **Research Projects**
ENQUIRIES: **Dr GG Marinus**
TELEPHONE:**021 938 5752**

Ethics Reference: **S15/08/171**

TITLE: Adverse drug reactions in paediatric in-patients in a South African tertiary hospital: A prospective observational study.

Dear Dr Makiwane MM

PERMISION TO CONDUCT YOUR RESEARCH AT TYGERBERG HOSPITAL.

In accordance with the Provincial Research Policy and Tygerberg Hospital Notice No 40/2009, permission is hereby granted for you to conduct the above-mentioned research here at Tygerberg Hospital.

DR D ERASMUS
CHIEF EXECUTIVE OFFICE

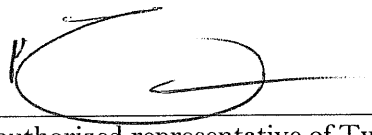
Date: 24 November 2015

Administration Building, Francie van Zijl Avenue, Parow, 7500 Private Bag X3, Tygerberg, 7505
tel: +27 21 938-6267 fax: +27 21 938-4890 www.capegateway.go.v.za

TYGERBERG HOSPITAL

ETHICS REFERENCE: S15/08/171

TITLE: Adverse drug reactions in paediatric in-patients in a South African tertiary hospital: A prospective observational study.

BY 

An authorized representative of Tygerberg Hospital

NAME Dr DS Erasmus

TITLE CEO

DATE 24 November 2015

Annexure: Conference abstract presentations:

Conference	**Venue**	**Date**	**Outcome**
All Africa Congress on Pharmacology and Pharmacy	Misty Hills Hotel and Conference Centre, Muldersdrift, Gauteng.	5 – 8 October 2016	Presentation won 2nd Prize Young Scientist – Category: Oral Presentations
Stellenbosch University Annual Academic Day	Stellenbosch University Faculty of Medicine & Health Sciences	11 August 2016	Oral presentation

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60th Annual Academic Day

Certificate awarded to

Memela Makiwane

HPCSA number: MP0527564

Participated in the 60th Annual Academic Day, Aug. 11, 2016

and earned the following CPD credits

Accreditation number:

MDB006-MD024-0045-8-2016

Session	Points
T4 Non-communicable Diseases Session 1	**1**
T7 Maternal and Child Health Session 2	**1**
T7 Maternal and Child Health Session 3	**1**
Main Programme	**1**
TOTAL	**4**

Prof. Nico C Gey van Pittius
Vice Dean: Research

South African Society
for Basic and Clinical
Pharmacology
Web: www.sapharmacol.co.za
E-mail: office@sapharmacol.co.za

YOUNG SCIENTIST AWARD IN CLINICAL PHARMACOLOGY - PODIUM PRESENTATION

Hereby it is certified that

MEMELA MAKIWANE

was awarded the 2nd prize
on 7 October 2016

President

Vice -President

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Ethics Letter

24-July-2017

Ethics Reference #: S15/08/171

Title: Adverse Drug Reactions in paediatric in-patients in a South African tertiary hospital: A prospective observational study

Dear Dr Memela Makiwane,

The Health Research Ethics Committee (HREC) reviewed and accepted your final progress report dated **24 July 2017.**

It is noted that this project is now completed and the HREC is looking forward to the submission of the Final Study Report when it is available.

Where to submit any documentation

Kindly submit **ONE HARD COPY** to Elvira Rohland, RDSD, Room 5007, Teaching Building, and **ONE ELECTRONIC COPY** to ethics@sun.ac.za .

Please remember to use your **protocol number (S15/08/171)** on any documents or correspondence with the HREC concerning your research protocol.

Federal Wide Assurance Number: 00001372
Institutional Review Board (IRB) Number: IRB0005240 for HREC1
Institutional Review Board (IRB) Number: IRB0005239 for HREC2

The Health Research Ethics Committee complies with the SA National Health Act No. 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 Part 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki and the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles, Structures and Processes 2015 (Departement of Health).

Yours sincerely,

Francis Masiye,
HREC Coordinator,
Health Research Ethics Committee 2.

STELLENBOSCH UNIVERSITY
Health Research Ethics Committee

24 JUL 2017

STELLENBOSCH UNIVERSITEIT
Gesondheidsnavorsing Etiekkomittee