

**A retrospective description of primary immunodeficiency
diseases at Red Cross War Memorial Children's Hospital,
Cape Town, South Africa, 1975 - 2017**

A Minor Dissertation

**In fulfilment for the requirements of the degree
*Master of Medicine (MMED) in Paediatrics***

By

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Table of Contents

| | <u>Page Number</u> |
|---|--------------------|
| Declaration..... | 1 |
| Abstract..... | 2 |
| Acknowledgements..... | 3 |
| Author contributions..... | 3 |
| List of tables and figures..... | 5 |
| Abbreviations..... | 6 |
| | |
| 1. Paper accepted for publication in the South African Medical Journal | 7 |
| A retrospective description of primary immunodeficiency diseases at Red Cross War Memorial Children’s Hospital, Cape Town, South Africa, 1975 – 2017 | |
| 1.1 Abstract..... | 10 |
| 1.2 Introduction..... | 11 |
| 1.3 Results..... | 13 |
| 1.4 Discussion..... | 15 |
| 1.5 Conclusion..... | 17 |
| 1.6 References..... | 18 |
| 1.7 Figures | 20 |
| 1.8 Tables..... | 22 |
| | |
| 2. Appendices..... | 27 |
| 2.1 Data collection sheet | 27 |
| 2.2 Ethics approval letter..... | 34 |
| 2.3 Hospital approval letter..... | 35 |
| 2.4 Latest progress report approved by Ethics Committee..... | 36 |
| 2.5 Protocol amendments approved by Ethics Committee..... | 37 |
| 2.6 Instructions to authors of the South African Medical Journal..... | 41 |
| 2.7 Letter to the editor of the South African Medical Journal..... | 60 |
| 2.8 South African Medical Journal’s comments..... | 61 |
| 2.9 Author response to the South African Medical Journal..... | 65 |
| 2.10 South African Medical Journal’s letter of acceptance for publication..... | 69 |
| 2.11 University of Cape Town MMed guidelines..... | 70 |

Declaration

I, Sashmi Moodley, hereby declare that the work on this dissertation is based on my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree to this or any other university.

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Abstract

Background. The primary immunodeficiency diseases (PIDs) constitute a diverse and ever-expanding group of inborn errors affecting a wide range of immune functions. They are not well documented in Sub-Saharan Africa. An important barrier to care is limited awareness of PIDs and their management among health care professionals. This fascinating spectrum of diseases is rapidly expanding worldwide, and not as rare as we think. Genetic characterization and newborn screening for primary Immunodeficiency diseases (PIDs) may be the gold standard in the first world setting but are neither practical nor feasible for our doctors. Yet, other low and middle income countries in the world have also established reasonable services and created registries for children with PIDs, including other African countries.

Objective. To describe the spectrum of PIDs at a tertiary paediatric hospital.

Methods. A retrospective descriptive study of PIDs diagnosed at Red Cross War Memorial Children's Hospital, Cape Town, South Africa between 1975 and 2017 was undertaken.

Results. 252 children with PIDs were identified, spanning 8 of the 9 categories listed in the 2017 classification of the International Union of Immunological Societies. Predominantly antibody deficiencies, combined immunodeficiencies with associated syndromic features, and immunodeficiencies affecting cellular and humoral immunity accounted for 79% of all PIDs. The mean age (standard deviation) at diagnosis was 46 (50) months and the male to female ratio was 1.5:1. A history of parental consanguinity was present in 3 children (1.2%). Recurrent infection was the most prevalent presenting phenotype, manifesting in 70.2% of the patients. Genetic or chromosomal confirmation was obtained in 42/252 (16.7%) of the children. Common interventions used to prevent infection were antimicrobial prophylaxis and immunoglobulin replacement therapy, administered to 37.7% and 36.9% of the patients respectively. Six of seven children who underwent haematopoietic stem cell transplantation (HSCT) had successful outcomes. The 7th patient died 2 months post-HSCT from overwhelming infection. Although we could not account for the children lost to follow up during the study period, 53 (21.0%) deaths were confirmed.

Conclusions. Several challenges exist in the recognition and treatment of children with PIDs in our setting. These include limited access to genetic diagnostics and HSCT. Sub-optimal treatment options contribute to the overall mortality of PIDs in South Africa. Greater awareness among clinicians treating children and more laboratory diagnostic capacity are needed to increase the recognition PIDs among children in South Africa. The treatment options that are available in South Africa are unevenly distributed. Hence, treatment capacity should be expanded throughout the country, especially advanced interventions such as HSCT. Ongoing reporting of registries such as ours and increased community awareness should strengthen the lobby for greater investment in rare diseases such as the PIDs.

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I would like to thank my supervisor Professor Brian Eley for always being available to guide me. His clear yet patient supervision is unmatched. I have learnt from him the details of research skills, time management and academic excellence. I thank my co supervisors for encouragingly contributing patient information and helping me expand my line of thought.

I am grateful for Spasina King, Michelle Kannemeyer and Simone Twaku who assisted with retrieval of the patient hospital folders and participated in the database management, and Dr Adelaide Masu who helped my statistical analysis. The National Health Laboratory Service at Groote Schuur Hospital is acknowledged for use of their florescent *in situ* hybridization data and the UCT Paediatric Registrar body for allowing me the time to balance my clinical and academic work.

I am forever indebted to my parents, Mr and Mrs Moodley, for teaching me to love books; to my beautiful children Isabella, Laila and Christopher Subrayen, for inspiring me to fly and to my husband, Thashen Subrayen, for catching us before we fall.

Author Contributions

Sashmi Moodley chose to research primary immunodeficiency diseases in children with the overall objective of advocating for rare diseases in South Africa. A literature search to craft the the protocol and journal article was conducted. The final protocol was approved by the Departmental Research Committee, Department of Paediatrics and Child Health, University of Cape Town. Ethics approval letters, hospital approval letters and change of title letters to the relevant parties were written, and all necessary approvals were obtained. Brian Eley provided close guidance together with constructive criticism on each of the project.

Sashmi Moodley approached each of the subspecialties at Red Cross War Memorial Children's Hospital (RCWMCH) for their lists of patients with confirmed or suspected primary immunodeficiency diseases. These departments included cardiology, haematology and oncology, rheumatology, allergology, gastroenterology, endocrinology, neurology, dermatology, pulmonology, chemical pathology and genetics. The department of cytogenetics at the National Health Laboratory Service was also approached for a list of RCWMCH patients with confirmed Chromosome 22q11.2 deletion syndrome. Sashmi Moodley and Spasina King obtained the patient files, extracted information required to complete the datasheets, and captured this information in the primary immunodeficiency disease electronic database. Michelle Kannemeyer and Simone Twaku also assisted with accessing patient files. Brian Eley reviewed all patient information to confirm that they all had primary immunodeficiency diseases. The data was analysed using Stata software. Adelaide Masu helped with statistical analysis.

Sashmi Moodley wrote the first complete draft of the paper, and constructed all tables and figures, guided by Brian Eley. The article was critiqued by the co-authors of the paper Elizabeth Goddard, Michael Levin, Chris Scott, Ann Van Eyssen, Alan Davidson, Rik Dedecker, Jo M Wilmshurst and Ariane Spitaels. These co-authors were the collaborators from sub-specialist services that contributed patients to the study cohort. Sashmi Moodley amended the draft paper in response to the co-author comments. All co-authors approved the final draft. Sashmi Moodley submitted the completed paper together with a covering letter to the South African Medical Journal for publication. The paper was peer-reviewed. Sashmi Moodley then revised the paper in response to the anonymous reviewer's comments, with Brian Eley's supervision. The revised paper was accepted for publication by the editor of the South African Medical

Journal, Dr Bridget Farham. Thereafter, Sashmi Moodley finalised this dissertation as per the requirements for the MMed with guidance from Brian Eley.

List of tables and figures

The following list of tables and figures are found in Chapter 1, Paper accepted for publication in the South African Medical Journal

Tables

Table 1: Spectrum of primary immunodeficiency diseases, 1975 – 2017

Table 2: Patient characteristics at the time of PID diagnosis

Table 3: Spectrum of PIDs with confirmed genetic or chromosomal abnormalities

Table 4: PIDs in children who died

Figures

Figure 1: Selection of patients with PID

Figure 2: Number of new PID diagnoses, 1975 – 2017

Abbreviations

| | |
|--------|---|
| AR | Autosomal Recessive |
| CVID | Common variable immunodeficiency |
| ESID | European Society for Immunodeficiency |
| HREC | Human Research Ethics Committee |
| HSCT | Haematopoietic stem cell transplantation |
| IUIS | International Union of Immunological Societies |
| IPEX | Immune dysregulation polyendocrinopathy enteropathy X-linked syndrome |
| IQR | Interquartile range |
| LMICs | Low and middle income countries |
| NHLS | National Health Laboratory Service |
| PAGID | Pan-American Group for Immunodeficiency |
| PIDs | Primary Immunodeficiency Diseases |
| RAG1 | Recombination activating gene-1 |
| RCWMCH | Red Cross War Memorial Children's Hospital |
| SAMJ | South African Medical Journal |
| SCID | Severe combined immunodeficiency |
| XL | X linked |

1. Paper accepted for publication in the South African Medical Journal

A retrospective description of primary immunodeficiency diseases at Red Cross War Memorial Children's Hospital, Cape Town, South Africa, 1975 – 2017

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1.1 Abstract

Background. The primary immunodeficiency diseases (PIDs) constitute a diverse and ever-expanding group of inborn errors affecting a wide range of immune functions. They are not well documented in Sub-Saharan Africa.

Objective. To describe the spectrum of PIDs at a tertiary paediatric hospital.

Methods. A retrospective descriptive study of PIDs diagnosed at Red Cross War Memorial Children's Hospital, Cape Town, South Africa between 1975 and 2017 was undertaken.

Results. 252 children with PIDs were identified, spanning eight of the nine categories listed in the 2017 classification of the International Union of Immunological Societies. Predominantly antibody deficiencies, combined immunodeficiencies with associated syndromic features, and immunodeficiencies affecting cellular and humoral immunity accounted for 199 (79%) children with PIDs. The mean age (standard deviation) at diagnosis was 46 (50) months and the male to female ratio was 1.5:1. A history of parental consanguinity was present in three children (1.2%). Recurrent infection was the most prevalent presenting phenotype, manifesting in 177 (70.2%) patients. Genetic or chromosomal confirmation was obtained in 42/252 (16.7%) of the children. Common interventions used to prevent infection were antimicrobial prophylaxis and immunoglobulin replacement therapy, administered to 95 (37.7%) and 93 (36.9%) of the patients respectively. Six of seven children who underwent haematopoietic stem cell transplantation (HSCT) had successful outcomes. The seventh patient died two months post-HSCT from overwhelming infection. Although we could not account for the children lost to follow up during the study period, 53 (21.0%) deaths were confirmed.

Conclusions. Several challenges exist in the recognition and treatment of children with PIDs in our setting. These include limited access to genetic diagnostics and HSCT. Sub-optimal treatment options contribute to the overall mortality of PIDs in South Africa.

1.2 Introduction

Primary immunodeficiency diseases (PIDs) are inborn errors of immunity; a large heterogeneous group of predominantly genetic conditions that predispose individuals to a wide spectrum of infection, autoimmunity, autoinflammation, lymphoproliferation, malignancy, clinically recognisable syndromes in which immunodeficiency is a feature, allergic manifestations and end-organ damage causing chronic dysfunction. Without optimal treatment many PIDs are life-limiting.^[1] Diagnosis is dependent on the type of infection and other presenting manifestations preceding diagnosis, immunological testing and, where possible confirmatory genetic testing.^[2]

The spectrum of PIDs is evolving rapidly with new PIDs being continuously described and molecularly characterised. Since 1970, the International Union of Immunological Societies (IUIS) has included 354 PIDs and 344 different gene defects in its consensus classification.^[3] Worldwide, PIDs affect more than six million people and in Africa an estimated 988,000 adults and children have PIDs, of whom approximately 2,500 have been diagnosed.^[4] In South Africa, the estimated total mid-2017 population was 56.52 million.^[5] If it is assumed that the prevalence of PIDs in South Africa is similar to that in well-resourced countries, then the total number of adults and children with PIDs in our country should range between 3,040 and 48,775. However, fewer than 500 PID cases have been reported from South Africa.^[6,7]

Children with PIDs have been managed at Red Cross War Memorial Children's Hospital (RCWMCH) for more than 40 years.^[8] An early review of the immunology laboratory database at the hospital during a 13-year period identified 93 children with PIDs, a mean of 6.6 new PID diagnoses per annum. Primary antibody deficiencies predominated, accounting for 56% of all PIDs, and the spectrum of PIDs was similar to that reported from Europe, and North and South America.^[9] An analysis of 168 children with PIDs managed over a 27-year period at RCWMCH, showed that the mean age at the time of diagnosis declined significantly over the study period, suggesting that awareness of these diseases among clinicians had improved.^[6] In contrast to the situation in North Africa where PIDs frequently occur in children with consanguineous parents, consanguinity was highly unusual in the RCWMCH cohort, occurring in less than 2% of the patients.^[6,10-12] High background consanguinity rates in North Africa and the Middle East alters the spectrum of PIDs compared to other geographical regions, with autosomal recessive conditions being more frequent than X-linked or autosomal dominant diseases.^[13]

The current IUIS classification of PIDs includes a broad spectrum of conditions.^[3] Consequently, at RCWMCH several sub-specialist services participate in the management of children with PIDs including rheumatology, haematology & oncology, cardiology, allergology, pulmonology gastroenterology and neurology. Previous descriptive studies from RCWMCH have been confined to PID patients managed by the immunology and infectious diseases services.^[9,6] The present study aims to provide a more comprehensive understanding of the spectrum of PIDs across all sub-specialist services at our hospital and further raise awareness of PIDs among South African clinicians.

1.3 Methods

Study design and setting

This retrospective, descriptive study was completed at RCWMCH, a 273-bed, tertiary-referral facility situated in the Western Cape Province and affiliated to the University of Cape Town. It accepts paediatric referrals from diverse sources, in both primary and tertiary settings. Intentionally a unique situation, providing sub-specialist consultation to doctors throughout South Africa, but predominantly from facilities managing children in the Western Cape Province. A dedicated service for the diagnosis and treatment of PIDs was established at RCWMCH in the mid-1970s.^[14] In 2008 the PID service became part of the infectious diseases service at the hospital. Since 1983 information on all children with PIDs (1) who were diagnosed and/or treated, or (2) for whom diagnostic / treatment advice was provided to their attending clinicians by the PID or infectious diseases services was maintained in a dedicated database, henceforth referred to as the PID database. Because of the multi-system nature of many PIDs, some children are increasingly being managed by sub-specialist services other than the infectious diseases service at RCWMCH and hence not included in the PID database. To address this gap in the PID database and describe the full spectrum of PIDs managed or supported by all sub-specialist services at RCWMCH between 1 January 1975 and 31 December 2017, the infectious diseases service collaborated with several specialist / sub-specialist services managing children with PIDs.

Classification of primary immunodeficiency diseases

Patients were classified according to the International Union of Immunological Societies (IUIS) 2017 report on inborn errors of immunity and the IUIS 2017 phenotypic classification^[3,15] and adapted where necessary using Stiehm's textbook on immune deficiencies.^[16] Because mutational analysis is not routinely available in South Africa most PID diagnoses are based on the clinical and immunologic phenotype, hence the nomenclature used to describe specific PIDs was appropriately adapted.^[6] Furthermore, diagnostic criteria formulated by the Pan-American Group for Immunodeficiency (PAGID) and the European Society for Immunodeficiency (ESID) were used to diagnose some conditions such as IgA deficiency and common variable immunodeficiency (CVID).^[17]

Data collection

Relevant clinical and laboratory data were extracted from hospital folders and the National Health Laboratory Service (NHLS) database using a standardised case record form that is used by the infectious diseases service in the management of patients with PIDs. Information included patient demographics, presenting problems, results of immunological investigation, treatment modalities, complications, and the outcome, if known. The data were transferred anonymously in a study-specific Excel spreadsheet.

Data analysis

Data were analysed using Stata software (StataCorp. 2013. Stat Statistical Software: Release 13. College Station, TX: StataCorp LP). Proportions were expressed as percentages. Continuous variables were tested for normality using the Shapiro-Wilks test. Mean and standard deviation or median and interquartile range (IQR) were used to describe the data as appropriate.

Ethics considerations

The research protocol was approved by the Human Research Ethics Committee, Faculty of Health Sciences, University of Cape Town (HREC Ref 191/2017) and the RCWMCH research committee. Patient consent was not obtained because the analysis was done retrospectively. The study was completed in accordance with the Declaration of Helsinki.

1.4 Results

Patient population

All children entered into the existing PID database during the study period were reviewed to confirm the accuracy of their diagnoses. Of 230 children in the database reviewed, 12 were excluded because there was no conclusive evidence that they had PIDs. The remaining 218 with PIDs were retained in the study database. Ten other specialist / sub-specialist services referred 206 children with possible PIDs. These 206 patients were derived from outpatient attendance lists, clinical databases, the National Health Laboratory Services (NHLS) cytogenetics database and senior clinician memory. Clinical and laboratory records of these patients were reviewed and a further 34 appropriately investigated children with PIDs were identified and added to the study database. Thus, 252 children with PIDs were identified and included in the current analysis (Figure 1).

Spectrum of PIDs

The number of new PID diagnoses in any five year period fluctuated throughout the study period with no clear trend. The 2010 to 2014 period realised the highest number of new PID diagnoses (Figure 2).

The spectrum of PIDs among the 252 children (Table 1) spanned eight of the nine categories listed in the 2017 IUIS report on inborn errors of immunity. Among the 252 patients, predominantly antibody deficiencies, combined immunodeficiencies with associated syndromic features, and immunodeficiencies affecting cellular and humoral immunity (Table 1) were most prevalent. This accounted for 79% of PIDs included in this study.

Patient characteristics

The mean age (standard deviation) at the time of diagnosis was 46 (50) months. The male to female ratio was 1.5:1. There were greater numbers of males in five of the eight PID categories (Table 1). Thirty-six patients (14.3%) were known to have a family history of PIDs. A history of parental consanguinity was present in three (1.2%) of the children, one each with chronic granulomatous disease, severe combined immunodeficiency caused by a mutation in recombination activating gene-1 (*RAG1*) deficiency and glycogen storage type 1b. The majority of patients, 181 (71.8%), lived in the Western Cape and a substantial number of patients were in the public sector of health (Table 2).

Clinical presentation

Recurrent infection was the commonest presenting phenotype manifesting in 177 (70.2%) of patients. Atypical infection and failure to thrive manifested in 38 (15.8%) and 51 (20.2%) patients, respectively. Invasive meningococcal infection was the presenting feature in nine children with complement component deficiencies, of whom six manifested with recurrent meningococcal infection and three with a single episode of infection before diagnosis. One child was diagnosed after screening based on a family history of complement C5 deficiency. Dysmorphic features or recognisable clinical syndromes occurred in 52 (20.6%) patients. The three commonest syndromes were DiGeorge, now formally called *22q11.2* deletion syndrome, Ataxia-telangiectasia and Hyper IgE syndrome, occurring in 23 (9.1%), 15 (6.2%) and 9 (3.6%) of the patients, respectively (Table 1). Six of the seven children with C1 inhibitor deficiency presented with angioedema, while the remaining patient, an older brother of one of the other

patients was screened based on the family history and diagnosed before he manifested clinically. The five children with autoinflammatory disorders presented with non-infectious manifestations, commonly persistent fever.

Genetic or chromosomal confirmation

Molecular characterisation is not routinely available in South Africa but was undertaken in a subset of the patient cohort. Single gene mutations were confirmed in 24 (9.5%) patients of the cohort and chromosomal deletions in a further 18 (7.1%) children (Table 3).

Management

The predominant interventions administered to prevent infection were antimicrobial prophylaxis, 95/252 (37.7%) and immunoglobulin replacement therapy, 93/252 (36.9%). Antimicrobial prophylaxis plus immunoglobulin replacement therapy was administered to 31/252 (12.3%) patients. Seven children underwent haematopoietic stem cell transplantation (HSCT). The first HSCT for a child with SCID caused by IL-2 receptor γ -chain deficiency took place in 1996 (Brian Eley, personal communication). Six of the seven patients had SCID and one IPEX syndrome. Six of these patients experienced complete immunological reconstitution and are well. The seventh patient who underwent HSCT for underlying SCID died two months after HSCT from presumed septicaemia complicated by multi-organ failure. Other treatment interventions included subcutaneous interferon- γ administration in two patients with chronic granulomatous disease. The treatment of patients with C1 inhibitor deficiency included fresh frozen plasma during acute attacks and tranexamic acid prophylaxis. In the patients with autoinflammatory disorders, treatment included colchicine (3 patients), methotrexate (2 patients) and adalimumab, an anti-tumour necrosis factor- α inhibitor (1 patient).

Mortality

During the study period, 53 (21.0%) patients died. The cause of death was not known in 12 patients. In the remaining 40 patients, the most frequent causes of death were presumed or proven septicaemia, 15 patients (37.5%) and pneumonia, nine patients (22.5%). Of 47 patients with a known date of death, death occurred within one year of PID diagnosis in 32 (68.1%), including 15 (31.9%) who died within one month of PID. Of the remainder, seven (14.9%) died between one and five years after PID diagnosis and eight (17.0%) died more than five years after PID diagnosis (Table 4).

1.5 Discussion

Worldwide, PIDs are an ever-expanding disease group as a result of the description of new genetic disorders. The burden of secondary immunodeficiencies such as HIV infection and severe acute malnutrition continues to overshadow that of the PIDs in low-and-middle-income countries (LMICs) including South Africa, resulting in limited investment in the diagnostic and treatment resources needed for PIDs. Despite the advancing knowledge base and expertise of PIDs national incidence and prevalence estimates are largely unknown. An important barrier to care is limited awareness of PIDs and their management among health care professionals, as well as in the broader society. A study completed in the United States and published in 2016 showed that few family practice physicians were aware of guidelines for diagnosing and managing PIDs compared to subspecialist immunologists, 4% versus 79%.^[18] In the present study we document the spectrum of PIDs among 252 children diagnosed at a tertiary hospital in South Africa over a period of more than 40 years. Although diagnosis depended mainly on clinical and immunological criteria, we were able to classify our patients using the latest IUIS classification. The spectrum of PIDs in this study spanned eight of the nine categories in the IUIS classification. The ninth category, phenocopies of inborn errors of immunity was only added to the IUIS classification very recently, in 2015, and many of the diseases in this category manifest in adulthood, hence the absence of these PIDs among our patients.^[3]

Parental consanguinity was identified in only 1.2 % of our patients.^[13] By contrast in the North African countries of Morocco, Tunisia and Egypt, parental consanguinity rates of 43.2%, 58.2% and 62.5% respectively were documented.^[10-12] These high parental consanguinity rates result in higher proportions of PIDs due to Mendelian autosomal recessive inheritance, lower proportions of PIDs due to Mendelian X-linked inheritance, and consequently a predominance of combined cellular and humoral immunodeficiency in comparison to the preponderance of predominantly antibody deficiencies in populations with low consanguinity rates.^[13] An analysis of the ESID registry in June 2014 showed that 56.78% of 19,355 children and adults with PIDs had predominantly antibody deficiencies.^[19] In our study predominantly antibody deficiencies account for 40.5% of all PIDs, whereas in the registries of Morocco and Tunisia predominantly antibody immunodeficiencies account for 22.8% and 17.7% of all PIDs respectively.^[11,12]

The mean age of our patients was 46 months similar to the mean age of children in the Egyptian study of 51 months.^[10] The mean ages at diagnosis in the Moroccan and Tunisian registries were 6.2 years and 5.3 years respectively.^[11,12] However, both these registries included children and adults with PIDs. A previous analysis from our hospital published in 2011 documented a mean age at diagnosis of 51 months and a statistically significant decline in mean age over time, suggesting that awareness of the PIDs had increased among clinicians at our hospital during the study period.^[6] Although most of our patients emanated from the public sector, 36.9% originated from the private sector. Given that approximately 20% of the South African population are serviced in the private sector, this result suggests that more effort may be needed to increase awareness of the PIDs among public sector clinicians.

Genetic or chromosomal confirmation of PID diagnosis was obtained in 16.7% of our patients, somewhat higher than 13.8% genetic confirmation reported in 2015 among PID patients in the Tunisian registry.^[11] In Europe where molecular testing is more accessible, the rate of genetic diagnostic confirmation is much higher having reached 36% of all patients registered with ESID registry in April 2018.^[20]

Most interventions for managing PIDs are available to a varying degree in South Africa, including optimal immunisation practice, antimicrobial therapy and prophylaxis, immunoglobulin replacement therapy and infection control measures.^[2] Some interventions such as interferon-1-inhibitors and HSCT are extremely expensive, limiting accessibility within the public sector. HSCT is the treatment of choice for many severe PIDs. Our findings demonstrate that it is possible to successfully undertake HSCT in patients with PIDs in South Africa. However, only a small proportion of more than 50 patients who may have benefitted were transplanted. Reasons for the low number of transplants include late presentation of patients often with severe complications of their underlying PIDs, the small donor pool in South Africa resulting in the unavailability of suitable matched unrelated donors, high cost of accessing donors affiliated to international registries, and no paediatric ICU facilities at the adult tertiary referral hospital where our paediatric transplants were undertaken. In 2012 the first HLA haplo-identical HSCT was performed for SCID. Before, 2012, only HLA identical or matched unrelated donors were considered for children with SCID. Transplantation programmes have also been started in North African countries such as Tunisia and Morocco.
[11, 12]

Unfortunately, we had limited access to patient outcomes, especially those lost to follow up. We are however able to describe the mortality of 21%, which compares with mortality documented in studies with similar challenges completed in Egypt, Morocco and Tunisia of 23.4%, 28.8% and 34.5% respectively.^[10-12] In our study, 36% of known deaths occurred in patients with SCID, and 68% of deaths including 19 preceded by SCID occurred during the 1st year after PID diagnosis indicating the need to focus on optimising the outcome of children with SCID because there is a high chance of achieving immunological cure after successful HSCT. In the Tunisian study, 17.2% of patients were lost to follow up indicating that maybe this is an important consideration for patients with PIDs residing in other LMICs.^[11]

Strengths and limitations

This study is the largest single centre description of PIDs in children in Sub-Saharan Africa to date. We were able to include more than 250 patients because we adopted an expanded search strategy among sub-specialist services at our hospital. Furthermore, despite limited genetic confirmation, we were able to classify our patients using the latest IUIS classification system. Because of the retrospective study design, there were limitations in the availability and completeness of the clinical data. Outcome data was limited to known deaths. Because some of the patients were treated by their referring doctors with minimal or no feedback, the true mortality prevalence was not established and hence we did not explore risk factors associated with death. We could not comprehensively document those lost to follow up and hence have an incomplete understanding of the true extent of this outcome measure amongst our patients. Review of patients referred by other sub-specialist services showed that a sizeable proportion was not adequately investigated for immunodeficiency. For example, of 73 patients with laboratory confirmed 22q11 deletion, 37 (50.7%) had not been investigated for immunodeficiency, and hence these could not be considered for inclusion in our study population. Likewise of 15 patients with right-sided isomerism 11 had not been investigated for asplenia. Furthermore, it is likely that more cases of PID were missed during the study period because either PIDs was not considered or the children presented with milder PID phenotypes. Although this reality prevented us from achieving complete description of PIDs at our hospital during the study period, our results did allow us to largely address the stated aim and provide direction for improving our clinical service.

1.6 Conclusion

In the present study we were able to collate the findings of 252 patients with a spectrum of 50 primary immunodeficiency diseases over a period of more than 4 decades. Greater awareness among clinicians treating children and more laboratory diagnostic capacity are needed to increase the recognition PIDs among children in South Africa. The treatment options that are available in South Africa are unevenly distributed. Hence, treatment capacity should be expanded throughout the country, especially advanced interventions such as HSCT. Ongoing reporting of registries such as ours and increased community awareness should strengthen the lobby for greater investment in rare diseases such as the PIDs.

1.7 References

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1.8 Figures

Figure 1

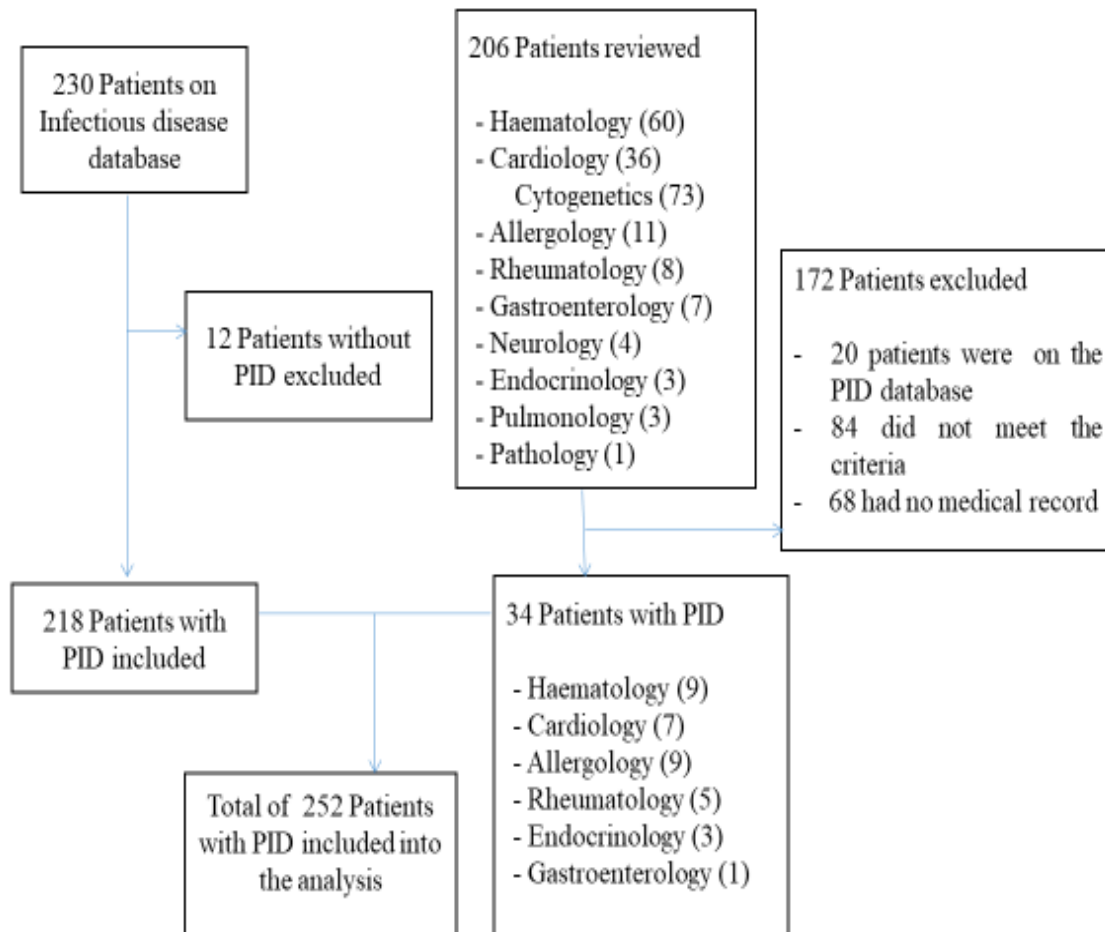


Figure 1 : Selection of patients with primary immunodeficiency diseases

Figure 2

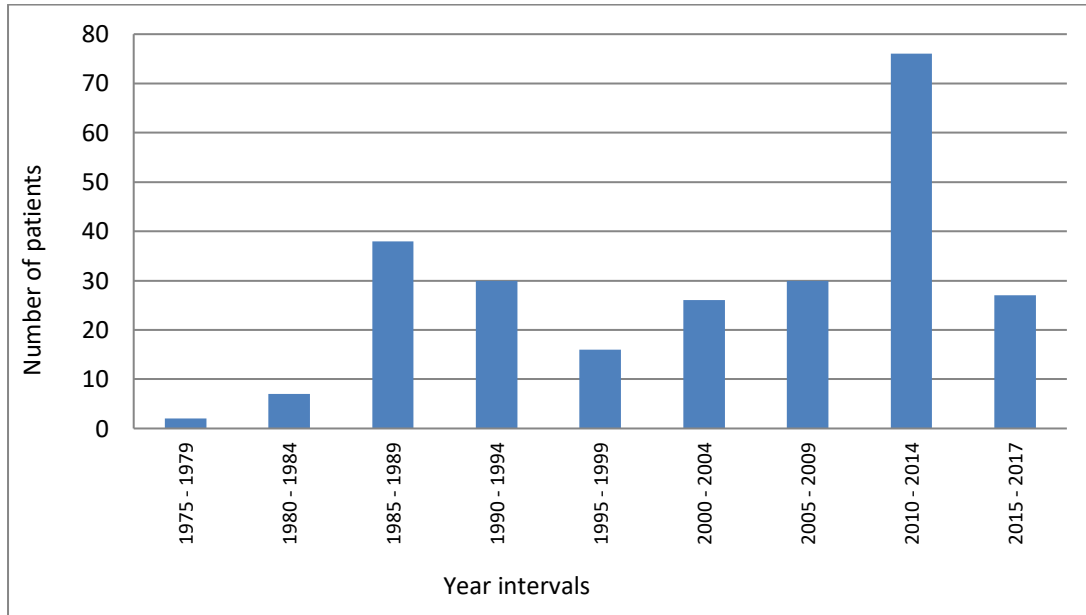


Figure 2: Number of new primary immunodeficiency diagnoses, 1975 - 2017

1.9 Tables

Table 1: Spectrum of primary immunodeficiency diseases, 1975 – 2017

| <u>PID category</u> | <u>Gender</u> | | |
|--|-------------------|--------------|----------------|
| | <u>Total (%)</u> | <u>Males</u> | <u>Females</u> |
| Immunodeficiencies affecting cellular and humoral immunity | 45 (17.9) | 30 | 15 |
| T-B+ Severe combined immunodeficiency (SCID) | 16 (6.3) | 15 | 1 |
| T-B-SCID | 9 (3.6) | 2 | 7 |
| CD40 ligand deficiency | 4 (1.6) | 4 | 0 |
| Hyper IgM syndrome (autosomal) | 2 (0.8) | | 2 |
| Hyper IgM syndrome (unspecified) | 3 (1.2) | 2 | 1 |
| Combined CD4 and CD8 deficiency | 8 (3.2) | 5 | 3 |
| Idiopathic CD4 lymphopaenia | 3 (1.2) | 1 | 2 |
| CD8 deficiency | 1 (0.4) | 1 | 0 |
| Combined immunodeficiencies with associated or syndromic features | 52 (20.6) | 26 | 26 |
| Wiskott-Aldrich syndrome | 4 (1.6) | 3 | 1 |
| Ataxia-telangiectasia | 15 (6) | 6 | 9 |
| Chromosome 22q11.2 deletion syndrome | 18 (7.1) | 10 | 8 |
| DiGeorge syndrome, genetic defect unknown | 5 (2) | 2 | 3 |
| Hyper IgE Syndrome, mutation undefined | 7 (2.8) | 4 | 3 |
| Hyper IgE,with STAT3 mutation | 1 (0.4) | 1 | 0 |
| Hyper IgE, without a mutation in <i>STAT3</i> , <i>DOC8</i> or <i>TYK2</i> | 1 (0.4) | 0 | 1 |
| Comel-Netherton syndrome | 1 (0.4) | 0 | 1 |
| Predominantly antibody deficiencies | 102 (40.5) | 66 | 36 |
| B ⁻ panhypogammaglobulinaemia | | | |
| XL agammaglobulinaemia | 18 (7.1) | 18 | 0 |
| AR hypogammaglobulinaemia | 2 (0.8) | 0 | 2 |
| B ⁺ Hypogammaglobulinaemia | | | |
| Common variable immunodeficiency | 28 (11.1) | 18 | 10 |
| Transient hypogammaglobulinaemia of infancy | 25 (9.9) | 18 | 7 |
| Hypogammaglobulinaemia undefined | 3 (1.2) | 1 | 2 |
| Selective IgA Deficiency | 12 (4.8)) | 7 | 5 |
| IgG subclass deficiency with IgA deficiency | 6 (2.4) | 1 | 5 |
| Isolated IgG subclass deficiency | 6 (0.02) | 3 | 3 |
| Specific antibody deficiency with normal Ig levels and normal B cells | 2 (0.8) | 0 | 2 |
| Diseases of immune dysregulation | 2 (0.8) | 1 | 1 |
| Chediak-Higashi Syndrome | 1 (0.4) | 0 | 1 |
| Immune dysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome | 1 (0.4) | 1 | 0 |
| Congenital defects of phagocyte number or function | 22 (8.7) | 15 | 7 |

| | | | |
|--|------------------|-------------------|------------------|
| Congenital neutropenias | | | |
| Congenital neutropaenia, AD inheritance | 2 (0.8) | 1 | 1 |
| Glycogen Storage disease Type 1b | 3 (1.2) | 1 | 2 |
| Cyclic neutropenia | 1 (0.4) | 1 | 0 |
| Shwachman- Diamond Syndrome | 1 (0.4) | 0 | 1 |
| Congenital neutropaenia, inheritance undefined | 5 (2) | 3 | 2 |
| Chronic granulomatous disease, confirmed XL inheritance | 1 (0.4) | 1 | 0 |
| Chronic granulomatous disease, AR inheritance | 1 (0.4) | 0 | 1 |
| Chronic granulomatous disease, mutation undefined | 7 (2.7) | 7 | 0 |
| Myeloperoxidase deficiency | 1 (0.4) | 1 | 0 |
| Defects in intrinsic and innate immunity | 6 (2.4) | 4 | 2 |
| Warts, hypogammaglobulinaemia, infections & myelokathexis (WHIM) syndrome | 1 (0.4) | 1 | 0 |
| Chronic mucocutaneous candidiasis | 1 (0.4) | 0 | 1 |
| Congenital asplenia with right-sided isomerism | 4 (1.6) | 3 | 1 |
| Autoinflammatory disorders | 6 (2.4) | 4 | 2 |
| Defects effecting the inflammasome | | | |
| Familial Mediterranean Fever | 2 (0.8) | 2 | 0 |
| Mevalonate kinase deficiency (Hyper-IgD Syndrome) | 1 (0.4) | 0 | 1 |
| Non-inflammasome-related conditions | | | |
| Pyrogenic sterile arthritis, pyoderma gangrenosum, acne (PAPA) syndrome | 1 (0.4) | 1 | 0 |
| Periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis (PFAPA) syndrome | 1 (0.4) | 1 | 0 |
| Chronic recurrent multifocal osteomyelitis (CRMO) syndrome | 1 (0.4) | 0 | 1 |
| Complement deficiencies | 17 (6.7) | 7 | 10 |
| C5 Deficiency | 2 (0.8) | 0 | 2 |
| C6 deficiency | 7 (2.7) | 4 | 3 |
| Complement deficiency, undefined | 1 (0.4) | 0 | 1 |
| C1 inhibitor deficiency | 7 (2.7) | 3 | 4 |
| All PID categories | 252 (100) | 153 (60.7) | 99 (39.3) |

PID= primary immunodeficiency disease; XL = X-linked; AR = autosomal recessive

Table 2: Patient Characteristics at the time of PID diagnosis

| Patient Characteristics | N = 252 |
|-------------------------------------|----------------|
| Age (months) (SD) | 46 (50) |
| Age Category (months), n (%) | |
| < 12 | 76 (30.1) |
| 12 - 60 | 98 (38.9) |
| > 60 | 78 (31.0) |
| Gender, n (%) | |
| Male | 153 (60.7) |
| Female | 99 (39.3) |
| Male to Female ratio | 1.5 : 1 |
| Family History of PIDs, n (%) | 36 (14.3) |
| Parental consanguinity, n (%) | 3 (1.2) |
| Provincial residence, n (%) | |
| Western Cape | 181 (71.8) |
| Eastern Cape | 25 (9.9) |
| Gauteng | 17 (6.7) |
| Free State | 7 (2.8) |
| Kwa Zulu Natal | 6 (2.3) |
| Northern Cape | 8 (3.2) |
| Unknown | 8 (3.2) |
| Health Sector classification, n (%) | |
| Private | 93 (36.9) |
| Public | 151 (59.9) |
| Unknown | 8 (3.2) |

PID = primary immunodeficiency disease; SD = standard deviation

Table 3: Spectrum of PIDs with confirmed genetic or chromosomal abnormalities

| Primary immunodeficiency disease | Genetic / chromosomal defect | Inheritance | OMIM | Number |
|---|-------------------------------------|--------------------|-------------|-----------------------|
| X linked agammaglobulinaemia | <i>BTK</i> | XL | 300300 | 5 related patients |
| CD40 ligand Deficiency | <i>CD40LG</i> | XL | 300386 | 3 male siblings |
| T ⁻ B ⁺ NK ⁻ SCID | <i>IL2RG</i> | AR | 308380 | 4 unrelated patients |
| T ⁻ B ⁻ NK ⁺ SCID | <i>RAG1</i> | AR | 179615 | 1 patient |
| Hyper IgE Syndrome | <i>STAT3</i> | AD | 102582 | 1 patient |
| X inked chronic granulomatous disease | <i>CYBB</i> | XL | 300481 | 1 patient |
| Hyper-IgD syndrome | <i>MVK</i> | AR | 260920 | 1 patient |
| C6 Deficiency | C6 | AR | 217050 | 3 unrelated patients |
| C5 Deficiency | C5 | AR | 120900 | 2 unrelated patients |
| Immune dysregulation, polyendocrinopathy, enteropathy, X linked (IPEX) syndrome | <i>FOXP3</i> | XL | 300292 | 1 patient |
| DiGeorge Syndrome | <i>22q11.2</i> deletion | | | 18 unrelated patients |

XL = X-linked; AR = autosomal recessive; AD = autosomal dominant; OMIM = Online Mendelian Inheritance in Man

Table 4: PIDs in children who died

| Primary immunodeficiency disease | Number (%) |
|---|-------------------|
| | N = 53 |
| Severe combined immunodeficiency (SCID) | 19 (35.8) |
| X-linked agammaglobulinaemia | 9 (17.0) |
| B+ hypogammaglobulinaemia | 4 (7.5) |
| Ataxia-telangiectasia | 4 (7.5) |
| DiGeorge syndrome | 4 (7.5) |
| CD40 ligand deficiency | 3 (5.7) |
| Chronic granulomatous disease | 3 (5.7) |

2. Appendicies

2.1 Immunology data collection sheet

Biographical data (If available, use sticker to complete some of the data fields)

Study number: _____ Folder number: _____

Date of birth(Y-M-D): _____ Date of testing: _____

Age (months): _____

Suburb (Cape Town) _____

Referral source

State Private Outpatient Inpatient, specify ward: _____

Cape Town Western Cape Another province, specify: _____

Referring doctor: _____ Contact number: _____

Indication(s) for investigation

Recurrent infection Failure to thrive Family history Reaction to live-attenuated vaccines,
specify: _____

Dysmorphic features, specify: _____

Other, specify: _____

History of chief complaint (e.g. list major infections & dates, spectrum of infections, frequency of infections, associated hospitalisation):

Family History

Consanguinity (Y / N) Primary immunodeficiency, specify: _____

_____ Early

childhood deaths, specify: _____

Family tree

Investigations

Previous investigations

| | Date | Results |
|---|------|---------|
| HIV rapid | | |
| HIV DNA PCR | | |
| White cell count (x 10 ⁹ /L) | | |
| Neutrophil count (x 10 ⁹ /L) | | |
| Lymphocyte count (x 10 ⁹ /L) | | |
| Total protein, Albumin | | |
| Mantoux | | |
| Sweat test | | |
| Allergy testing | | |
| Other tests | | |
| | | |
| | | |

Immunoglobulins (g/L)

| | Results | Reference range |
|------------------------|---------|-----------------|
| IgG | | |
| IgA | | |
| IgM | | |
| IgE | | |
| IgG ₁ | | |
| IgG ₂ | | |
| IgG ₃ | | |
| IgG ₄ | | |
| Measles antibody titre | | |
| Tetanus antibody titre | | |

| | | |
|-----------------------------|--|--|
| Pneumococcal antibody titre | | |
| Other (specify) | | |

Lymphocyte subsets (x 10⁹/L)

| | Percentage count | Absolute count | Reference range (absolute count) |
|-----------------------------|------------------|----------------|----------------------------------|
| CD3+ | | | |
| CD3+ CD4+ (Helper cells) | | | |
| CD3+CD8+ (Suppressor cells) | | | |
| CD19/20+ (B-cells) | | | |
| CD16/56+ (NK cells) | | | |
| DR+ (activated lymphocytes) | | | |

Lymphocyte stimulation tests

| Patient results | |
|---------------------------|--|
| Phycohaemagglutinin (PHA) | |
| Stimulation index | |
| Concanavalin A (Con A) | |
| Stimulation index | |
| Protein A (Prot A) | |
| Stimulation index | |
| Pokeweed (PWM) | |

| | |
|---------------------------|--|
| Stimulation index | |
| Control results | |
| Phycohaemagglutinin (PHA) | |
| Stimulation index | |
| Concanavalin A (Con A) | |
| Stimulation index | |
| Protein A (Prot A) | |
| Stimulation index | |
| Pokeweed (PWM) | |
| Stimulation index | |

Complement tests

| | Results | Reference range |
|-----------------------------|---------|-----------------|
| Total haemolytic complement | | |
| Component assay (specify): | | |
| | | |

Oxidative burst test

| Patient results | |
|-----------------------------------|--|
| Oxidising neutrophils: resting | |
| Oxidising neutrophils: stimulated | |
| Control results | |
| Oxidising neutrophils: resting | |

| | |
|-----------------------------------|--|
| Oxidising neutrophils: stimulated | |
|-----------------------------------|--|

Other tests (specify): _____

Sample bank

- serum DNA PBMCs EBV-transformed cells

Other (specify): _____

Comment (results)

Diagnosis

Associated problems (at diagnosis)

Treatment

- Antibiotic prophylaxis IVIG BMT

Other (specify): _____

Treatment details (e.g. duration IVIG, BMT type/induction):

Complications & outcome (e.g. complications after diagnosis, hospitalisation, cancers, death, lost-to-follow-up; include dates)

2.2 Ethics approval letter



UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee



Room E52-24 Old Main Building
Grootte Schuur Hospital
Observatory 7925
Telephone [021] 404 7682 • Facsimile [021] 406 6411
Email: nosi.tsama@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

28 March 2017

HREC REF: 191/2017

Prof B Eley
Paediatrics & Child Health
Room 520, 5th Floor
ICH Building
Red Cross Children's Hospital

Dear Prof Eley

PROJECT TITLE: A COMPREHENSIVE RETROSPECTIVE DESCRIPTIVE STUDY OF PRIMARY IMMUNODEFICIENCY DISEASES AT RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL, CAPE TOWN, SOUTH AFRICA, 1983-2016 (MMed candidate- Dr S Moodley)

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

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

Approval is granted for one year until the 30th March 2018.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student Dr S Moodley will be involved in this study.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate Institutional approval before the research may occur.

Please quote the HREC REF in all your correspondence.

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

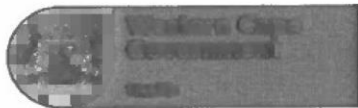
Yours sincerely

PP **PROFESSOR M BLOCKMAN**
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.

HREC 191/2017

2.3 Hospital approval letter

Dr Jane Kawadza
Manager: Medical Services
Email: Jane.Kawadza@Westerncape.gov.za
Tel: +27 21 658 5788 fax: +27 21 658 5166
RXH: RCC90



Prof Eley
Red Cross War Memorial Children's Hospital

Dear Prof Eley

APPROVAL OF RESEARCH

PROJECT TITLE: A COMPREHENSIVE RETROSPECTIVE DESCRIPTIVE STUDY OF PRIMARY IMMUNODEFICIENCY DISEASES AT RED CROSS WAR MEMORIAL CHILDRENS HOSPITAL (RCWMCH) , CAPE TOWN , SOUTH AFRICA, 1983 - 2016

It is a pleasure to inform you that approval is hereby granted to conduct the above-mentioned study at Red Cross War Memorial Children's Hospital.



Yours sincerely,

A handwritten signature in black ink, appearing to read "Jane Kawadza".

Dr J Kawadza
Manager: Medical Services
Date: 11.09.17

2.4 Latest progress report approved by Ethics Committee

FHS017: Annual Progress Report / Renewal

Record Reviews/Audits/Collection of Biological
Specimens/Repositories/Databases/Registers

HREC office use only (FWA00001637; IRB00001938)

This is notification of annual approval, including any documentation described below.

Approved Annual report Approved until/next renewal date 30.03.2020
 Not approved See attached comments

Signature Chairperson of the HREC Date Signed 24/5/19

Principal Investigator to complete the following: *Paul van der Merwe*

1. Protocol Information

HREC REF Number 21 May 2019
 HREC REF Number 191/2017 Current Ethics Approval was granted until 30 March 2018
 Protocol title A comprehensive retrospective descriptive study of primary immunodeficiency diseases at Red Cross War Memorial Children's Hospital, Cape Town, South Africa 1983-2016.
 Brian Ele
 Department / Office Room 520, 5th floor ICH building, Red Cross War Memorial Children's Hospital, Klipfontein Road, Rondebosch, 7701
 Internal Mail Address Email: bri

1.1 Does this receive US Federal funding? Yes No

2. Protocol status tick

Research-related activities are ongoing
 Data collection is complete, data analysis is complete

Please indicate (in the block below) the titles and HREC reference numbers of any projects currently making use of the

N/A

3. Protocol summary

Total number of records or specimens collected, reviewed or stored since the original 246
 Total number of records or specimens collected, reviewed or stored since last 246
 Have any research-related outputs (e.g. publications, abstracts, conference presentations) from this project? If so, please list them with HREC reference numbers Yes No

4. Signature and date

Signature of PI Date 21 May 2019

2.5 Protocol amendments approved by Ethics committee



Form FHS006: Protocol Amendment

| | | |
|---|---|---|
| HREC office use only (FWA00001637; IRB00001938) | | |
| <input checked="" type="checkbox"/> Approved | <input checked="" type="checkbox"/> Type of review: Expedited | <input type="checkbox"/> Full committee |
| This serves as notification that all changes and documentation described below are approved. | | |
| Signature Chairperson of the HREC | | Date |
| <p>Note: All <u>major</u> amendments must include a <u>partial PI Synopsis</u> justifying the changes for the amendment. Please note that incomplete amendment submissions will not be reviewed.</p> | | |
| Comments from the HREC to the Principal Investigator: | | |
| <p>Note: The approval of this protocol amendment does not grant annual approval. Please complete the <u>FHS016 / FHS017</u> form for annual approval at least one month before study expiration.</p> | | |

Principal Investigator to complete the following:

1. Protocol information

| | | |
|---|---|---|
| Date (when submitting this form) | 21 May 2019 | |
| HREC REF Number | 191/2017 | |
| Protocol title | A comprehensive retrospective descriptive study of primary immunodeficiency diseases at Red Cross War Memorial Children's Hospital, Cape Town, South Africa 1983-2016. | |
| Protocol number (if applicable) | N/A | |
| Principal Investigator | Brian Eley | |
| Department / Office Internal Mail Address | Room 520, 5 th floor ICH building, Red Cross War Memorial Children's Hospital, Klipfontein Road, Rondebosch, 7701; Email: brian.eley@uct.ac.za | |
| 1.1 Is this a major or a minor amendment? (see FHS006hlp) Major (tick box) Minor (tick box) | <input type="checkbox"/> Major | <input checked="" type="checkbox"/> Minor |
| 1.2 Does this protocol receive US Federal funding? | <input type="checkbox"/> Yes | <input checked="" type="checkbox"/> No |

1.2 If the amendment is a major amendment and receives US Federal Funding, does the amendment require full committee approval?



| | | |
|---|---|-----------------------------|
| <p>Note: Any protocol amendments for Full Committee review MUST be submitted on the monthly HREC submission dates. Please email an electronic copy to ethics@uct.ac.za</p> <p>2. List of Proposed Amendments with Revised Version Numbers and Dates Please itemise on the page below, all amendments with revised version numbers and dates, which need approval.</p> <p>This page will be detached, signed and returned to the PI as notification of approval. Please add extra pages if necessary.</p> | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| | <p>2. List of Proposed Amendments with Revised Version Numbers and Dates Please itemise on the page below, all amendments with revised version numbers and dates, which need approval.</p> <p><small>copy: ethics@uct.ac.za</small></p> | |

Title change to: "A retrospective description of primary immunodeficiency diseases at Red Cross War Memorial Children's Hospital, Cape Town, South Africa, 1975-2017."

In the data collection to date we've discovered two patients who were diagnosed before 1983 hence the need to change the start of the study period from 1983 to 1975.

There has been a delay in finalizing the study because Dr Moodley (MMed student) was focusing on completing her FCPaed studies and the exit examination, hence the need to extend the end date of the study from 2016 to 2017. This implies that we will add another 6 patients to the study cohort.

The changes to the protocol and synopsis are tracked on new versions of these documents, enclosed in this application

3. Protocol status (tick ✓)

- Open to enrolment
- No participants have been enrolled

- Closed to enrolment (tick ✓)
- Research-related activities are ongoing
- Research-related activities are complete, long-term follow-up only
- Research-related activities are complete, data analysis only

4. Proposed changes will affect: (tick ✓ all the categories that apply)

Protocol

- Study objectives, design (including investigator's brochure, clinical activities, study length)
- Study instruments, questionnaires, interview schedules
- Sample size
- Recruitment methods
- Eligibility criteria (inclusion and exclusion criteria)
- Drug/device (composition, amount, schedule, route of administration, combination with other drugs/devices, safety information)

| | |
|---|--|
| <input type="checkbox"/> | Data collection/ analysis |
| <input type="checkbox"/> | Principal Investigator. (Please attach revised conflict of interest and PI declaration statements. Refer sections 7 and 8.4 in the New Protocol Application Form FHS013) |
| <input type="checkbox"/> | Consent form and information sheet |
| <input type="checkbox"/> | Recruitment materials (e.g. advertisements) |
| <input type="checkbox"/> | Administrative (e.g. change in sponsor's name, change in contact information) |
| <input type="checkbox"/> | Other. Please specify: |
| 4.1 In your opinion, will there be any increase in risk, discomfort or inconvenience to participants? | |
| | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |
| If yes, please provide a detailed justification/explanation: | |
| This is a retrospective study | |

| | |
|--|--|
| 4.2 What follow-up action do you propose for participants who are already enrolled in the study? | |
| <input type="checkbox"/> | Inform current participants as soon as possible |
| <input type="checkbox"/> | Re-consent current participants with revised consent/assent forms (append) |
| <input checked="" type="checkbox"/> | No action required |
| <input type="checkbox"/> | Other. Please describe: |

5. Detailed description of the change(s)

Please attach, for each amendment, a summary of all changes which clearly indicates:

- Old wording (e.g. ~~striketrough~~ text, CHANGED FROM and CHANGED TO)
- New wording (e.g. *italicized*, **bold**, tracked)
- Detailed rationale/ justification/ explanation for each change

6. Ethics Review Levy – cost including vat

Cost for Major Amendments - R3 691.20
 (Protocols funded by UCT (e.g. departmental funding student research) and by certain grant funding organizations (e.g. MRC, NRF, CANSA,) are exempt from charges)

For invoicing purposes, please provide:

| | |
|----------------|--|
| Sponsor's name | |
| Contact person | |



| | |
|------------------|--|
| Address | |
| Telephone number | |
| Email Address | |

7. Signature

| | |
|--|--------------|
| My signature certifies that I will maintain the anonymity and/ or confidentiality of information collected in this research. If at any time I want to share or re-use the information for purposes other than those disclosed in the original approval I will seek further approval from the HREC. | |
| Signature of PI | BJR _____ |
| Date | 21 May 2019 |

2.6 Instructions to authors of the South African Medical Journal

The SAMJ has launched a new submission and tracking system. Authors will be required to register a profile on the Editorial Manager platform in order to submit a manuscript.

To submit a manuscript, please proceed to the SAMJ Editorial Manager website:

www.editorialmanager.com/samj

To access and submit an article already in production, please see the guidelines [here](#).

Author Guidelines

Please view the [Author Tutorial](#) for guidance on how to submit on Editorial Manager.

Please take the time to familiarise yourself with the policies and processes below. If you still have any questions, please do not hesitate to ask our editorial staff (tel.: +27 (0)21 532 1281, email: submissions@hmpg.co.za).

SAMJ policies

- [Types of articles considered by the SAMJ](#)
- [Article Processing Charges](#)
- [Authorship](#)
- [Conflict of interest](#)
- [Research ethics committee approval](#)
- [Clinical trials](#)
- [Protection of patient's rights to privacy](#)
- [Copyright notice](#)
- [Privacy statement](#)
- [Ethnic classification](#)
- [CPD](#)

Manuscript preparation

- [Preparing an article for anonymous review](#)
- [General article format/layout](#)
- [Preparation notes by article type](#)
- [Illustrations](#)
- [Tables](#)
- [References](#)

From submission to acceptance

- [Submission and peer-review](#)
- [Production process](#)
- [Changing contact details or authorship](#)

Publication

- [Online versus print](#)
- [Errata and retractions](#)
- [Indexing](#)

SAMJ Policies

Type of articles considered by the SAMJ

The *SAMJ* will no longer limit the articles accepted to those that have 'general medical content', but is intending to capture the spectrum of medical and health sciences, grouped by relevance to the country's burdens of disease. This content will include research in the social sciences and economics that is relevant to the medical issues around our burden of disease. Please see '[A new vision for the SAMJ – and a call for papers](#)' for a full discussion of the new directions for the *SAMJ*.

We accept the following types of articles:

Research

Reviews

Clinical trials

Editorials

In Practice (Previously Forum incl. Case Reports)

Correspondence

Obituaries

Book reviews

Ad hoc supplements e.g. guidelines, conference/congress abstracts, Festschrifts*

The following articles are by invitation only:

Guest editorial

Continuing Medical Education (CME)

*Contact claudian@hmpg.co.za for information on submitting ad hoc/commissioned supplements, including guidelines, conference/congress abstracts, Festschrifts, etc.

Publication Fees

All articles published in the *South African Medical Journal* are open access and freely available online upon publication. This is made possible by applying a business model to offset the costs of peer review management, copyediting, design and production, by charging a publication fee of R5 250 (ex vat) for each research article published. The charge applies only to **Research** articles submitted after 1 March 2017. The publication fee is standard and does not vary based on length, colour, figures, or other elements.

When submitting a Research article to the *SAMJ*, the submitting author must agree to pay the publication fee should the article be accepted for publication. The publication fee is payable when your manuscript is editorially accepted and before production commences for publication. The submitting author will be notified that payment is due and given details on the available methods of payment. Prompt payment is advised; the article will not enter into production until payment is received. Queries can be directed to claudian@hmpg.co.za.

Please refer to the section on 'Sponsored Supplements' regarding the publication of supplements, where a charge is applicable. Queries can be directed to dianes@hmpg.co.za or claudian@hmpg.co.za

Authorship

Named authors must consent to publication. Authorship should be based on: (i) substantial contribution to conceptualisation, design, analysis and interpretation of data; (ii) drafting or critical revision of important scientific content; or (iii) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to www.icmje.org)

If authors' names are added or deleted after submission of an article, or the order of the names is changed, all authors must agree to this in writing.

Please note that co-authors will be requested to verify their contribution upon submission. Non-verification may lead to delays in the processing of submissions.

Author contributions should be listed/described in the manuscript.

Conflicts of interest

Conflicts of interest can derive from any kind of relationship or association that may influence authors' or reviewers' opinions about the subject matter of a paper. The existence of a conflict – whether actual, perceived or potential – does not preclude publication of an article. However, we aim to ensure that, in such cases, readers have all the information they need to enable them to make an informed assessment about a publication's message and conclusions. We require that both authors and reviewers declare all sources of support for their research, any personal or financial relationships (including honoraria, speaking fees, gifts received, etc) with relevant individuals or organisations connected to the topic of the paper, and any association with a product or subject that may constitute a real, perceived or potential conflict of interest. If you are unsure whether a specific relationship constitutes a conflict, please contact the editorial team for advice. If a conflict remains undisclosed and is later brought to the attention of the editorial team, it will be considered a serious issue prompting an investigation with the possibility of retraction.

Research ethics committee approval

Authors must provide evidence of Research Ethics Committee approval of the research where relevant. Ensure the correct, full ethics committee name and reference number is included in the manuscript.

If the study was carried out using data from provincial healthcare facilities, or required active data collection through facility visits or staff interviews, approval should be sought from the relevant provincial authorities. For South African authors, please refer to the guidelines for submission to the [National Health Research Database](#). Research involving human subjects must be conducted according to the principles outlined in the Declaration of Helsinki. Please refer to the National Department of Health's guideline on [Ethics in Health research: principles, processes and structures](#) to ensure that the appropriate requirements for conducting research have been met, and that the HPCSA's [General Ethical Guidelines for Health Researchers](#) have been adhered to.

Clinical trials

As per the recommendations published by the International Committee of Medical Journal Editors (ICMJE), clinical trial research is any research that assigns individuals to an intervention, with or without a concurrent comparison/control group to study the cause-and-effect relationship between the intervention and health outcomes. All clinical trials should be registered with the appropriate national clinical trial registry (or any international primary register, if relevant), and the trial registration number should be cited at the end of the abstract. All clinical trial reports must also contain a data sharing statement as per the recommendations of the ICMJE. Statements are to indicate:

- whether individual deidentified participant data will be shared;
- what data in particular will be shared; whether additional, related documents will be available;

- when the data will become available and for how long; by what access criteria data will be shared.

Please see the ICJME announcement for further details and illustrative examples of data sharing statements: [ICMJE Data Sharing Statements for Clinical Trials](#)

Since 1st December 2005, all clinical trials conducted in South Africa have been required to be registered in the South African National Clinical Trials Register. The SAMJ therefore requires that clinical trials be registered in the relevant public trials registry at or before the time of first patient enrollment as a condition for publication. The trial registry name and registration number must be included in the manuscript.

Please refer to the general guidelines for all papers at the top of this article for additional requirements with respect to ethics approval, funding, author contributions, etc. The format of original research articles should be followed for reporting of clinical trial results.

Patient Consent

Information that would enable identification of individual patients should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) has given informed written consent for publication and distribution. We further recommend that the published article is disseminated not only to the involved researchers but also to the patients/participants from whom the data was drawn. Refer to [Protection of Research Participants](#). The signed consent form should be submitted with the manuscript to enable verification by the editorial team.

Other individuals

Any individual who is identifiable in an image must provide [written agreement](#) that the image may be used in that context in the *SAMJ*.

Copyright notice

Copyright remains in the Author's name. The work is licensed under a [Creative Commons Attribution - Noncommercial Works License](#). Authors are required to complete and sign an [Author Agreement form](#) that outlines Author and Publisher rights and terms of publication. The **[Author Agreement form](#)** should be uploaded along with other submissions files and any submission will be considered incomplete without it.

Material submitted for publication in the *SAMJ* is accepted provided it has not been published or submitted for publication elsewhere. Please inform the editorial team if the main findings of your paper have been presented at a conference and published in abstract form, to avoid copyright infringement. All research already published as 'Conference proceedings' needs to be substantially re-written, with a new title, a new abstract and new and important results to back up any study before it will be considered for a new publication. The *SAMJ* does not hold itself responsible for statements made by the authors.

Previously published images

If an image/figure has been previously published, permission to reproduce or alter it must be obtained by the authors from the original publisher and the figure legend must give full credit to the original source. This credit should be accompanied by a letter indicating that permission to reproduce the image has been granted to the author/s. This letter should be uploaded as a supplementary file during submission.

Privacy statement

The *SAMJ* is committed to protecting the privacy of its website and submission system users. The names, personal particulars and email addresses entered in the website or submission system will not be made available to third parties without the user's permission or due process. By registering to use the website or submission system, users consent to receive communication from the *SAMJ* or its publisher HMPG on matters relating to the journal or associated publications. Queries with regard to privacy may be directed to publishing@hmpg.co.za.

Ethnic/race classification

Use of racial or ethnicity classifications in research is fraught with problems. If you choose to use a research design that involves classification of participants based on race or ethnicity, or discuss issues with reference to such classifications, please ensure that you include a detailed rationale for doing so, ensure that the categories you describe are carefully defined, and that socioeconomic, cultural and lifestyle variables that may underlie perceived racial disparities are appropriately controlled for. Please also clearly specify whether race or ethnicity is classified as reported by the patient (self-identifying) or as perceived by the investigators. Please note that it is not appropriate to use self-reported or investigator-assigned racial or ethnic categories for genetic studies.

Continuing Professional Development (CPD)

SAMJ is an HPCSA-accredited service provider of CPD materials. Principal authors can earn up to 15 CPD continuing education units (CEUs) for publishing an article; co-authors are eligible to earn up to 5 CEUs; and reviewers of articles can earn 3 CEUs. Each month, *SAMJ* also publishes a CPD-accredited questionnaire relating to the academic content of the journal. Successful completion of the questionnaire with a pass rate of 70% will earn the reader 3 CEUs. Administration of our CPD programme is managed by Medical Practice Consulting. To complete questionnaires and obtain certificates, please visit [MRP Consulting](#)

Manuscript preparation

Preparing an article for anonymous review

To ensure a fair and unbiased review process, all submissions are to include an anonymised version of the manuscript. The exceptions to this are Correspondence, Book reviews and Obituary submissions.

Submitting a manuscript that needs additional blinding can slow down your review process, so please be sure to follow these simple guidelines as much as possible:

- An anonymous version should not contain any author, affiliation or particular institutional details that will enable identification.
- Please remove title page, acknowledgements, contact details, funding grants to a named person, and any running headers of author names.
- Mask self-citations by referring to your own work in third person.

General article format/layout

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, which will delay publication.

General:

- Manuscripts must be written in UK English.
- The manuscript must be in Microsoft Word format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes).
- Please make your article concise, even if it is below the word limit.
- Qualifications, **full** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Include sections on Acknowledgements, Conflict of Interest, Author Contributions and Funding sources. If none is applicable, please state 'none'.
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).
- Units should be preceded by a space (except for % and °C), e.g. '40 kg' and '20 cm' but '50%' and '19°C'.
- Please be sure to insert proper symbols e.g. μ not u for micro, α not a for alpha, β not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.
- If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

SAMJ is a generalist medical journal, therefore for articles covering genetics, it is the responsibility of authors to apply the following:

- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.
- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.

****NB:** Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.

- Define all genes, proteins and related shorthand terms at first mention, e.g. '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.'
- Use the latest approved gene or protein symbol as appropriate:

- Human Gene Mapping Workshop (HGMW): genetic notations and symbols
- HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
- Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

Preparation notes by article type

- [Research](#)
- [Editorials](#)
- [CME](#)
- [In Practice and Case reports](#)
- [Reviews](#)
- [Clinical trials](#)

- [Correspondence](#)
- [Obituaries](#)
- [Book reviews](#)
- [Guidelines](#)

Research

Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.

Do not replicate data in tables and in text .

Structured abstract

- This should be 250-400 words, with the following recommended headings:
 - **Background:** why the study is being done and how it relates to other published work.
 - **Objectives:** what the study intends to find out
 - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
 - **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
 - **Conclusion:** must be supported by the data, include recommendations for further study/actions.
- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

[Here](#) is an example of a good abstract.

Main article

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.

The following are additional heading or section options that may appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc) that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.
- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results

- Start with description of the population and sample. Include key characteristics of comparison groups.
- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number needed to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
- E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the \pm symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

- Statement of principal findings
- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies
- The meaning of the study – e.g. what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

Conclusions

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.

Editorials

Guideline word limit: 1 000 words

These opinion or comment articles are usually commissioned but we are happy to consider and peer review unsolicited editorials. Editorials should be accessible and interesting to readers without specialist knowledge of the subject under discussion and should have an

element of topicality (why is a comment on this issue relevant now?) There should be a clear message to the piece, supported by evidence.

Please make clear the type of evidence that supports each key statement, e.g.:

- expert opinion
- personal clinical experience
- observational studies
- trials
- systematic reviews.

CME (by invite only)

CME is intended to provide readers with practical, up-to-date information on medical and related matters. It is aimed at those who are not specialists in the field.

From January 2016, all CME articles will be printed in full in the *SAMJ*. Please try to adhere strictly to the guidelines on word count as we have a page limit for the print issue of the *SAMJ*. We reserve the right to place some tables and reference lists online if this is necessary for space.

In practice, this means that each CME topic usually covers two issues of the print issue of the *SAMJ*.

The guest editor, in consultation with the editor, is responsible for convening a team of authors, deciding on the subjects to be covered and for reviewing the manuscripts submitted. The suggestion is for 4 - 5 articles, although there is some room for flexibility contingent on discussions with the editor.

For queries about these guidelines please feel free to contact the CME editor, Dr Bridget Farham, by email (ugqirha@iafrica.com) or telephone (+27 (0)21 789 2331).

Review process

The guest editor reviews the articles and returns them to the CME editor for review and final approval.

Guest editorials

Guideline word limit: 1 000 words

- Include the guest editor's personal details (qualifications, positions, affiliation, e-mail address, and a short personal profile (50 words)).
- If possible, include a photograph of the author(s) at high enough resolution for print. It is preferable to provide two guest editorials, one for each issue, so that the content of the articles in each issue is covered.

Articles

Guideline word limit: 2 000 - 3 000 words

- Each article requires an abstract of ± 200 words.
- The editor reserves the right to shorten articles but will send a substantially shortened article back for author approval.

Personal details

Please supply: Your qualifications, position and affiliations and MP number (used for CPD points); Address, telephone number and fax number, and your e-mail address; and a short personal profile (50 words) and a few words about your current fields of interest.

In Practice

Guideline word limit: 2 000 - 3 000 words

This section includes articles that would previously have been accepted into the Forum section, and case reports.

In practice articles are those that draw attention to specific issues of clinical, economic or political interest regarding medicine and healthcare in southern Africa. They are assigned to a topic:

Case report
Clinical practice
Clinical alert
Issues in medicine
Issues in public health
Healthcare delivery
Consensus/Position statement
Medicine and the environment
Medicine and the law
Cochrane corner

An In Practice article should follow the following format – sub-headings are not necessary, but may be used for clarity:

- Author affiliations and qualifications: to be the same as for Research. Provide all authors' names and initials, qualifications and full affiliations, and corresponding author.
- Short abstract: does not need to be structured, but should capture the essential features of the article
- Introduction: the reason for the article and the issue being addressed
- Recent research, discussion, local policy around the issue – include your own research where appropriate
- All statements should be referenced and, if opinion only, this should be stated
- Discussion: how this article adds to the discussion around a particular topic
- If a clinical practice or policy point is at issue, this needs to be emphasised, using a box with highlights if appropriate.

Essentially In practice is an opportunity for a more discursive approach to topics of clinical, economic or political importance in southern African health systems. It is not an opportunity to put forward unsubstantiated opinions!

Case reports

The *SAMJ* has recently started to accept case reports. The cases must come from Africa, preferably southern Africa unless the condition is common to all African countries, and must be either a completely new description of a clinical condition or result (use Google!) or a case that highlights important practice or management issues.

Please use the following format for case reports:

- Title of case: do not include the words 'a case report' in the title
- Summary/abstract: up to 150 words summarising the case presentation and outcome
- Background: why is this case important and why did you write it up?
- Case presentation: presenting features, medical, social, family history as appropriate
- Case management: should be according to best practice, and if not, please explain why
- Investigations, if relevant: save space by simply saying 'normal' if, for example, renal function was completely normal, rather than listing normal results, highlight the abnormal – or indeed the normal if this is clinically significant
- Differential diagnosis, if relevant
- Treatment, if relevant
- Outcome and follow-up
- Discussion – a VERY BRIEF review of similar published cases
- Teaching points: 3 - 5 bullet points
- References: as per the *SAMJ* house style
- Tables and figures: keep to a minimum. Use clinical images where relevant – we need hi-res versions for print, and identifiable persons must have a consent form
- Patient consent: please include a statement about patient consent to a written case report. This should be uploaded as a supplementary file.

Clinical trials

Guideline word limit: 4000 words

As per the recommendations published by the International Committee of Medical Journal Editors (ICMJE), clinical trial research is any research that assigns individuals to an intervention, with or without a concurrent comparison/control group to study the cause-and-effect relationship between the intervention and health outcomes. All clinical trials should be registered with the appropriate national clinical trial registry (or any international primary register, if relevant), and the trial registration number should be cited at the end of the abstract. Since 1st December 2005, all clinical trials conducted in South Africa have been required to be registered in the [South African National Clinical Trials Register](#). The *SAMJ* therefore requires that clinical trials be registered in the relevant public trials registry at or before the time of first patient enrollment as a condition for publication. The trial registry name and registration number must be included in the manuscript.

Please refer to the general guidelines for all papers at the top of this article for additional requirements with respect to ethics approval, funding, author contributions, etc. The format of original research articles should be followed for reporting of clinical trial results.

Review articles

Guideline word limit: 4 000 words

These are welcome, but should be either commissioned or discussed with the Editor before submission. A review article should provide a clear, up-to-date account of the topic and be aimed at non-specialist hospital doctors and general practitioners.

Please ensure that your article includes:

- Abstract: unstructured, of about 100-150 words, explaining the review and why it is important
- Methods: Outline the sources and selection methods, including search strategy and keywords used for identifying references from online bibliographic databases. Discuss the quality of evidence.
- When writing: clarify the evidence you used for key statements and the strength of the evidence. Do not present statements or opinions without such evidence, or if you have to, say

that there is little or no evidence and that this is opinion. Avoid specialist jargon and abbreviations, and provide advice specific to southern Africa.

- Personal details: Please supply your qualifications, position and affiliations and MP number (used for CPD points); address, telephone number and fax number, and your e-mail address; and a short personal profile (50 words) and a few words about your current fields of interest.

Correspondence (Letters to the Editor)

Guideline word limit: 500 words

Letters to the editor should relate either to a paper or article published by the SAMJ or to a topical issue of particular relevance to the journal's readership

- May include only one illustration or table
- Must include a correspondence address.

Book reviews

Guideline word limit: 400 words

Should be about 400 words and must be accompanied by the publication details of the book. Provide a hi-res image of the cover if possible (with permission from the copyright holder).

Obituaries

Guideline word limit: 400 words

Should be offered within the first year of the practitioner's death, and may be accompanied by a photograph.

Guidelines

Guidelines should always be discussed with the Editor prior to submission.

Because of the intensive review process required to ensure Guidelines are independent, evidence-based and free from commercial bias, they are usually published as a supplement to the *SAMJ*, the costs of which must be covered by sponsorship, advertising or payment by the guideline authors/association. We will provide a quote based on the expected length of the guideline and whether it is to appear online only, or in print, which must be accepted by the body putting the guidelines together before submitting the work to the SAMJ.

The Editor reserves the right to determine the scheduling of supplements. Understandably, a delay in publication must be anticipated dependent upon editorial workflow.

All guidelines should include a clear, transparent statement about all sources of funding and an explicit, clear statement of conflicts of interest of any of the participants in the guidelines about industry funding for lectures, research, conference participation etc.

All guidelines should be structured according to [Agree II](#).

Please access this website before putting the guidelines together, download the Agree 11 instrument and use this to put the guidelines together.

All submitted guidelines will be sent to the local Agree II appraisal committee for review and must be endorsed by an appropriate body prior to consideration and all conflicts of interest expressed.

A structured abstract not exceeding 400 words (recommended sub-headings: *Background, Recommendations, Conclusion*) is required. Sections and sub-sections must be numbered

consecutively (e.g. 1. Introduction; 1.1 Definitions; 2.etc.) and summarised in a Table of Contents.

Illustrations/photos/scans

- If illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.
- Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'. Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
- All images must be of high enough resolution/quality for print.
- All illustrations (graphs, diagrams, charts, etc.) must be in PDF or jpeg form.
- Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.
- Scans/photos showing a specific feature e.g. *Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain)*. –include an arrow to show the tumour.
- Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author
- Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
- Number each table in Arabic numerals (Table 1, Table 2, etc.) and refer to consecutively in the text.
- Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.
- Ensure each table has a concise title and column headings, and include units where necessary.
- Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Do not: Use [Enter] within a row to make 'new rows':

Rather:

Each row of data must have its own proper row:

Do not: use separate columns for n and %:

Rather:

Combine into one column, n (%):

Do not: have overlapping categories, e.g.:

Rather:

Use <> symbols or numbers that don't overlap:

References

NB: Only complete, correctly formatted reference lists in Vancouver style will be accepted. Reference lists must be generated manually and not with the use of reference manager software. Endnotes must **not** be used.

- Authors must verify references from original sources.
- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,^[2] and others.^[3,4-6]
- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
- Approved abbreviations of journal titles must be used; see the [List of Journals in Index Medicus](#).
- Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
- Volume and issue numbers should be given.
- First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.
- Wherever possible, references must be accompanied by a digital object identifier (DOI) link. Authors are encouraged to use the DOI lookup service offered by [CrossRef](#):
 - On the Crossref homepage, paste the article title into the 'Metadata search' box.
 - Look for the correct, matching article in the list of results.
 - Click Actions > Cite
 - Alongside 'url =' copy the URL between { }.
 - Provide as follows, e.g.: <https://doi.org/10.7196/07294.937.98x>

Some examples:

- *Journal references:* Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. *Stat Med* 1998;289(1):350-355. <http://dx.doi.org/10.1000/hgjr.182>
- *Book references:* Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.
- *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.
- *Internet references:* World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. <http://www.who.int/whr/2002> (accessed 16 January 2010).
- Legal references

- Government Gazettes:

National Department of Health, South Africa. National Policy for Health Act, 1990 (Act No. 116 of 1990). Free primary health care services. Government Gazette No. 17507:1514. 1996.

In this example, 17507 is the Gazette Number. This is followed by :1514 - this is the notice number in this Gazette.

- Provincial Gazettes:

Gauteng Province, South Africa; Department of Agriculture, Conservation, Environment and Land Affairs. Publication of the Gauteng health care waste management draft regulations. Gauteng Provincial Gazette No. 373:3003, 2003.

- Acts:

South Africa. National Health Act No. 61 of 2003.

- Regulations to an Act:

South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic medicine services. Government Gazette No. 35099, 2012. (Published under Government Notice R176).

- Bills:

South Africa. Traditional Health Practitioners Bill, No. B66B-2003, 2006.

- Green/white papers:

South Africa. Department of Health Green Paper: National Health Insurance in South Africa. 2011.

- Case law:

Rex v Jopp and Another 1949 (4) SA 11 (N)

Rex v Jopp and Another: Name of the parties concerned

1949: Date of decision (or when the case was heard)

(4): Volume number

SA: SA Law Reports

11: Page or section number

(N): In this case Natal - where the case was heard. Similarly, (C) would indicate Cape, (G) Gauteng, and so on.

NOTE: no . after the v

- *Other references (e.g. reports) should follow the same format: Author(s). Title. Publisher place: Publisher name, year; pages.*
- Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'.
- Unpublished observations and personal communications in the text must **not** appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

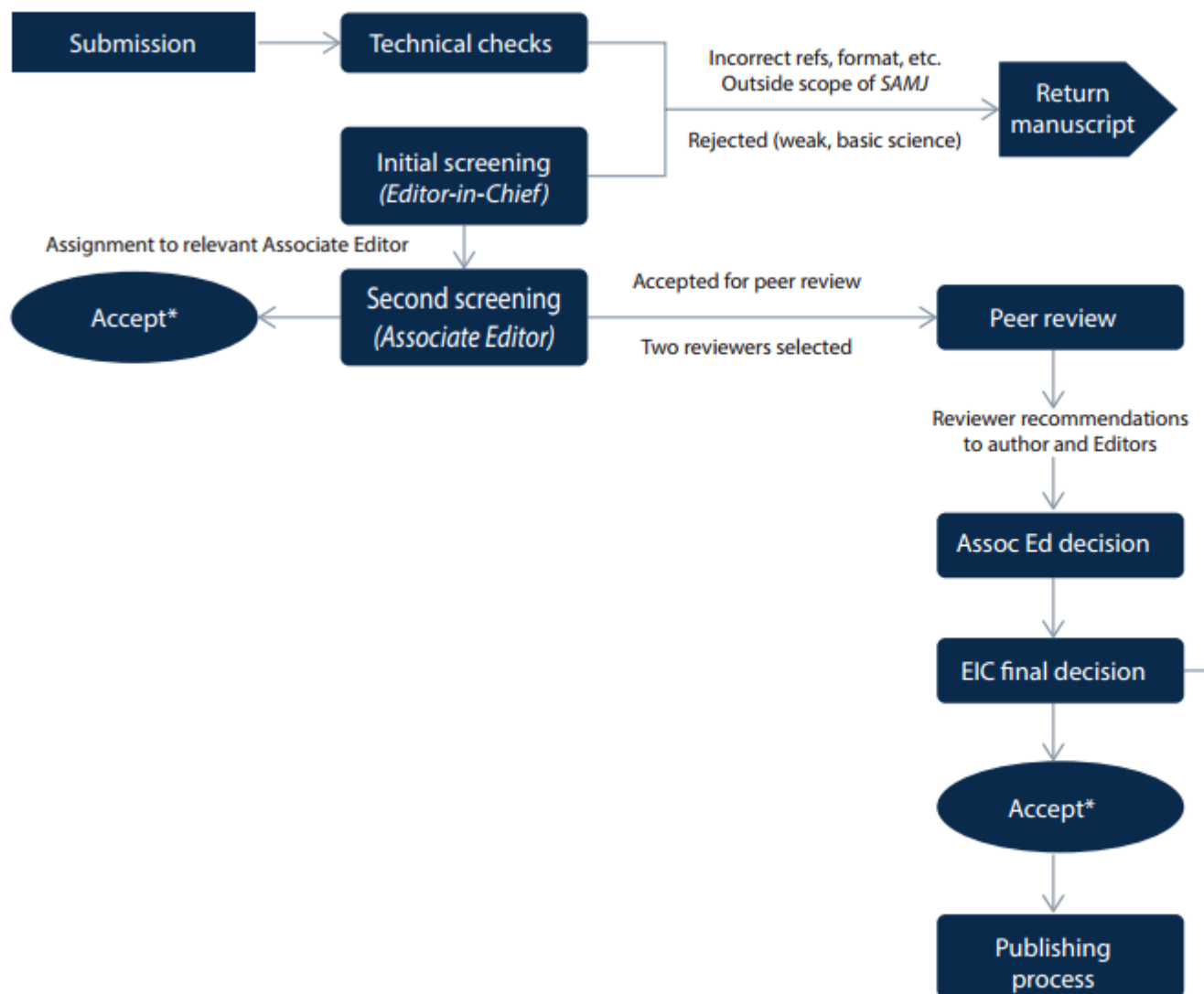
From submission to acceptance

Submission and peer-review

To submit an article:

- Please ensure that you have prepared your manuscript in line with the SAMJ requirements.
- All submissions should be submitted via [Editorial Manager](#)
- The following are required for your submission to be complete:
 - Anonymous manuscript (unless otherwise stated)
 - **Author Agreement form**
 - Manuscript
 - Any supplementary files: figures, datasets, patient consent form, permissions for published images, etc.
- Once the submission has been successfully processed on Editorial Manager, it will undergo a technical check by the Editorial Office before it will be assigned to an editor who will handle the review process. If the author guidelines have not been appropriately followed, the manuscript may be sent back to the author for correcting.

Peer-review process



*Manuscripts accepted at this point are limited to Editorials, Correspondence, Obituaries, Book reviews, Abstracts, CME
 **Some minor revisions may be requested

Production process

The following process will follow:

1. An accepted manuscript is passed to a Managing Editor to assign to a copyeditor (CE).
2. The CE copyedits in Word, working on house style, format, spelling/grammar/punctuation, sense and consistency, and preparation for typesetting.
3. If the CE has an author queries, he/she will contact the corresponding author and send them the copyedited Word doc, asking them to solve the queries by means of track changes or comment boxes.
4. The authors are typically asked to respond within 1-3 days. Any comments/changes must be clearly indicated e.g. by means of track changes. Do not work in the original manuscript - work in the copyedited file sent to you and make your changes clear.
5. The CE will finalise the article and then it will be typeset.
6. Once typeset, the CE will send a PDF of the file to the authors to complete their final check, while simultaneously sending to the 2nd-eye proofreader.

7. The authors are typically asked to complete their final check and sign-off within 1-2 days. No major additional changes can be accommodated at this point.
8. The CE implements the authors' and proofreader's mark-ups, finalises the file, and prepares it for the upcoming issue.

Changing contact details or authorship

Please notify the Editorial Department of any contact detail changes, including email, to facilitate communication.

Publication

Online v. print

The *SAMJ* is an online journal. The online version of the journal is the one that has the widest circulation, is indexed by bibliographic databases including PubMed and SciELO, and is accessible in academic libraries. A printed edition, containing material selected by the Editor is also published each month and distributed to the membership of the South African Medical Association.

Online

- The full text of all accepted articles is published in full online, open access.
- Citation information of each article is based on its online publication.
- You may want to make use of the advantages of online publication e.g. specify web links to other sources, images, data or even a short video.

Print

- Not all articles will be selected for print.
- An article may be selected for print in a different month from that in which it was published online.
- Research articles will appear *in abstract form only*, if selected for a print edition.

Errata and retractions

Errata

Should you become aware of an error or inaccuracy in yours or someone else's contribution after it has been published, please inform us as soon as possible via an email to publishing@hmpg.co.za, including the following details:

- Journal, volume and issue in which published
- Article title and authors
- Description of error and details of where it appears in the published article
- Full detail of proposed correction and rationale

We will investigate the issue and provide feedback. If appropriate, we will correct the web version immediately, and will publish an erratum in the next issue. The correction will be

indexed, as PubMed has a function for linking errata back to the original article. All investigations will be conducted in accordance with guidelines provided by the Committee on Publication Ethics ([COPE](#)).

Retractions

Retraction of an article is the prerogative of either the original authors or the editorial team of HMPG. Should you wish to withdraw your article before publication, we need a signed statement from all the authors.

Should you wish to retract your published article, all authors have to agree in writing before publication of the retraction.

Send an email to publishing@hmpg.co.za, including the following details:

- Journal, volume and issue to which article was submitted/in which article was published
- Article title and authors
- Description of reason for withdrawal/retraction.

We will make a decision on a case-by-case basis upon review by the editorial committee in line with international best practices. Comprehensive feedback will be communicated with the authors with regard to the process. In case where there is any suspected fraud or professional misconduct, we will follow due process as recommended by the Committee on Publication Ethics (COPE), and in liaison with any relevant institutions.

When a retraction is published, it will be linked to the original article.

Indexing

The *SAMJ* has an impact factor of 1.5.

Published articles are covered by the following major indexing services. As such articles published in the *SAMJ* are immediately available to all users of these databases, guaranteed a global and African audience:

- Index Medicus (Medline/PubMed)
- ExcerptaMedica (EMBASE)
- Biological Abstracts (BIOSIS)
- Science Citation Index (SciSearch)
- Current Contents/Clinical Medicine
- Scopus
- AIM
- AJOL
- Crossref
- Sabinet
- Scielo

Sponsored supplements

Contact claudian@hmpg.co.za for information on submitting ad hoc/commissioned supplements, including guidelines, conference/congress abstracts, Festschriften, etc.

Submission Preparation Checklist

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

1. Named authors consent to publication and meet the requirements of authorship as set out by the journal.
2. The submission has not been previously published, nor is it before another journal for consideration. All research already published as 'Conference proceedings' needs to be substantially re-written, with a new title, a new abstract and new and important results to back up any study before it will be considered for a new publication.
3. The text complies with the stylistic and bibliographic requirements in **Author Guidelines**.
4. The manuscript is in Microsoft Word document format. The text is single-spaced, in 12-point Times New Roman font, and contains no unnecessary formatting.
5. Illustrations/figures are high resolution/quality (not compressed) and in an acceptable format (PDF or jpeg). These must be submitted individually as 'supplementary files' (not solely embedded in the manuscript).
6. For illustrations/figures or tables that have been published elsewhere, the author has obtained written consent to republication from the copyright holder.
7. Where possible, references are accompanied by a digital object identifier (DOI).
8. An abstract has been included where applicable.
9. The research was approved by a Research Ethics Committee (if applicable)
10. Any conflict of interest (or competing interests) is indicated by the author(s).

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2.7 Letter to the editor of the South African Medical Journal



UNIVERSITY OF CAPE TOWN
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5 June 2019

The Editor
South African Medical Journal

Dear Dr Farham

Enclosed manuscript entitled 'A retrospective description of primary immunodeficiency diseases at Red Cross War Memorial Children's Hospital, Cape Town, South Africa, 1975 – 2017'

I have just qualified as a paediatrician in South Africa. I write this article for every colleague of every level from the general practitioner to the training paediatrician, to every one of those well versed in the field of child health.

Diagnosing a child with primary immune deficiency in our South African setting of a sea of secondary immunodeficiencies like HIV infection and malnutrition is daunting. Thus, many remain underdiagnosed and under-reported, yet simple investigations and treatment options implemented early could improve their outcome and limit morbidity and mortality.

This fascinating spectrum of diseases is rapidly expanding worldwide, and not as rare as we think. Genetic characterization and newborn screening for primary Immunodeficiency diseases (PIDs) may be the gold standard in the first world setting but are neither practical nor feasible for our doctors. Yet, other low and middle income countries in the world have also established reasonable services and created registries for children with PIDs, including other African countries. The African Society for Immunodeficiencies (ASID) host campaigns throughout Africa, advocating for patient and physician education.

In this paper we describe the biggest case series of 252 children with PIDs at a single centre over 4 decades in Sub-Saharan Africa to date.

The child with the recurrent, unusual or persistent infection who fails to thrive must be the recognized as a warning sign for a possible PID by the primary clinician and referred for expert opinion, feasible investigations and early intervention. We are able to describe the spectrum of diseases classified according to the International Union of Immunological Societies (IUIS).

We, the co-authors write this for every child and family with PIDs in South Africa, Africa and the world. We hope that the SAMJ will be a portal of advocacy for all children, rare, and precious.

I confirm that all co-authors have approved the final manuscript. Furthermore, this manuscript has not been submitted to another journal nor previously published.

Please consider this manuscript for publication in the SAMJ. I look forward to your response.

Yours in good faith

Sashmi Moodley, MBCHB(UKZN), DCH(SA), Dip HIV Man(SA), FCPaed(SA), corresponding author

2.8 South African Medical Journal's comments

From: SAMJ <em@editorialmanager.com>

Date: 2019/07/01 11:33 (GMT+02:00)

To: Sashmi Moodley <sashmi.moodley@yahoo.com>

Subject: Decision on your Submission to SAMJ

Ref.: SAMJ14200

A retrospective description of primary immunodeficiency diseases at Red Cross war Memorial Children's Hospital, Cape Town, South Africa, 1975 - 2017
South African Medical Journal

Dear Dr Moodley,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript.

For your guidance, reviewers' comments are appended below.

If you are prepared to undertake the work required, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript.

Your revision is due by Jul 29, 2019. Please let us know if you require additional time.

To submit a revision, go to <https://www.editorialmanager.com/sami/> and log in as an Author. You will see a menu item called Submission Needing Revision.

Best wishes

Bridget Farham, PhD
Editor
South African Medical Journal

Reviewers' comments:

Reviewer's Responses to Questions

Please comment on your General impression of this manuscript - bear the following in mind:

Is the article relevant?

Does it offer anything new?

Are there similar studies in our region/outside the region?

Does it add to the existing medical body of knowledge?

On first glance, are the methods, results and conclusions reasonable?

Do the conclusions actually draw on the results?

Does the article have a clear message?

Will it help SAMJ readers make better clinical decisions and, if so, how?

Is a general medical journal the right place for it?

Reviewer #1: This is an interesting and important study as it documents a neglected field of paediatrics, updating previous literature by attempting to comprehensively include children managed at a children's hospital across all sub-specialist disciplines.

The study also serves to raise awareness among general paediatricians about the importance of considering PID in children presenting with recurrent infections/ and or particular medical conditions. the importance being that there may be specific, life-saving and curative treatment available as well as preventative measures that could limit disease complications

Please comment on the Methods and analysis presented in this manuscript

Study design

Is the research question and planned outcomes clearly defined?

Was the sample adequate and sufficiently described?

Are the methods adequately described and appropriate to the study objectives?

Statistical considerations

Are simple statistical methods applied appropriately?

Reviewer #1: The study design and methods are clearly and succinctly laid out. Descriptive statistics are used to adequately describe the data

Please comment on the Results, Discussion and Conclusions presented in this manuscript

Results

Is the population/sample adequately described?

Are the results clearly presented?

Are they credible and do they answer the research question?

Are tables clear and useful, not simply mirroring data discussed in the Results text?

Reviewer #1: The results are clearly presented and provide good information that complements the text in the results section.

The population and patient selection are well described

Some revised formatting of the two figures would enhance the clarity(reduce blurring) of the inserted images.

Discussion

Are the results well discussed in light of previous evidence and the literature?

Are the limitations of the study sufficiently discussed?/ Are the strengths and weakness discussed?

Is the meaning and relevance of the study discussed?

Reviewer #1: The results are well discussed and appropriately compared with relevant international, particularly, sub-Saharan African data. The database has been meticulously built however, some acknowledgement of the fact that there are likely more cases that are completely missed by management in areas where the possibility of PID is not considered, additionally, some of the PIDs may be present in milder forms.

Conclusion

Are the implications of the research summarised?

Do the authors make relevant recommendations for future research or application?

Reviewer #1: The researchers are to be acknowledged for achieving their stated aims and for seeking to raise awareness of this important set of paediatric conditions and in their efforts in attempting to be as comprehensive as possible within the limitations described.

Reviewer #1: Some minor typos need correction, insertion of missing legends to tables and figures and improvement on the resolution quality of the two figures is suggested

There is additional documentation related to this decision letter. To access the file(s), please click the link below. You may also login to the system and click the 'View Attachments' link in the Action column.

[View Attachments](#)

2.9 Author response to South African Medical Journal



UNIVERSITY OF CAPE TOWN

DEPARTMENT OF PAEDIATRICS AND CHILD HEALTH

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3 July 2019

The Editor
South African Medical Journal

Dear Dr Farham

Ref.: SAMJ14200

A retrospective description of primary immunodeficiency diseases at Red Cross War Memorial Children's Hospital, Cape Town, South Africa, 1975 - 2017

Thank you for your much awaited reply. I hereby submit my list of changes to the manuscript as guided by the reviewer.

Hope this meets with the team's approval.

Yours in good faith

Dr Sashmi Moodley

MBCHB (UKZN), DCH (SA), Dip HIV Man(SA), FCPaed (SA)

Response to reviewer's comments :

1. Please comment on your General impression of this manuscript - bear the following in mind:

Is the article relevant?

Does it offer anything new?

Are there similar studies in our region/outside the region?

Does it add to the existing medical body of knowledge?

On first glance, are the methods, results and conclusions reasonable?

Do the conclusions actually draw on the results?

Does the article have a clear message?

Will it help SAMJ readers make better clinical decisions and, if so, how?

Is a general medical journal the right place for it?

Reviewer #1: This is an interesting and important study as it documents a neglected field of paediatrics, updating previous literature by attempting to comprehensively include children managed at a children's hospital across all sub-specialist disciplines.

The study also serves to raise awareness among general paediatricians about the importance of considering PID in children presenting with recurrent infections/ and or particular medical conditions. the importance being that there may be specific, life-saving and curative treatment available as well as preventative measures that could limit disease complications

Author: Appreciated.

2. Please comment on the Methods and analysis presented in this manuscript

Study design

Is the research question and planned outcomes clearly defined?

Was the sample adequate and sufficiently described?

Are the methods adequately described and appropriate to the study objectives?

Statistical considerations

Are simple statistical methods applied appropriately?

Reviewer #1: The study design and methods are clearly and succinctly laid out. Descriptive statistics are used to adequately describe the data

Author: Appreciated.

Reviewer comment X2: Could this not be rectified, particularly if this is a unique database not only for the study hospital but for RSA?

Author response: We did rectify this problem in the current study. To make this clear, the final sentence of the section entitled “Study design and setting” was changed to: To address this gap in the PID database and describe the full spectrum of PIDs managed or supported by all sub-specialist services at RCWMCH between 1 January 1975 and 31 December 2017, the infectious diseases service collaborated with several specialist / sub-specialist services managing children with PIDs.

3. Please comment on the Results, Discussion and Conclusions presented in this manuscript

Results

Is the population/sample adequately described?

Are the results clearly presented?

Are they credible and do they answer the research question?

Are tables clear and useful, not simply mirroring data discussed in the Results text?

Reviewer #1: The results are clearly presented and provide good information that complements the text in the results section.

The population and patient selection are well described

Some revised formatting of the two figures would enhance the clarity(reduce blurring) of the inserted images.

Author: Apologies for the blurring of the figures in the manuscript. They have been revised in a PDF version and will be uploaded as separate files from the manuscript.

4. Discussion

Are the results well discussed in light of previous evidence and the literature?

Are the limitations of the study sufficiently discussed? Are the strengths and weakness discussed?

Is the meaning and relevance of the study discussed?

Reviewer #1: The results are well discussed and appropriately compared with relevant international, particularly, sub-Saharan African data. The database has been meticulously built however, some acknowledgement of the fact that there are likely more cases that are completely missed by management in areas where the possibility of PID is not considered, additionally, some of the PIDs may be present in milder forms.

Author: Thank you for this comment. We agree that PIDs were probably missed during the study period. Consequently, the following sentence was added to the section entitled “strengths and

limitations”: “Furthermore, it is likely that more cases of PID were missed during the study period because either PIDs was not considered or the children presented with milder PID phenotypes.”

5. Conclusion

Are the implications of the research summarised?

Do the authors make relevant recommendations for future research or application?

Reviewer #1: The researchers are to be acknowledged for achieving their stated aims and for seeking to raise awareness of this important set of paediatric conditions and in their efforts in attempting to be as comprehensive as possible within the limitations described.

Author: Appreciated.

Reviewer comment X5: Not part of your conclusion. Belongs in the discussion.

Author: The first 3 sentences of the conclusion have been moved to the first paragraph of the discussion. Consequently, minor changes were made to the first paragraph of the discussion to accommodate this revision.

6. Reviewer #1: Some minor typos need correction, insertion of missing legends to tables and figures and improvement on the resolution quality of the two figures is suggested

Author: Apologies for typos. They have been corrected as directed. Legends have been inserted to tables and figures. The 2 figures have been clarified and resaved in PDF format as separate files from the manuscript.

2.10 South African Medical Journal 's letter of acceptance for publication

SAMJ <em@editorialmanager.com>

To:Sashmi Moodley

Jul 10 at 7:58 AM

CC: "Brian Eley" brian.eley@uct.ac.za, "Elizabeth Goddard" liz.goddard@uct.ac.za, "Michael Levin" michael.levin@uct.ac.za, "Chris Scott" chris.scott@uct.ac.za, "Ann Van Eyssen" annvaneyssen@icloud.com, "Alan Davidson" alan.davidson@uct.ac.za, "Rik De Decker" rik.dedecker@uct.ac.za, "Jo Wilmshurst" jo.wilmshurst@uct.ac.za, "Ariane Spitaels" ariane.spitaels@uct.ac.za

Ref.: SAMJ14200

A retrospective description of primary immunodeficiency diseases at Red Cross War Memorial Children's Hospital, Cape Town, South Africa, 1975 - 2017
South African Medical Journal

Dear Dr Moodley,

We are pleased to tell you that your work has now been accepted for publication in South African Medical Journal.

Please note that as per the author guidelines, page-fee charges have been implemented since March 2017 for all research articles. Please find payment form attached herewith. As soon as proof of payment and the completed form have been received, we will send your article into production. (Please note that we are unable to process American Express card payments). Please send proof of payment to claudian@hmpg.co.za

Thank you for submitting your work to the journal.

Best wishes

Bridget Farham, PhD
Editor
South African Medical Journal

2.11 University of Cape Town MMed guidelines

(Excluding Public Health Medicine, Occupational Medicine and Family Medicine)

As approved in PC: September 2017

UNIVERSITY OF CAPE TOWN FACULTY OF HEALTH SCIENCES

MMed Part III (minor dissertation)

Guidelines for candidates, supervisors and examiners

The MMed minor dissertation is one of three examination components of the MMed degree. This minor dissertation carries one third of the weight of a full master's dissertation in terms of its credit weighting, i.e. 60 credits (nominally 600 hours of work). In order to register as a specialist in South Africa, the Health Professions Council of South Africa (HPCSA) requires all specialist trainees who register for training after 1 January 2011 to have completed a relevant research study. The MMed Part III fulfils HPCSA research requirements as well as research requirements by the specialties who include a research project as part of their examination process by the Colleges of Medicine of South Africa (CMSA).

Educational aims

The research project should demonstrate that the student:

- can work independently and ethically under supervision (contributions/assistance must be acknowledged);
- is sufficiently acquainted with the relevant literature to provide appropriate motivation for the research question;
- can plan research or clinical audit (write a protocol), which is approved by an assessor group (delegated by the head of department) and ethics committee where relevant, that contributes new or additional data to the collective knowledge base (the specific data has not been presented as part of other research), but need not produce a unique contribution to the scientific literature;
- uses an appropriate method/design/technique and analysis;
- can adequately present and discuss the significance of the results of the study;
- can present the study in an academically acceptable manner.

Type and scope of the research

The following types of studies are acceptable:

- A clinical audit with or without a repeat data collection cycle;
- A systematic review of the literature on its own **with** extraction and extrapolation of data **OR** a meta-analysis using recognised research methods (eg Cochrane, PRISMA);
- A research study – pro-/retrospective lab or clinical or database review;
- Description and analysis of a case series or cohort, deemed sufficient to supply new knowledge/data, even if only contextual or exploratory;
- Epidemiological research;
- Health service/systems/education research;
- Qualitative research;

Noting:

- *The sample size* can be limited by time (Registrars have limited time allocated/available to collect data and write it up concurrently with their clinical training) - data collection and write up should be possible to complete within two consecutive or cumulative months.
- *Data analysis* may use simple descriptive statistics alone – more advanced analysis can be used, but the student must demonstrate (in the write up) insight into the choice of analysis.

MMed Minor dissertation guidelines (Excluding Public Health Medicine, Occupational Medicine and Family Medicine)

As approved in PC: September 2017

- The above limitations may be associated with the use of descriptive cohort studies based on medical record review; exploratory or pilot studies with small convenience samples; or audits without a repeat data collection cycle to prove quality improvement (QI). Despite limitations, these studies can provide an adequate basis for learning research methodology and can add new data to the collective knowledge base – they may also provide the basis for further publishable work such as a second audit to complete a full QI cycle. As long as these limitations are appropriately acknowledged, these studies should still be acceptable.
- The topic, study design and scope of research may depend on the particular discipline and must be agreed on in consultation with the supervisor(s). The topic must be approved as being suitable for MMed dissertation by the Departmental Research Committee (DRC) and/or

a group appointed for this purpose by the head of department.

Submission formats

The dissertation may be presented in one of three formats:

I: Publication-ready format;

II: Published (or accepted for publication) Paper format

III: Monograph format.

As disciplines differ in their requirements, it is important that the format chosen is acceptable to the discipline and appropriate College within the CMSA.

Research protocol

NOTE: All communication from UCT regarding the MMed and the examination process will occur via student UCT e-mailaddress – [student number]@myuct.ac.za. Students must also make sure they have username and password and are able to access the PeopleSoft Student Administration Self Service.

Candidates intending to register for the MMed Part III are required to submit a research protocol for approval to their respective Departmental Research Committees (DRC). The research protocol should briefly summarise the existing knowledge on the topic and justify the research question; it should clearly describe the objectives and methodology and should be structured according to the guidelines in Form FHS015. Write a synopsis according to Form FHS014. Complete a new protocol application form FHS 013. All FHS forms are available at

<http://www.health.uct.ac.za/fhs/research/humanethics/forms>.

The candidate must then obtain approval from the UCT Faculty of Health Sciences Research Ethics Committee (HREC) prior to conducting their research. Studies that involve the audit of clinical records or services also require formal HREC approval. Any primary research that is taking place in a provincial or local authority health facility, such as public sector hospitals or clinics, must also be submitted to the provincial government for approval, after the UCT Research Ethics Committee approval has been obtained. **Approval to access public sector facilities for research is needed for all provincial and local authority facilities.** There are five points where approval for research can be applied for; Groote Schuur Hospital, Red Cross War Memorial Children's Hospital, Tygerberg Hospital), the local authorities and "all other province". Teaching hospitals and the local authorities approve research projects in-house. "All other province" approvals are done via the Directorate: Health Impact Assessment (Sub-directorate: Research) at provincial head office. If research crosses these boundaries, up to five approvals may be needed. Further details can be found at <https://www.westerncape.gov.za/general-publication/health-research-approval-process>

The Provincial Health Research Committee does not approve research proposals itself, but oversees this approval process by reviewing difficult applications on referral.

The proposal contents should comply with requirements stipulated in Form D1a. This full research protocol together with FHS 013, a copy of the HREC approval letter and completed Forms D1 (Protocol approval), D3 (supervisor appointment form), and D1a must be submitted to the postgraduate administration office, for approval by the Professional Masters Committee (PMC) Chair MMed Minor dissertation guidelines (Excluding Public Health Medicine, Occupational Medicine and Family Medicine)

As approved in PC: September 2017

and the Board of the Faculty of Health Sciences, prior to commencement of the research. If the title, aims, objectives or any other aspect of the research change following initial submission, an amendment must be submitted to HREC. **All D-forms are available from the post graduate faculty office or on the UCT Vula Mmed/Mphil site (All registrars and supervisors must be added to this site – your departmental programme manager must send names and email addresses to gregory.doyle@uct.ac.za in order to be added to the site).**

Timelines

Submission of the research protocol for approval should generally be made within the first 12 - 24 months of the registrar programme (this varies between disciplines). Heads of Departments or Divisions should meet with their registrars at least biannually to review progress towards their research project. Unless otherwise stipulated by your Division / Department, the research project should generally be completed by the end of Year 3. For a number of specialties, a dissertation must be submitted before writing the Part II examination. Often the research component of specialist training is only initiated after successful completion of the Part I examination.

Supervisors

The supervisor must: have research experience, ideally a Master's degree, equivalent (eg appropriate publications), or higher; be able relate to the candidate's research project; be available for regular discussion and advice; and be someone with whom the candidate can develop a good working relationship. If the primary supervisor does not have adequate experience, then a secondary

supervisor who has appropriate experience will need to be appointed in addition. **Supervisors who have not had extensive experience supervising are required to attend a supervisor training course.** Where specialised equipment and/or laboratory work is required for the study, the supervisor should assist in facilitating access to appropriate facilities.

The primary supervisor may be based outside the candidate's home department, faculty or university. In such a case, a member of UCT staff will also be required as co-supervisor in addition to the primary supervisor, to serve as a guide and link to UCT faculty and discipline-specific procedures. Primary supervisors retain responsibilities to the candidate and the university until the dissertation process is complete. In addition to the forms mentioned above, the supervisor and student must complete D2a which describes the contractual memorandum of agreement (MOU) between supervisor and student regarding the minor dissertation.

The dissertation

Submission of all formats of the dissertation should include the following:

The title page should contain the candidate's name, dissertation title and the name of the university. It must also state the degree, e.g. Master of Medicine (MMed) in, Medicine, Paediatrics, etc.

The Table of contents

The declaration page should include a statement to the effect that the research reported is based on independent work performed by the candidate and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree to any other university. It must also state that this work has not been reported or published *prior to registration* for the abovementioned degree.

The abstract should summarise the study rationale, methods, results, discussion and conclusion in fewer than 500 words.

Acknowledgements and contributions. This section should acknowledge and describe the support or input from supervisors and other co-author(s) if applicable. In a dissertation derived from work started by others, e.g. analysis of data collected for another project, the origin of the data and the candidate's contribution must be clearly stated. The candidate must complete the dissertation after his/her registration for the degree and therefore under supervision. In a published manuscript from a MMed Minor dissertation guidelines (Excluding Public Health Medicine, Occupational Medicine and Family Medicine)

As approved in PC: September 2017

multi-authored project, the candidate must be first author.

List of Tables

List of Figures

Abbreviations

The remainder of the dissertation must be presented in one of three formats:

I: Publication-ready format;

II: Published (or accepted for publication) paper format

III: Monograph format.

I: Publication format

The dissertation must include a manuscript in publication-ready format. The body of the dissertation must be structured as follows:

Chapter 1: Introduction and Literature review

This section must give the background and context of the research question and must include a review of the literature relevant to the subject matter and methods of the study. The review should summarise and interpret the existing knowledge in the field with relevance to the research setting and should identify knowledge gaps and hence the rationale for the dissertation. This chapter should end with a clear statement reflecting the aims and objectives of the research reported in the publication-ready manuscript. References quoted in this chapter should appear at the end of the chapter, not at the end of the thesis. This chapter should be between 2 000 and 5 000 words.

Chapter 2: Publication-ready Manuscript

This chapter must be presented in the form of a manuscript of an article for a named peer reviewed journal, meeting all the requirements of the "Instructions for Authors" of that journal, including the word count and referencing style. Unless specially motivated, the journal chosen should allow for at least 2000 words (not more than 5000 words) excluding abstract, tables, figures and references. The "Instructions to Authors" of the journal must be appended. The co-authors should be listed in the appropriate order, and each of their contributions to the manuscript stated. The journal chosen for publication must be appropriate to the subject matter of the dissertation and listed in the citation index of the Institute for Scientific Information (ISI) or accredited by the Department of Education (<http://www.lib.uct.ac.za/medical/index.php?html=/libs/accredjnl.htm&libid=24>); *other journals with similar review processes, particularly South African journals may be acceptable if permission is obtained from the PMC Chair after appropriate motivation is provided.*

Note 1: In this format, the candidate need not have submitted the article for publication, nor is the acceptance of the article for publication a requirement for passing the degree. However, the norm is to publish the study with the supervisor(s) as co-author(s), and candidates are strongly encouraged to submit their manuscript for publication after examination of the minor dissertation.

NOTE 2: IF THE RESEARCH IS A FULL SYSTEMATIC REVIEW, THERE IS NO NEED FOR A SEPARATE CHAPTER 1 – THE REVIEW SHOULD BE SUBMITTED AS ONE CHAPTER.

Appendices

Append all supporting documents including:

- Questionnaire/data capture instrument(s)
- Consent forms and any related participant information sheets
- Technical appendices, including, if considered necessary, any additional tables not included in the main manuscript for the examiner to have available. These should be accompanied by a brief narrative.
- Official Ethics approval letter from the Faculty Research Ethics Committee (except for a full systematic review) and any other approvals required (e.g. Provincial Government).
- Instructions to Authors of the chosen journal

MMed Minor dissertation guidelines (Excluding Public Health Medicine, Occupational Medicine and Family Medicine)

As approved in PC: September 2017

II: Published (or accepted for publication) paper format

A manuscript that has already been published or accepted for publication in a journal that is listed in the citation index of the Institute for Scientific Information (ISI) or accredited by the Department of Education (*other journals with similar review processes, particularly South African journals may be acceptable if permission is obtained from the PMC Chair after appropriate motivation is provided*), may be submitted **if the candidate was the first author, the candidate's contribution was completed under supervision during his/her registration for the degree, and the paper is in line with the educational aims and scope of research described in the first part of this document.**

The dissertation must be submitted in similar format to the publication-ready format – the only differences being: a separate literature review is not required; the accepted publication is submitted as a single chapter following the same format as described above under “Chapter 2”; and the reviewer comments from the journal should be attached as an appendix. *When this format is used, the contributions of all the authors must be very clearly stated under a sub-heading in the “Acknowledgments and contributions” section in the first part of the thesis.*

III: Standard monograph format

Some disciplines and constituent Colleges of the Colleges of Medicine of South Africa require a standard monograph presented in a comprehensive and scholarly style to be submitted as part of the examination. The length is typically 16 000 to 20 000 words in length, but may vary. If the length is not stipulated, the monograph should be 6000 – 16000 words, excluding references and tables.

A recommended structure for the body of the dissertation is as follows;

Chapter 1: Introduction and Literature review

(see guidelines above)

Chapter 2: Methods

Material and methods of the study must be fully described and factually presented.

Chapter 3: Results

Chapter 4: Discussion and conclusions

Appendices

(see guidelines above - omit the instructions to authors)

Language and writing

Clear, grammatically correct English is essential.

Supervisors may assist candidates in developing scientific communication skills but they are not required to do detailed editing or correction of spelling, grammar, or style. Training in scientific writing is available at the Health sciences Writing Centre. Registrars need to make an appointment via the website: <http://www.writingcentre.uct.ac.za/about/healthsciences>

Candidates should refer to Form D4, Guidelines on the Layout and Style of the Dissertation or Thesis.

As long as the dissertation is readable and internally consistent, any of a number of styles are acceptable. For a publication-ready manuscript, references should be formatted according to the instructions to authors for the journal selected, and candidates should use the same style throughout their dissertation. For a monograph format manuscript, the Harvard style for referencing is

MMed Minor dissertation guidelines (Excluding Public Health Medicine, Occupational Medicine and Family Medicine)

As approved in PC: September 2017

recommended, but not compulsory. For reference management, Refworks or Endnote can be

downloaded from the ICTS or UCT library website.

Candidates should look at previous examples of Master's dissertations in the library. Master's dissertations are available in the Health Sciences Library. A search will need to be done to obtain a list of titles and authors. This search can be done using search words (e.g. dissertation, health, health sciences, etc.). The librarian can be asked for assistance. Some of these dissertations are available via: <http://www.medical.lib.uct.ac.za/hsl/theses-dissertations>

Annual approval

After 1 year, apply to HREC for continuing approval Form FHS016 (for intervention study) or FHS017 (for record review) or submit a study closure form, FHS010, if the study is complete. If registration in MMed III is required for more than one year then complete form D2(b) and submit to Post Grad Office when re-registering.

Submission of dissertations

On completion, the dissertation and a Turn-it-in originality report must be submitted to the Faculty Postgraduate Office. The candidate should inform the Faculty Officer one month in advance of the intention to submit, using Form D8 (Intention to submit) online with PeopleSoft system and should subsequently submit their dissertation using the same system – **guidelines for this process and the use of Turn-it-in are on the Mmed/Mphil Vula Website and detailed guidelines are also available in the UCT student help document: “ Digital submission of a thesis/dissertation for examination and library access”**. This document is available online at

http://www.uct.ac.za/usr/current_students/postgrad/digital_upload_dissertations_theses.pdf

Supervisors will be requested by the Faculty Postgraduate Officer to submit a letter supporting submission, and clearly specifying whether the format of submission, so that the appropriate instructions are sent to the examiners. This letter should be supplied by the primary supervisor. If this supervisor is external, the internal supervisor must be kept informed at every stage of the process.

Please note: In the event that any of your external examiners request a hard copy of your dissertation/ thesis, you will be required to supply this. The Faculty office will inform you should this be necessary.

Specific submission requirements may be set by individual disciplines or constituent Colleges of the CMSA, and registrars are obliged to ensure that their research projects and dissertations meet these specific requirements. UCT Dissertation submission deadlines:

1. March 15th for June graduation
2. August 15th for December graduation

Note on fees: To avoid attracting fees, dissertations need to be submitted before the beginning of the first quarter (first day of academic year), and before the start of the second semester (mid July) to qualify for a 50% fee rebate.

Examiners

The full dissertation will be submitted for examination through the Postgraduate Office to two examiners (nominated by the supervisors and HOD) – at least one examiner must be external to UCT. An internal examiner must not be involved in the research.

It is the supervisors' responsibility to submit names of three potential examiners (or two examiners who have already agreed to examine pending approval of the Post Graduate Office) to the Faculty Officer when the candidate is ready to submit. Appointment of examiners from outside South Africa is encouraged. These nominations need to be approved by the Deputy Dean: Postgraduate Affairs on behalf of the Faculty Board and submitted to the Faculty Board for ratification via a Dean's Circular.

MMed Minor dissertation guidelines (Excluding Public Health Medicine, Occupational Medicine and Family Medicine)

As approved in PC: September 2017

Details required for each examiner are: academic qualifications, postal and/or physical address, telephone and fax numbers and e-mail address, and one paragraph description of their standing in the relevant field (drawn from their CV if need be). The examiners will be sent a copy of these guidelines as well as a guideline for marking. *The candidate may not be informed of the identity of the examiners.* After the outcome of the minor dissertation has been finalised, the examiners' identities are made known if the examiners have indicated that they do not object to this.

Publication agreement

The university has a moral responsibility to publish all research undertaken when publication is stated as an anticipated output. A candidate who fails to submit a manuscript to a journal for publication within 1 year of submission of their thesis, must accept that their supervisor(s) are entitled to publish their data on their behalf, with the student as co-author - this should be stated in the memorandum of understanding.