SEVERE ALLERGIC REACTIONS

AT A TERTIARY PAEDIATRIC SERVICE

2014 – 2016

by

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DECLARATION

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

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ABSTRACT

Introduction:

Anaphylaxis is a severe, life-threatening generalized hypersensitivity reaction. The European Anaphylaxis Registry was established to review and improve medical management of these patients, facilitate accurate comparisons between centres, highlight public health implications, and examine trends in treatment over time. This is replicated here in a South African setting.

Methods:

Participants comprised patients treated at Red Cross War Memorial Children's Hospital (RCWMCH) for severe allergic reactions between January 2014 and August 2016. Recruitment was by applying relevant ICD-10 coding to the hospital's clinical summary system of admissions and discharges, the pharmacy's records of adrenaline autoinjector dispensing, and referrals from the allergy department's clinical staff. Participants who were screened but did not meet inclusion criteria after preliminary questioning and/or folder review were excluded. 156 episodes were analyzed. A local web-based registry was established, and used to capture data collected via a questionnaire in interviews at the RCWMCH Allergy Clinic.

Results:

Males, younger children, and participants of coloured ethnicity were more frequently affected. Skin and mucosa was most commonly involved, followed by respiratory and gastrointestinal upset, with cardiovascular and other systemic involvement occurring infrequently. More than 40% of episodes were graded as severe. Specific IgE was the most frequently requested testing. Nearly two-thirds of patients were seen with a recurrent episode. Food-related triggers predominated and decreased with age: particularly peanut, hen's egg, fish, cashew nuts and cows' milk. There was a strong correlation with atopic conditions, in excess of international trends.

Adrenaline was rarely used, by both lay persons when previously prescribed, and by professional attenders. Hospital admissions were infrequent, and no deaths were recorded. Prophylactic measures were almost universally instituted, but the success thereof could be improved.

Conclusion:

This is the first local comprehensive description of anaphylactic trends. Further areas of research are suggested: to investigate the propensity for allergic reactions in the coloured population, our much higher rate of association with other atopic disorders compared to international patterns, comparison of our baseline comorbid conditions for contextual analysis, and a review of barriers to care. Ongoing education and training to patients, parents, teachers, and health care workers is identified as a major area requiring intensification.

ACKNOWLEDGEMENTS AND CONTRIBUTIONS

- Sabine Dölle and the team at NORA: for laying the groundwork with their original projects[16,57,74], provision of the questionnaire utilized by the European Anaphylaxis Registry, and assistance with addressing queries related to interpretations of patient responses and database development.

- Mike Levin, supervisor extraordinaire: for imagining this project, facilitating the many steps involved, being patient with intercurrent exams and illness and injury, and persistence to completion.

- Ebrahim Jacobs from RCWMCH information systems: for accessing patient data according to ICD-10 coding, Hushendree Naicker for the provision of pharmacy dispensing reports, and the staff at the RCWMCH Records Department for allowing the search and review of relevant patient folders.

- Sr Dorothy Brown and the team at the RCWMCH Allergy Clinic, for entertaining and facilitating interviews alongside a very busy clinical service.

- Annemie Stewart from UCT's Clinical Research Centre: for establishment of an electronic Anaphylaxis Database, and patience with all the adjustments before production.

- UCT SCAH Departmental Research Awards: for provision of funding for the formation of our Anaphylaxis Database.

- Kirsten Reichmuth: for assistance with statistical analysis, in pretty locations with caffeine and carbs.

- Our greatest teachers: the patients and parents who so willingly shared their experiences, and proved that allergies are what they have and not who they are. We can never thank you enough, and hope your contributions improve care to other patients locally and further afield.

- The trees to my apple: Achmat and Aziza Chippendale, for living an example of lifelong learning and contribution to society; and the rest of the family and friends: for their perseverance with this seemingly never-ending task.

- And always, our Creator, Alhamdulillah.

‘Acquire knowledge and teach people.
Learn along with it dignity, tranquility and humility for those who teach you,
and humility for those whom you teach.’
- Umar ibn al-Khattab

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ABBREVIATIONS

AAAAI: the American Academy of Allergy, Asthma and Immunology

ACAAI: the American College of Allergy, Asthma and Immunology

ADSA: Association for Dietetics in South Africa

ALLSA: Allergy Society of South Africa

EAACI: the European Academy of Allergy and Clinical Immunology

CPR: cardiopulmonary resuscitation

DRC: Departmental Research Committee

HREC: Human Reseach Ethics Committee

ICD10: International Statistical Classification of Diseases and Related Health Problems, 10th edition

IM: intramuscular

IV: intravenous

NORA: the network of severe allergic reactions

NSAID: non-steroidal anti-inflammatory drug

RCWMCH: Red Cross War Memorial Children's Hospital

SAGES: South African Gastroenterology Society

SAR: systemic allergic reaction

SCAH: School of Child and Adolescent Health

UCT: University of Cape Town

WAO: World Allergy Organization

CHAPTER 1:

INTRODUCTION

AND

LITERATURE REVIEW

LITERATURE REVIEW

Anaphylaxis is defined as “a severe, life-threatening generalized or systemic hypersensitivity reaction”[1]. These are generally caused by IgE-dependent immunological mediation, but IgE-independent mechanisms and direct mast cell stimulation have also been implicated, as well as idiopathic, and recently IgG-mediated reactions[2].

Several grading systems exist to categorize anaphylactic reactions. Ring and Messner initially proposed a simplified classification system based on organ systems involved and reaction severity (Appendix A)[3]. In 2010, WAO described two categories of adverse effects secondary to allergen immunotherapy administration[4]: local reactions and systemic allergic reactions (SAR), ranging from mild rhinitis to multi-organ system involvement and fatal arrest. Grading is assessed retrospectively by the health care professional. Recently, a modified version was proposed[5] to classify SARs from any cause, taking into consideration route of administration of allergen, first symptoms/signs, and timing of onset of reaction and treatment, with the aim to allow for better safety comparisons across different venues and treatment protocols. The classic initial grading system was utilized for this project, to facilitate comparison with identical European studies.

The World Allergy Organization (WAO)[2,6,7,8], the European Academy of Allergy and Clinical Immunology (EAACI)[9], the American Academy of Allergy, Asthma and Immunology (AAAAI), the American College of Allergy, Asthma and Immunology (ACAAI)[10], and the Allergy Society of South Africa (ALLSA)[11,12] are in consensus[13] on their recommendations for the assessment and management of anaphylaxis.

- The diagnosis of anaphylaxis is primarily a clinical one, where optimal management is based on the early recognition of characteristic symptoms and signs following exposure to a likely or known trigger. These symptoms are usually of sudden onset, and

can be multi-systemic, particularly respiratory compromise, reduced blood pressure, signs of end-organ dysfunction, involvement of skin and mucosal tissue, and/or persistent gastro-intestinal upset. Laboratory testing, including tryptase, plays a supporting role, especially in ruling out differential diagnoses. Special care needs to be taken when diagnosing particular groups, like in the extremes of age and with pregnant women.

- Triggers vary by age and geography, and over time. Patient-specific risk factors and individual co-factors can impact the severity of anaphylactic episodes. These include age, medical conditions (e.g. asthma, cardiovascular diseases, mast cell disorders, acute infection, pre-menstrual status), lifestyle entities (e.g. exercise, ethanol, and emotional stress) and drugs like non-steroidal anti-inflammatories (NSAIDs), β-blockers, and ACE-inhibitors.
- Swift emergency treatment with intramuscular (IM) adrenaline is vital, with repeat dosing 5-15 minutes apart as required. Emergency unit and personnel preparedness is advocated, in the form of a written and frequently rehearsed protocol. In addition, removing the trigger, calling for help, and positioning the patient in a supine position with elevation of the lower extremities are also advised. Further emergency care includes oxygen and airway management, intravenous (IV) access and fluid resuscitation, and cardiopulmonary resuscitation (CPR) as necessary. Second-line agents endorsed, if needed, are antihistamines, glucocorticoids, inhaled β_2-agonist and inhaled adrenaline. These are echoed in ALLSA's algorithm for treatment of severe anaphylactic reactions (Appendix B)[11]. Close frequent, preferably continuous monitoring is recommended, for at least four hours, but up to twenty-four hours in individuals at high risk for biphasic reactions.
- The importance of long-term management with prevention of recurrence is emphasized. Before discharge, an emergency action plan, an adrenaline auto-injector if indicated, and medical identification are advised. Follow-up with a physician, preferably an

allergist/immunologist, is strongly advocated: for trigger identification, optimization of co-morbid medical management, comprehensive risk assessment, individualized risk-reduction strategies, ongoing education and training, and consideration of immune modulation therapy. In a study reviewing the outcome of such a system[14], it was found that more than a third of patients had an alteration in the diagnosis or suspected trigger after review by sub-specialists, and 6% of patients underwent immunotherapy or desensitization in the long-term. This is re-iterated by Zieger et al[15], describing the important role of "the allergist as leaders, innovators, and educators".

- The need for further anaphylaxis studies and efforts at global partnerships are suggested, and an international research agenda is advised.

A proposal by a pan-European conglomerate of ten participating countries advocates establishment of a collaborative severe allergic reaction database[16], to improve medical care of patients and highlight public health implications. Standardized information on incidence, triggering allergens, aggravating factors, demography and medical management was found to be lacking and urgently needed. Benefits would include appraisal of risk management strategies, identification of new allergens, clearer patient education regarding risk factors, motivation for food businesses modification and government agency preventative strategies based on results.

This task proves more challenging by under-reporting and inadequate capturing of data in registries and by Emergency Departments.[17,18,19,20] This has largely been attributed to under-recognition and misdiagnosis by medical staff, as well as miscoding by the frequently used data capturing methods. An alternative suggestion to study the characteristics of patients with anaphylaxis is indirectly by reviewing adrenaline auto-injection dispensing patterns.[21,22,23,24,25]

Systematic reviews of epidemiological research[26,27] quote incident rates of anaphylaxis to be between 1.5 and 7.9 per 100 000 person years, an estimated 0.3% of the general population. Controversy abounds regarding this being a true increase compared to reports from previous years, versus improved recognition and recording by health care workers. Incidence reduces with age, with events occurring up to three times more often in the first four years of life. The commonest triggers are food, drugs, insect stings and latex, with food allergies occurring frequently in the younger patients, and more reactions to drugs and bee stings in the elderly. Geography plays a role, with higher prevalence noted in areas with less sunlight. Anaphylactic episodes recur in up to a third of patients, but deaths are rare: an estimated 0.12 – 1.06 per million patient-years.

In addition to these, various case reports and series, as well as longitudinal retrospective cohort studies, were published over the last fifteen years. Factors assessed were not uniform across all publications, but included incidence, prevalence, risk factors, exposures, management options and outcomes of patients presenting at health institutions with anaphylaxis and severe allergic reactions, based on emergency department coding records or existing databases. We reviewed eight studies from the United Kingdom[28,29,30,31,32,33,34,35]; six from the USA[36,37,38,39,40,41], four from a German-Austrian-Swiss collaboration[42,43,44,45]; two Spanish[46,47] and Australian[48,49]; and single published papers from Canada[50], Denmark[51] Turkey[52], Italy[53], Thailand[54], Puerto Rico[55], China[56], and a 10-country pan-European conglomerate[57]. Identical paediatric-based studies were also reviewed, eight from the USA[58,59,60,61,62,63,64,65], three Australian[24,66,67], two Israeli[68,69], and single reports from Italy[70], Chile[71], Canada[72], a German-Austrian-Swiss collaboration[73], Central Europe[74], Iran[75], and the UK[76]. To summarise:

- Allergic diseases are common, affecting males and females of all ages, social classes, and ethnicities.[33,34] It represents a substantial burden of morbidity and health cost.[33,72]

- There is consensus regarding an increase in incidence, lifetime prevalence, and prescribing of adrenaline prescription in recent years.[28,30,31,32,46,48,49,62] The prevalence in the general population is quoted as at least 1.6% and likely higher[36].
- Prevalence and hospitalizations in children are increasing[39,46,60,65,67], as are food-related events[46,50].
- Hospital admissions for anaphylaxis are rising, but there is no increase in mortality[28,48,49], except drug-induced deaths[48]. This was attributed to changes in patient and personnel awareness and behaviors to the diagnosis and management of anaphylaxis[28].
- Triggers can be identified in one-third[55] to nearly 90% of episodes[56]. The commonest triggers identified are wasp and bee venom, animal proteins, legumes, and analgesic drugs, the frequencies of which is age-dependant[42]. In adults and the elderly, the commonest triggers are drugs and insects[28,44], while in children and adolescents it is food[28,44,47,60,61,64,73,75]. Male and black patients are more likely to have a food trigger[38].
- Concomitant disorders identified in children are asthma, allergic rhinitis, and eczema[44,45,61]. In adults it is cardiovascular diseases.[44]
- Risk factors for admission includes
    - Gender: females[54], females of childbearing age[34]; only one study claimed anaphylaxis to be more common in boys[68]
    - Higher latitudes: noted in the southern UK[34], northern USA[38,39,40], southern regions of Australia[24], Italy[70], and reflected in Chilean children from different geographical demographics[71]
    - Improved socio-economic background: demonstrated in the UK[34], Australia[24] and Israel[68]
    - Not universally, ethnic minority groups. Increase in incidence, different trigger factors and occasionally severity of symptoms, when compared to their counterparts in certain areas: particularly Black patients in the USA[38,41], including the paediatric population[59,61,63] (with Hispanics less affected[63]);

non-Danish patients to certain drugs in Denmark[51]; Bedouin children in Southern Israel[68]; and Eurasian, Caucasian, Korean and Japanese in Singapore[22]. Regional variation has been shown in Italy[40], Australia[24,66], Chile[71] and the USA[39,40]. To note, when ethnicity has been looked at, generally the UK[29,33,34] and certain areas of the USA[37,58,65] have had a similar incidence across all racial groups.

- Immediate recognition and treatment is crucial.[35,49,56,61,67,75] The commonest presentations are cutaneous followed by respiratory symptoms[54,73], then cardiovascular and gastrointestinal tract[73].
- Adrenaline is underused in Emergency Departments for anaphylaxis[41,42,43,50,53,60,62,64,72,73]. This is attributed to frequent misdiagnosis[50,53,62,64], and fear of adrenaline side-effects[50].
- Biphasic reactions can occur in more than 5% of patients, with 20% of those being very severe, prompting advice for longer observational times[56].
- Patients are generally not well equipped to deal with future episodes, and require ongoing education and public health initiatives[36,60,62]. These include patient-centered, as well as parent-friendly and school-based programmes[60,69,72,76].
- Long-term follow up is recommended[54,67,69]. Appropriate interventions can improve the negative effect of allergic reactions on quality of life[61,69].
- Registries are important for epidemiological reasons, to improve medical understanding of the disease, as well as to address management issues[44,73] and comparative studies[57,72,75].

To elaborate on this, the network of severe allergic reactions (NORA), a collaboration between eleven European nations, recognized anaphylaxis research being reported differently between countries, and identified the need for standardized data collection to facilitate accurate comparison between referral centres and countries[57]. The European Anaphylaxis Registry was formed, collecting data from medical records using an online

questionnaire, from fifty-nine institutions in Germany, France, Switzerland, Austria, Spain, Poland, the United Kingdom, Greece, Bulgaria, Italy, and Ireland. Their results show food and insect bites being the most common triggers, and less frequently drugs. Most reactions are within thirty minutes of exposure, with the skin most often affected, although this varied with the eliciting factor. Steroids and antihistamines were the preferred treatment modalities, with adrenaline being used in only 13.7% to 27.6%. In children and adolescents[74], most incidents happened in private homes. Cow's milk and hen's egg were most frequently implicated in the first two years of life, hazelnut and cashews in pre-school ages, and peanuts in all children. A shift occurs from food- to insect- and drug-induced events in the first decade of life. Nearly a third of children were lay-treated, with adrenaline utilization trends increasing over the last few years. Intensive care admissions and fatal reactions were rare. This project is ongoing, with yearly intakes collected to analyze evolution of anaphylaxis trends. This is replicated here in a South African setting for this study, with review of self-classified ethnicity as an additional factor[77].

There is remarkably limited data on anaphylaxis from the African continent. Most are case reports and series describing reactions to specific organisms (hydatid[78,79,80,81], anisakis[82], snakes[83,84], bee stings[85,86], non-biting midges[87]), plants[88], foods[89] (specifically mopane worms[90] and cow's milk[91]), medication (ACE-inhibitors[92], snake antivenom[93], urografin[94], protamine sulphate[95], vancomycin[96], BCG vaccination[97,98]), blood transfusion[99], and in certain special circustances (in ENT[100], pregnant women[101], and latex in a hospital setting[102,103]).

In African children, anaphylactic shock is described during surgery for a hydatid cyst [80], and a case of a severe anaphylaxis is described after exposure to a trace-amount of cow's milk protein[91]. A cohort study looking at a series of severe food reactions at Red Cross Children's Hospital requiring adrenaline auto-injector prescription[89] found the majority of patients affected were of mixed ancestry; peanut, cow's milk and hen's egg

were the most common triggers; multiple foods were frequently implicated; asthma is a significant risk factor; and a significant proportion of patients had allergic co-morbidity.

Other South African studies include a review on the rationale for adrenaline use in anaphylaxis[104], and a consensus document by the South African Food Allergy Working Group, comprising the Allergy Society of South Africa (ALLSA), the South African Gastroenterology Society (SAGES), and the Association for Dietetics in South Africa (ADSA), providing local guidelines for the assessment, investigation and management of food allergies[12]. These are in keeping with international guidelines, but adapted to our resource-limited settings. There are no register-based African studies.

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CHAPTER 2:

PUBLICATION-READY MANUSCRIPT

STRUCTURED ABSTRACT

Introduction:

Anaphylaxis is a severe, life-threatening generalized hypersensitivity reaction. The European Anaphylaxis Registry was established to review and improve medical management of these patients, facilitate accurate comparisons between centres, highlight public health implications, and examine trends in treatment over time. This is replicated here in a South African setting.

Methods:

Participants comprised patients treated at Red Cross War Memorial Children's Hospital (RCWMCH) for severe allergic reactions between January 2014 and August 2016. Recruitment was by applying relevant ICD-10 coding to the hospital's clinical summary system of admissions and discharges, the pharmacy's records of adrenaline autoinjector dispensing, and referrals from the allergy department's clinical staff. Participants who were screened but did not meet inclusion criteria after preliminary questioning and/or folder review were excluded. 156 episodes were analyzed. A local web-based registry was established, and used to capture data collected via a questionnaire in interviews at the RCWMCH Allergy Clinic.

Results:

Males, younger children, and participants of coloured ethnicity were more frequently affected. Skin and mucosa was most commonly involved, followed by respiratory and gastrointestinal upset, with cardiovascular and other systemic involvement occurring infrequently. More than 40% of episodes were graded as severe. Specific IgE was the most frequently requested testing. Nearly two-thirds of patients were seen with a recurrent episode. Food-related triggers predominated and decreased with age: particularly peanut, hen's egg, fish, cashew nuts and cows' milk. There was a strong correlation with atopic conditions, in excess of international trends.

Adrenaline was rarely used, by both lay persons when previously prescribed, and by professional attenders. Hospital admissions were infrequent, and no deaths were recorded. Prophylactic measures were almost universally instituted, but the success thereof could be improved.

Conclusion:

This is the first local comprehensive description of anaphylactic trends. Further areas of research are suggested: to investigate the propensity for allergic reactions in the coloured population, our much higher rate of association with other atopic disorders compared to international patterns, comparison of our baseline comorbid conditions for contextual analysis, and a review of barriers to care. Ongoing education and training to patients, parents, teachers, and health care workers is identified as a major area requiring intensification.

MAIN ARTICLE

INTRODUCTION

Anaphylaxis is "a severe, life-threatening generalized or systemic hypersensitivity reaction"[1] graded according to organ systems involved and reaction severity[2].

Guidelines by the World Allergy Organization (WAO)[3], the European Academy of Allergy and Clinical Immunology (EAACI)[4], the American Academy of Allergy, Asthma and Immunology (AAAAI), the American College of Allergy, Asthma and Immunology (ACAAI)[5], and the Allergy Society of South Africa (ALLSA)[6,7] are in accord[8]:

- Diagnosis of anaphylaxis is clinical, based on the recognition of characteristic symptoms and signs following exposure to a likely or known trigger. These include respiratory compromise, reduced blood pressure, signs of end-organ dysfunction, involvement of skin and mucosal tissue, and/or persistent gastro-intestinal upset.
- Laboratory testing plays a supporting role, especially in ruling out differential diagnoses.
- Triggers vary by age and geography, and over time.
- Patient-specific risk factors and individual co-factors can impact the incidence and severity of anaphylactic episodes.
- Swift emergency management is vital, and frequently rehearsed Emergency Unit protocols are advocated. Intramuscular (IM) adrenaline is first-line treatment[9], with repeat dosing as required. Removal of the trigger, calling for help, and supine positioning of the patient with elevation of the lower extremities is advised. Oxygen and airway management, intravenous (IV) access and fluid resuscitation, and cardiopulmonary resuscitation (CPR) needs to be instituted if necessary. Antihistamines, glucocorticoids, inhaled β_2-agonist and inhaled adrenaline are the second-line agents of choice. (Appendix A)[6].

- Close frequent, preferably continuous monitoring is recommended, and for a prolonged period in individuals at risk for biphasic reactions.
- Long-term management with prevention of recurrence is emphasized. This comprises issuing an emergency action plan, an adrenaline auto-injector if indicated, and medical identification before discharge. Follow-up with an allergist/immunologist is strongly advocated: for trigger identification, optimization of co-morbid medical management, comprehensive risk assessment, individualized risk-reduction strategies, ongoing education and training, and consideration of immune modulation therapy.
- The need for further anaphylaxis studies and efforts at global partnerships is advised.

Research in this area is generally challenging, due to under-reporting and low quality of captured of data in registries and by Emergency Departments.[10] These have largely been attributed to under-recognition and misdiagnosis by medical staff, as well as miscoding by the frequently used data capturing methods. An alternative suggestion to study the characteristics of patients with anaphylaxis is by reviewing adrenaline auto-injection dispensing patterns.[11]

A proposal by a pan-European conglomerate of ten participating countries advocates establishment of a collaborative severe allergic reaction database[12], to improve medical care of patients and highlight public health implications. Standardized information on incidence, triggering allergens, aggravating factors, demography and medical management was found to be lacking and urgently needed. Benefits include appraisal of risk management strategies, identification of new allergens, clearer patient education regarding risk factors, motivation for food businesses modification and government agency preventative strategies based on results. Facilitation of accurate comparisons between centres would also be optimized.

These Central European countries collaborated to form the network of severe allergic reactions (NORA). Fifty-nine institutions in Germany, France, Switzerland, Austria, Spain, Poland, the United Kingdom, Greece, Bulgaria, Italy and Ireland collectively documented data from medical records using an online questionnaire, as The European Anaphylaxis Registry[13]. This project is ongoing, with yearly updates including more global partners, to analyze evolution of anaphylaxis trends and treatment. Their review of children and adolescents[14] is replicated here in a South African setting.

There is limited data on anaphylaxis from the African continent, and even less in the paediatric population: all being case reports and series describing reactions to specific triggers. There are no epidemiological or register-based African studies. With this review of our patient demographics and management, we plan to motivate for further locally-based, internationally-standardized anaphylaxis registries and research.

OBJECTIVES

- To describe patients at Red Cross War Memorial Children's Hospital (RCWMCH) who experienced severe allergic reactions, analyze the episodes, and review their subsequent management.
- To establish a dedicated electronic anaphylaxis database, for continued data collection and review after this study is completed.
- To establish links with local and international bodies, to facilitate comparative studies and future collaborative efforts.

METHODS

STUDY DESIGN

A retrospective case series describing and analyzing characteristics and management of paediatric patients treated at RCWMCH for severe allergic reactions and anaphylaxis over a thirty-two month period.

SETTING

RCWMCH is a dedicated paediatric hospital in Cape Town, providing secondary, tertiary and quaternary care to an average of 250 000 patients per year[15], referred from the Western Cape, the rest of South Africa, and across broader Africa[16]. The Division of Asthma and Allergy provides diagnostic and treatment services on an inpatient, outpatient and outreach basis, providing multi-disciplinary care with established collaborations between associated services, including gastroenterology, dietetics, dermatology, pulmonology, ophthalmology, otolaryngology and infectious diseases.[17] Approval was received from the UCT Human Research Ethics Committee (HREC), the Departmental Research Committee (DRC) and institutional approval from RCWMCH.

PARTICIPANTS

- Population

  All children who experienced a severe allergic reaction while under the care of the paediatric services at RCWMCH between January 2014 and August 2016.

- Recruitment

  The institutional clinical summary system of admissions and discharges (CLINICOM) was used to detect patients meeting the relevant coding criteria, according to the International Statistical Classification of Diseases and Related Health Problems, 10th edition (ICD10) Version 2015[18]:

  - T78.0 (Anaphylactic shock due to adverse food reaction)
  - T78.2 (Anaphylactic shock, unspecified)

- T80.5 (Anaphylactic shock due to serum)
- T88.6 (Anaphylactic shock due to adverse effect of correct drug or medicament properly administered)

In addition, patients identified by the hospital pharmacy's records of adrenaline autoinjector dispensing, and referrals from the allergy department's clinical staff, were used to add patients missed on the above screening. Afflicted children lost to follow-up were traced if possible and re-booked for enrolment and optimization of clinical care. On questioning and with retrospective folder reviews, patients not meeting criteria for relevant reactions in the study period were excluded (Figure 1).

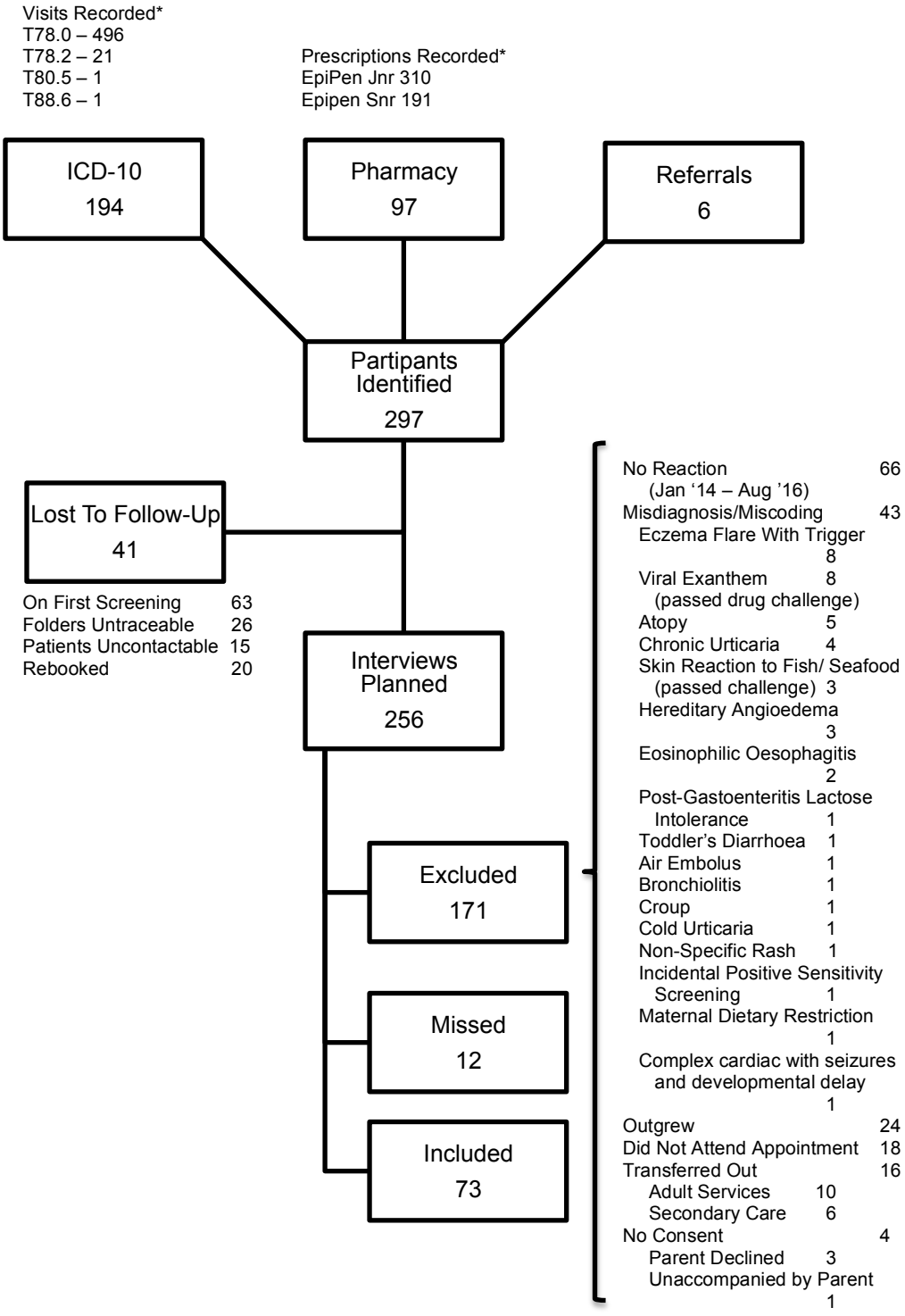

Figure. 1: Selection of Participants

* Recorded Visits

(as opposed to rest of graph: number of patients)

Face-to-face interviews with patients and parents were conducted with consent (Appendix B), coinciding with routine Allergy Clinic visits, in two collection periods: August 2016 – November 2016, and July 2017 – October 2017. Of the 73 patients meeting inclusion criteria, each child experienced between one and eight reactions in the time specified, amounting to 156 episodes analyzed. (Figure 2)

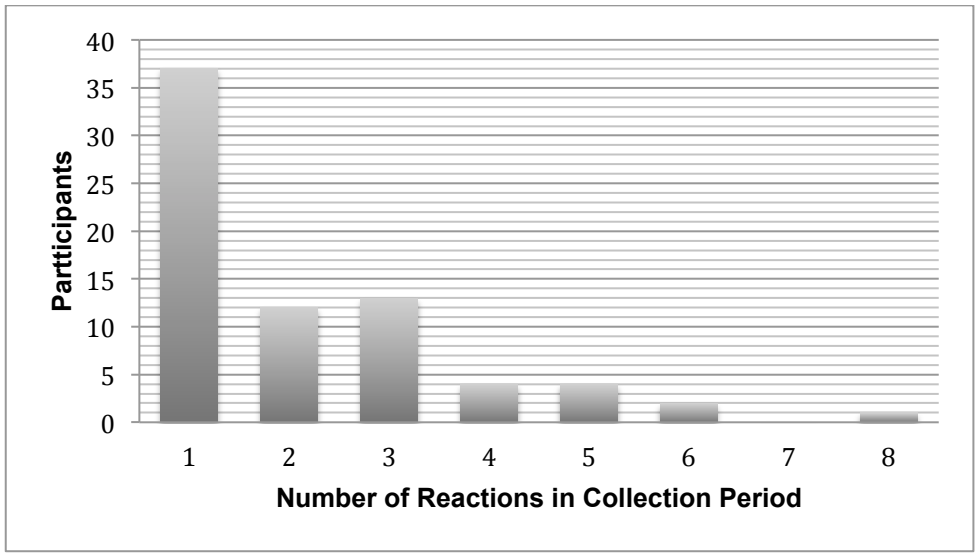

Figure 2: Number of Reactions per Participant in Collection Period

MEASUREMENTS

- Instruments
    - Utilization of a questionnaire (Appendix C) initially developed by NORA and validated by double-entry congruency[19], modified for the South African setting. The questionnaire was then programmed into an online database.

      We added self-defined ethnicity, as per the latest StatsSA census classification[20]. Race was not included in the European study, but a systematic review of the literature[21] shows African ethnicity as a potential risk factor for fatal anaphylactic episodes, with limited data on the effect of race on non-fatal episodes. We hope, by reviewing the interaction of race on different variables in our setting, particularly associated eliciting agents and comorbid diseases, to identify

areas of focus for potential future individual optimization of care.

- Establishment of an electronic web-based registry on REDCap, a clinical data management system, facilitated by the UCT's Clinical Research Centre, in collaboration with NORA and fashioned on the online data entry system used for the European Anaphylaxis Registry.

- Variables
  - Demographics: age at episode, sex, ethnicity.
  - Symptomatology: range, onset, timing, fatality, location, and recurrence. In addition, severity was assessed by reviewing a composite of symptoms, based on the classification system by Ring and Messner.[2] (Table 1)
  - Diagnostic investigations
  - Previous diagnoses and advice
  - Eliciting triggers and dosage
  - Exacerbating factors and concomitant diseases
  - Treatment: emergency, prophylaxis, follow-up
  - Further comments (as free text)

GRADE*	SKIN	ABDOMEN	RESPIRATORY TRACT	CARDIOVASCULAR SYSTEM
I	Itch Flushing Urticaria Angioedema			
II	Itch Flushing Urticaria Angioedema	Nausea Cramps	Rhinorrhoea Hoarseness Dyspnoea	Tachycardia (rise ≥ 20 bpm) Hypotension (SBP drop ≥ 20 mm Hg) Arrhythmia
III	Itch Flushing Urticaria Angioedema	Vomiting Defecation	Laryngeal Oedema Bronchospasm Cyanosis	Shock
IV	Itch Flushing Urticaria Angioedema	Vomiting Defecation		Circulatory Arrest

Table 1: Ring and Messner grading scale for anaphylactic reactions

*according to the worst manifestation, none is obligatory

DATA MANAGEMENT

Patient details were collected for initial identification purposes and informed consent, then numerically encrypted and utilized in this anonymous format for database entry and analysis. The subsequently established REDCap Anaphylaxis Registry was access-restricted, with only approved investigative staff allowed usage. Data was analysed using Stata version 14 of 2015.

RESULTS

DEMOGRAPHICS

Males and younger participants were more frequently affected, with a significant proportion being of self-defined coloured ethnicity. The median age at reaction was 3.0 years (IQR 1.7 – 5.25).

SYMPTOMATOLOGY

Skin and mucosal surfaces were almost universally involved, followed by respiratory compromise, with gastro-intestinal upset and cardiovascular symptoms less common (Figure 3). Half of the instances recorded were classified as mild, with only 8 cases (5.1%) being Grade 2, and the remainder (44.9%) being Grade 3 (Table 2). Four episodes (2.6%) occurred with a biphasic reaction, all of them 4-12 hours after exposure. There were no fatalities analysed in the collection period. All reactions happened in South Africa, with 6 (4.5%) of cases associated with a foreign national. A fifth of incidences occurred secondary to a medically-supervised allergen challenge in a health care setting, with 65% of events occurring at home.

DIAGNOSTIC TESTING

Only 12 cases (7.7%) had no allergen identified. Skin prick testing and specific IgE assays were the mainstay of diagnosis, being utilized in 54.5% and 84.0% of reactions respectively, and being positive in nearly all tested (98.6% and 100%). Tryptase levels were rarely reviewed in our setting (4.5% of reactions).

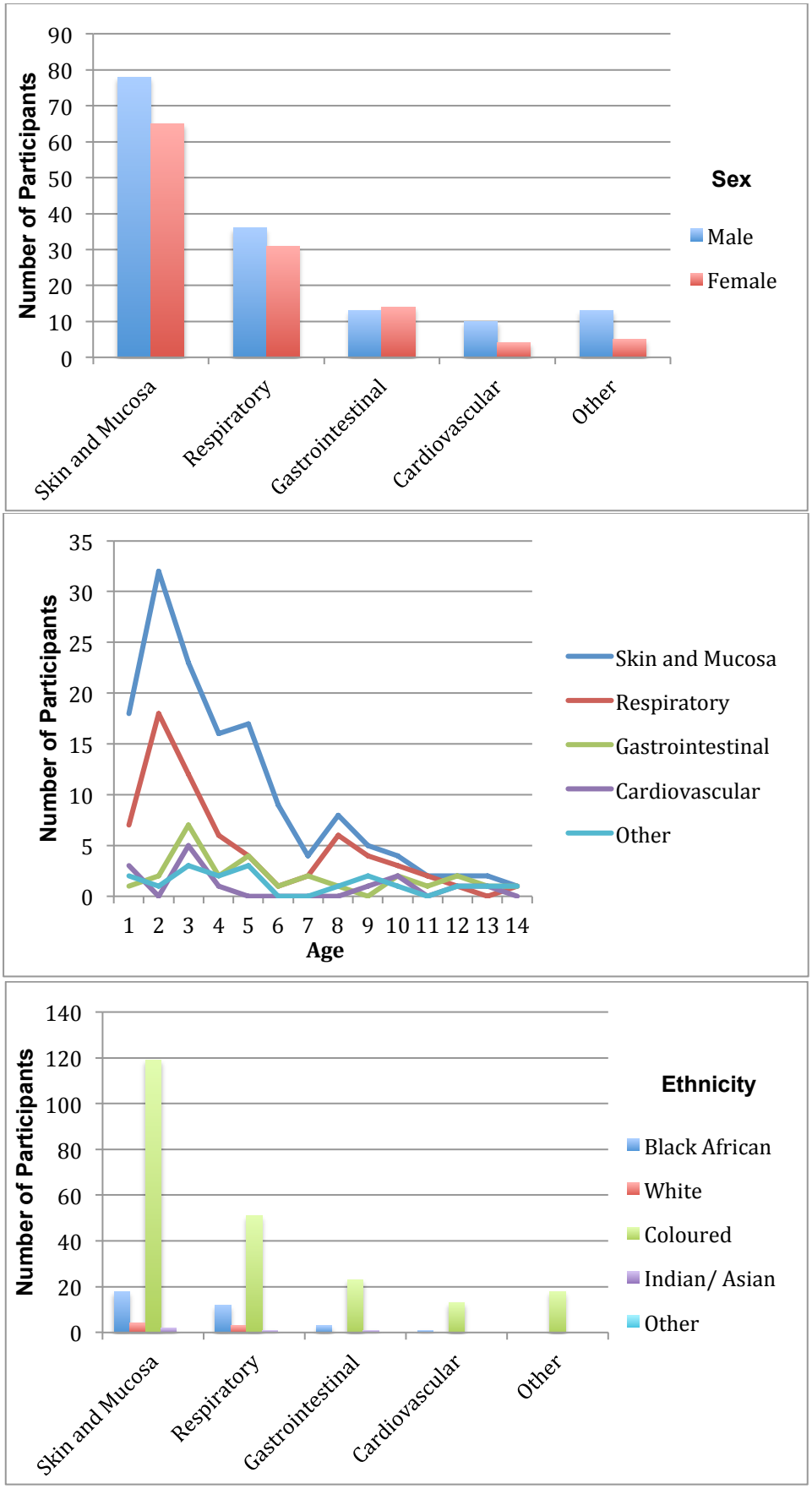

FIGURE 3: Distribution of Symptomatology

	GRADE 1	GRADE 2	GRADE 3	TOTAL
TOTAL	78 (50.0%)	8 (5.1%)	70 (44.9%)	156 (100%)
DEMOGRAPHICS				
Sex				
Male	44 (28.2%)	2 (1.3%)	39 (25.0%)	85 (54.5%)
Female	34 (21.8%)	6 (3.8%)	31 (19.9%)	71 (45.5%)
Age				
0 – 5 years	69 (43.4%)	5 (3.2%)	48 (30.8%)	122 (78.2%)
6 – 14 years	9 (5.7%)	3 (1.9%)	22 (14.1%)	34 (21.8%)
Ethnicity				
Black African	7 (4.5%)	2 (1.3%)	11 (7.1%)	20 (12.8%)
White	1 (0.6%)	0	3 (1.9%)	4 (2.6%)
Coloured	69 (44.2%)	6 (3.8%)	54 (34.6%)	129 (82.7%)
Indian/ Asian	1 (0.6%)	0	2 (1.3%)	3 (1.9%)
SYMPTOMATOLOGY				
Symptoms				
Skin and Mucosa	78 (50.0%)	7 (4.5%)	58 (37.2%)	143 (91.7%)
Respiratory	4 (2.6%)	5 (3.2%)	58 (37.2%)	67 (42.9%)
Gastro-intestinal	1 (0.6%)	4 (2.6%)	22 (14.1%)	27 (17.3%)
Cardiovascular	0	4 (2.6%)	10 (6.4%)	14 (9.0%)
Other	3 (1.9%)	2 (1.3%)	13 (8.3%)	18 (11.5%)
Timing				
unknown	0	0	3 (1.9%)	3 (1.9%)
0 – 10 mins	59 (37.8%)	6 (3.8%)	56 (35.9%)	121 (77.6%)
11 – 30 mins	7 (4.5%)	0	2 (1.3%)	9 (5.8%)
31 – 60 mins	4 (2.6%)	1 (0.6%)	6 (3.8%)	11 (7.1%)
61 – 120 mins	7 (4.5%)	1 (0.6%)	3 (1.9%)	11 (7.1%)
2 – 4 hrs	1 (0.6%)	0	0	1 (0.6%)
> 4 hrs	0	0	0	0
Biphasic	1 (0.6%)	1 (0.6%)	2 (1.3%)	4 (2.6%)
Fatality	0	0	0	0
Location				
Home	49 (31.4%)	6 (3.8%)	47 (30.1%)	102 (65.4%)
Medical Practice	20 (12.8%)	2 (1.3%)	10 (6.4%)	32 (20.5%)
Relative/Friend's	5 (3.2%)	0	7 (4.5%)	12 (7.7%)
School/ Kindergarten	1 (0.6%)	0	3 (1.9%)	4 (2.6%)
Restaurant/ TakeAway	1 (0.6%)	0	2 (1.3%)	3 (1.9%)
Garden/ Park	2 (1.3%)	0	0	2 (1.3%)
Unknown	0	0	1 (0.6%)	1 (0.6%)
DIAGNOSTIC TESTING				
Allergen Confirmed	71 (45.5%)	8 (5.1%)	65 (41.7%)	144 (92.3%)
Before Episode	46 (29.5%)	6 (3.8%)	42 (26.9%)	94 (60.3%)
At or After Episode	25 (16.0%)	2 (1.3%)	23 (14.7%)	50 (32.0%)
COUNSELLING				
Previously Diagnosed	53 (34.0%)	7 (4.5%)	46 (29.5%)	106 (67.9%)
Avoidance Advice	52 (33.3%)	6 (3.8%)	45 (28.8%)	103 (66.0%)
Management Advice	52 (33.3%)	6 (3.8%)	43 (27.6%)	101 (64.7%)
TRIGGERS				
Known	74 (47.4%)	8 (5.1%)	66 (42.3%)	148 (94.9%)
Reasonable Suspicion	4 (2.6%)	0	1 (0.6%)	5 (3.2%)
Food: Type				
Peanut	21 (13.5%)	3 (1.9%)	23 (14.7%)	47 (30.1%)
Hen's Egg	18 (11.5%)	3 (1.9%)	12 (7.7%)	33 (21.2%)
Fish	9 (6.4%)	0	3 (1.9%)	12 (7.7%)
Cashews	5 (3.2%)	0	7 (4.5%)	12 (7.7%)
Cow's Milk	2(1.3%)	0	7 (4.5%)	9 (5.8%)
Preservative (Na Benz)	5 (3.2%)	0	3 (1.9%)	8 (5.1%)
Hazelnut	3 (1.9%)	0	1 (0.6%)	4 (2.6%)
Shrimp/Scampi	2 (1.3%)	0	2 (1.3%)	4 (2.6%)

Sesame	1 (0.6%)	0	2 (1.3%)	3 (1.9%)
Lentil	2 (1.3%)	0	0	2 (1.3%)
Pea	2 (1.3%)	0	0	2 (1.3%)
Mixed Nuts	1 (0.6%)	0	1 (0.3%)	2 (1.3%)
Coconut	1 (0.6%)	1 (0.6%)	0	2 (1.3%)
Banana	0	0	2 (1.3%)	2 (1.3%)
Almond	1 (0.6%)	0	0	1 (0.6%)
Bean	0	0	1 (0.6%)	1 (0.6%)
Calamari	0	0	1 (0.6%)	1 (0.6%)
Chocolate	0	0	1 (0.6%)	1 (0.6%)
Colouring Agents	1 (0.6%)	0	0	1 (0.6%)
Crayfish	1 (0.6%)	0	0	1 (0.6%)
Legumes	1 (0.6%)	0	0	1 (0.6%)
Pistachio	0	1 (0.6%)	0	1 (0.6%)
Food: Packaging				
Prepacked	45 (28.8%)	4 (2.6%)	39 (25.0%)	88 (56.4%)
Non-Prepacked	33 (21.2%)	3 (1.9%)	28 (17.9%)	64 (41.0%)
Food: Quantity				
< 1 tsp	61 (39.1%)	6 (3.8%)	51 (32.7%)	118 (75.6%)
1 teaspoon	14 (9.0%)	0	10 (6,4%)	24 (15.4%)
1 tablespoon	3 (1.9%)	1 (0.6%)	4 (2.6%)	8 (5.1%)
unknown	0	0	2 (1.3%)	2 (1.3%)
Drugs: Ibuprofen	0	1 (0.6%)	0	1 (0.6%)
EXACERBATING FACTORS				
Concomitant Disease				
Eczema	73 (46.8%)	6 (3.8%)	61 (39.1%)	140 (89.7%)
Allergic Rhinitis/ Conjunctivitis	70 (44.9%)	6 (3.8%)	66 (42.3%)	142 (85.3%)
Associated Food Allergy (Separate Trigger)	63 (40.4%)	4 (2.6%)	48 (30.8%)	115 (73.7%)
Asthma	49 (31.4%)	1 (0.6%)	56 (35.9%)	106 (67.9%)
Anaemia	7 (4.5%)	2 (1.3%)	7 (4.5%)	16 (10.3%)
Speech Delay	5 (3.2%)	2 (1.3%)	4 (2.6%)	11 (7.1%)
Failure to Thrive	6 (3.8%)	1 (0.6%)	3 (1.9%)	10 (13.5%)
Gastroeosophageal Reflux Disease	0	2 (1.3%)	6 (3.8%)	8 (5.1%)
Chronic Suppurative Otitis Media	3 (1.9%)	2 (1.3%)	3 (1.9%)	8 (5.1%)
Papular Urticaria	1 (0.6%)	1 (0.6%)	1 (0.6%)	3 (1.9%)
Eosinophilic Oesophagitis	2 (1.3%)	0	1 (0.6%)	3 (1.9%)
Chronic Constipation	2 (1.3%)	0	1 (0.6%)	3 (1.9%)
ADHD	2 (1.3%)	0	1 (0.6%)	3 (1.9%)
Oppositional Defiant Disorder	2 (1.3%)	0	1 (0.6%)	3 (1.9%)
Squint	1 (0.6%)	2 (1.3%)	0	3 (1.9%)
Bronchiolitis Obliterans	1 (0.6%)	0	1 (0.6%)	2 (1.3%)
Perthe's Disease	0	1 (0.6%)	1 (0.6%)	2 (1.3%)
IgA deficiency	1 (0.6%)	0	0	1 (0.6%)
Epilepsy	0	0	1 (0.6%)	1 (0.6%)
Vestibular Migraines	0	1 (0.6%)	0	1 (0.6%)
Autism	0	0	1 (0.6%)	1 (0.6%)
Adjustment Disorder	0	1 (0.6%)	0	1 (0.6%)
Conduct Disorder	0	0	1 (0.6%)	1 (0.6%)
TREATMENT				
<u>First Line</u>				
Attendant				
Solely Lay	42 (26.9%)	3 (1.9%)	27 (17.3%)	72 (46.2%)
Solely Professional	24 (15.4%)	3 (1.9%)	21 (13.5%)	48 (30.8%)

Lay Then Professional	4 (2.6%)	2 (1.3%)	14 (9.0%)	20 (12.8%)
None	8 (5.1%)	0	8 (5.1%)	16 (10.3%)
Treatment: Lay				
Adrenaline Autoinjector	2 (1.3%)	0	9 (5.8%)	11 (7.1%)
Antihistamine	45 (28.8%)	5 (3.2%)	33 (21.2%)	83 (53.2%)
β-2 agonists	0	0	10 (6.4%)	10 (6.4%)
Corticosteroids	0	0	1 (0.6%)	1 (0.6%)
Treatment: Professional				
Adrenaline IM	1 (0.6%)	2 (1.2%)	9 (5.8%)	12 (7.7%)
Adrenaline IV	0	0	1 (0.6%)	1 (0.6%)
Adrenaline Inhaled	0	0	1 (0.6%)	1 (0.6%)
Antihistamine IV	0	0	1 (0.6%)	1 (0.6%)
Antihistamine po	26 (16.7%)	4 (2.6%)	17 (10.9%)	47 (30.1%)
β-2 agonists Inhaled	1 (0.6%)	1 (0.6%)	13 (8.3%)	15 (9.6%)
Corticosteroids po	0	1 (0.6%)	0	1 (0.6%)
Oxygen	0	0	7 (4.5%)	7 (4.5%)
Other	2 (1.3%)	1 (0.6%)	10 (6.4%)	13 (8.3%)
2nd Dose Adrenaline	0	0	0	0
Second Line	1 (0.6%)	3 (1.9%)	15 (9.6%)	19 (12.2%)
Treatment				
Corticosteroids po	1 (0.6%)	2 (1.3%)	9 (5.8%)	12 (7.7%)
Antihistamine po	0	2 (1.3%)	5 (3.2%)	7 (4.5%)
β-2 agonists Inhaled	0	0	1 (0.6%)	1 (0.6%)
Corticosteroids IV	0	0	1 (0.6%)	1 (0.6%)
Admission				
Hospital	2 (1.2%)	2 (1.2%)	17 (10.9%)	21 (13.5%)
ICU	0	0	0	0
PROPHYLAXIS				
Measures				
Avoidance Counselling	78 (50.0%)	8 (5.1%)	70 (44.9%)	156 (100%)
Drug Prescription	78 (50.0%)	8 (5.1%)	70 (44.9%)	156 (100%)
Management Plan	78 (50.0%)	8 (5.1%)	70 (44.9%)	156 (100%)
Specific Immunotherapy	0	0	0	0
Medic Alert Bracelet	45 (28.8%)	5 (3.2%)	54 (34.6%)	104 (67.9%)
Drugs				
Adrenaline Autoinjector	47 (30.1%)	6 (3.8%)	63 (40.4%)	116 (74.4%)
Adrenaline Inhaler	0	0	0	0
Antihistamines	78 (50.0%)	8 (5.1%)	70 (44.9%)	156 (100%)
β-2 agonists	49 (31.4%)	1 (0.6%)	63 (40.4%)	113 (72.4%)
Corticosteroids	2 (1.6%)	0	3 (1.9%)	5 (3.2%)

Table 2: Comparisons in Patient Severity

ELICITING TRIGGERS

Three instances (1.9%) were caused by an unknown allergen, one (0.6%) by drugs (ibuprofen), and the remainder by a food-related trigger (Figure 4). The vast majority of food reactions were caused by very small amounts of food ingested; 75.6% less than one teaspoon. Of those having reactions to prepacked foods (88), 60 (68.2%) had the trigger in the product name or listed in the ingredients, in the "may contain" advice box in three cases (3.4%), and 25 (28.4%) could not recall the labeling. In those having reactions to non-prepacked foods (64), 39 (60.9%) were homemade, 20

(31.3%) catered, three (4.7%) from a fishmonger, and two (3.1%) from a bakery.

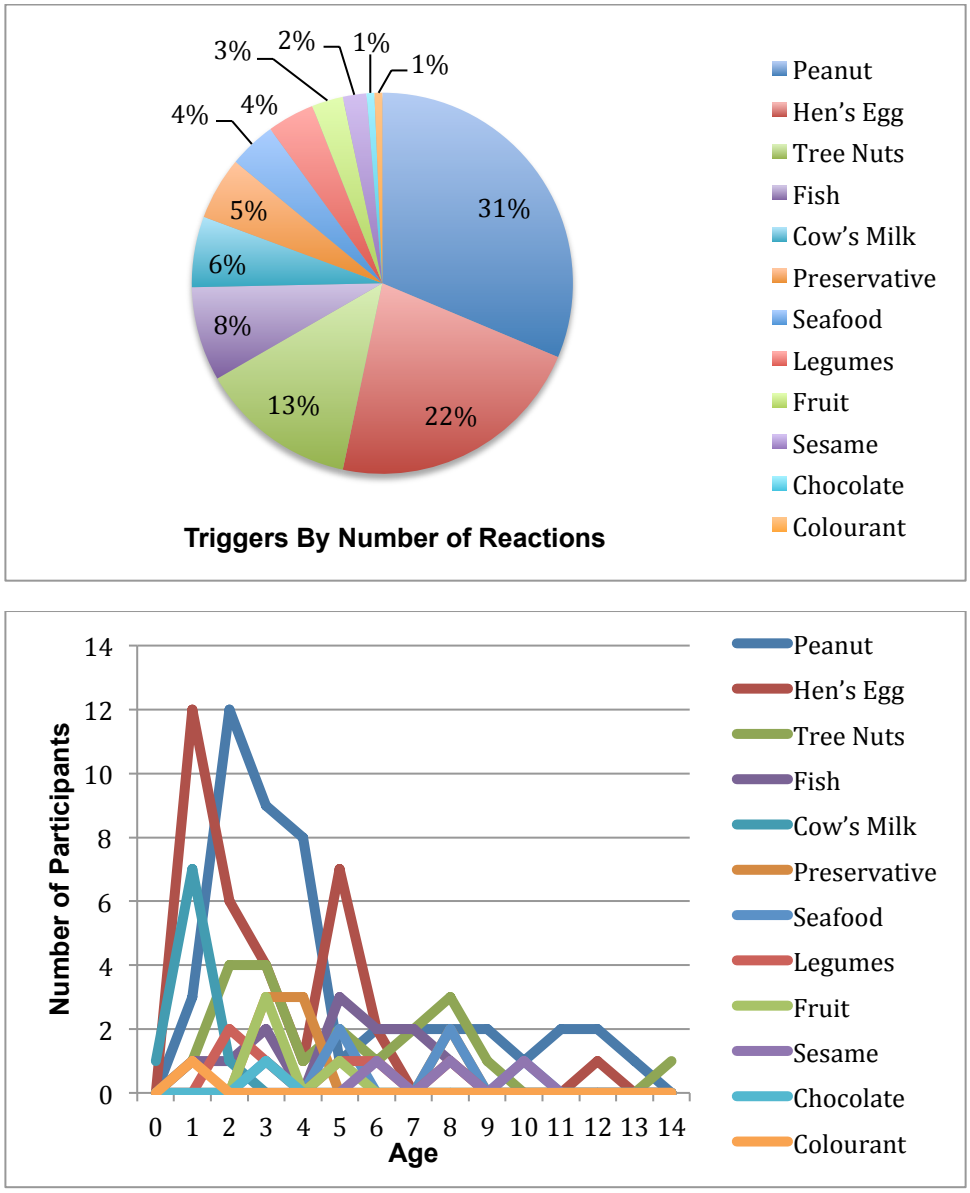

Figure 4: Distribution of Eliciting Triggers

EXACERBATING FACTORS

Atopic conditions had a strong correlation with severe allergic reactions, with 89.7% having eczema, 85.3% allergic rhinoconjunctivitis and 67.9% asthma (Table 2). In 115 (72%) of instances, the patients had an associated food allergy to a second food. No other co-factors were identified in our sample population.

MANAGEMENT

First Line

10.3% (16 of 156) of instances went untreated. A lay person was the first responder in 92 (59.0%) of cases. Of those managed by a lay person first, 87 (95.6%) was a family member, usually the parent, three cases (3.3%) were self-managed, and one (1.1%) was a nursery school teacher. When primary care was managed by a professional, 37 of the 67 (55.2%) was by an emergency doctor or general practitioner, with the allergy specialist only involved in the care of 29 cases (43.3%). All allergen challenges (32 of the total 156, translating to 20.5%) were managed by the supervising allergy specialists.

The majority of first-line lay-person treatment was antihistamine (83 of the 92: 90,2%). Adrenaline auto-injector use in those patients previously prescribed (84) was rare, in 12 cases (14.3%) not being present at the time of the reaction, and with 40 (47.6%) available but not used. Similarly with previously prescribed inhaled β2-agonists (96): available and not used in 60 (62.5%), prescribed but not available with one (1.0%); prior oral antihistamines prescription (139): available and not used in 19 (13.7%), prescribed but not available with 6 (4.3%); and with oral corticosteroids (2 cases): prescribed and available but not used in two both (100%). These excludes the hospital-associated allergen challenges.

29.4% of all professional care (20 of 68) was preceded by lay treatment. Adrenaline was administered as first line care by the attending health professional intramuscularly (12 cases, 17.6%), intravenously once, (1.5%), and as an inhalant (once, 1.5%) in cases managed professionally (68). Antihistamine orally (47 of 68, 69.1%) and inhaled β2-agonists (15 cases, 22.1%) were the mainstay of professional treatment, with intravenous antihistamines and oral corticosteroid administered once each (1.5%).

Second Line

19 instances (13.6%) required second-line therapy, mostly oral corticosteroids (12 of these 19, 63.2%) or a second dose of antihistamine (7 instances, 36.8%).

Admissions

No patients admitted to hospital (13.5% of the total), required intensive care.

Prophylaxis

Prophylactic measures were instituted before and after the recorded reactions to varying degrees (Table 3). Of the 104 instances replying positively to Medic Alert Identification, 4 (8.7%) have applied and are still awaiting their bracelets, two (3.8%) had theirs stolen, in three instances (2.9%) it was lost, one (2.9%) was using a second one, and in eight cases (7.7%) the child refuses to wear them.

	PRIOR TO REACTION	PRIOR TO DISCHARGE	DURING PRIMARY CARE FOLLOW-UP	DURING SPECIALIST FOLLOW-UP	NIL
COUNSELLING ABOUT AVOIDANCE OF TRIGGER	103 (66.0%)	62 (39.7%)	/	153 (98.1%)	3 (1.9%)
PRESCRIPTION OF EMERGENCY DRUGS	124 (79.5%)	63 (40.4%)	/	156 (100.0%)	0
Adrenaline Autoinjector	84 (53.8%)	24 (15.4%)	/	116 (74.5%)	39 (25.0%)
Adrenaline Inhaler	/	/	/	/	/
Antihistamines	139 (89.1%)	55 (35.3%)	/	156 (100.0%)	0
β-2 agonists	96 (61.5%)	23 (14.7%)	/	113 (72.4%)	43 (27.6%)
Corticosteroids	2 (1.3%)	2 (1.3%)	/	3 (1.9%)	151 (96.8%)
TRAINING IN EMERGENCY MANAGEMENT PLAN	117 (75.0%)	48 (30.8%)	/	156 (100.0%)	0
SPECIFIC IMMUNOTHERAPY	/	/	/	/	/
MEDIC ALERT IDENTIFICATION	77 (49.4%)	0	/	27 (17.3%)	52 (33.3%)

TABLE 3: Timing of Prophylactic Measures

RECURRENCE

101 (64.7%) of all episodes were preceded by a previous reaction to the same allergen. Of these, 36 (35.6%) had a single preceding event, 28 (27.7%) had two, 7 (6.9%) three, 26 (25.7%) more than three, and in 4 instances (3.96%) an unknown quantity of reactions. 89 (88.1%) of these preceding episodes were severe, with 37 (36.6%) recalled as milder than the recorded event. The commonest organ systems previously involved were skin (97, 96.0%) and respiratory (73, 72.3%), with gastrointestinal (18, 17.8%) and cardiovascular (5, 5.0%) involvement being rarer.

The allergen involved was confirmed by diagnostic testing before the current recorded reaction in 94 (93.0%) of these cases.

In 106 episodes, patients were aware of an underlying allergy to the offending agent, this diagnosis being by a general practitioner or emergency physician in 22 instances (20.8%), an allergy specialist in 77 (72.6%), and self-diagnosed by the parent in the remaining 7 (6.6%). This 106 is slightly more than the number of participants who experienced a previous reaction (101), as some children had the current offending allergen identified as a potential trigger on investigation after an event following exposure to a different allergen.

On review of risk reduction strategies to participants who experienced previous reactions, 90 of the 101 (89.1%) received advice regarding allergen avoidance, and 88 (87.1%) advice on management in the emergency situation. 94 (93%) of these participants were prescribed emergency drugs before the recorded episode, of these 64 (63.3%) had adrenaline autoinjectors, 99 (98.0%) antihistamines, 70 (69.3%) inhaled β2-agonists, and two (2.0%) oral corticosteroids. 58 (57.4%) had a medical alert identification previously issued to them.

DISCUSSION

KEY FINDINGS

In keeping with international studies[14,21], severe allergic reactions were more common in males ($p = 0.058$) and children in the younger age groups ($p < 0.0001$). For comparison, we contrasted our findings with the European

Anaphylaxis Registry, who identically reviewed 1970 children from 90 centres in ten countries.

We had disproportionately more participants who self-classified as coloured affected, but no significant effect of race on severity ($p = 0.428$). This distribution could only partially be explained by socio-economic disparities and differing health seeking behavior between socio-demographic groups in Cape Town, as this coloured proportion (82.7%) was not congruent to the spectrum of patients seeking health care at RCWMCH for other medical conditions (52.0%, $p < 0.0001$), or the Western Cape (48.8%[22], $p < 0.0001$) and South African (8.9%[23], $p < 0.0001$) racial profiles.

The pattern of systemic involvement is in keeping with global trends. The severity distribution differs from the European Anaphylaxis Registry[14]: more Grade 1 and 3 here, than Grade 2 and 3 with our counterparts. This could be accounted for by a lower threshold for inclusion locally, due to a thorough recruitment process, rather than requiring primary care doctor reporting to a central research agency. The timing between exposure and reaction is less than 10 minutes in the majority of our patients, similar to international studies. We recorded proportionately less biphasic reactions, with our patterns occurring at 4 – 12 hours after exposure, instead of the more than 12 hours in the NORA cohort. A comparatively larger proportion of our reactions happened at home.

Diagnostic testing seemed to be used appropriately in our resource-limited setting, with the majority of triggers identified, an almost universal positive pick-up rate by the tests utilized and low rates of multiple allergen screens and negative results. Most diagnosis was in follow-up with the allergy sub-specialist, in identical proportions to the above studies. Two-thirds of patients were noted to be allergic to the offending allergen before the recorded event, also similar to the European data. Almost all were advised regarding avoidance of the elicitor and emergency managements, but the practical effectiveness of this needs to be addressed, in view of the relatively high rate of recurrent reactions and non-use of the prescribed medications in the emergency situation.

With our comparatively smaller sample size, no reactions were associated with insects and antibiotics, or with immunotherapy. In the European study,

peanuts, cows' milk and hen's eggs predominate as a food trigger, decreasing with age. Our trend is similar, with the addition of fish and tree nuts (particularly cashew nuts) playing a larger role, potentially due to our increased incidence of ingestion of the former, and possible decreased awareness of the latter.

The association of allergic reactions in our population to atopic disorders and food hypersensitivity to a second trigger mirrors the European trend, but at a more than three-fold increase in rate: incidence of eczema is 89.7% in our participants (compared to 26.3% in the European database), allergic rhinitis 85.3% (21.2%), asthma 67.9% (22.9%), and food allergies to a different agent 73.7% (0.5%). This can only partly be explained by the tertiary setting of patient sampling, and opens up further suggestions for investigative research. The co-morbid anaemia and failure to thrive may be caused by highly restrictive diets in subjects with multiple food allergy. These prevalence rates, along with those of the neuro-developmental and -psychiatric conditions, are difficult to interpret without a baseline population comparison. No other major exacerbating factors were diagnosed.

A large proportion of all episodes were solely managed by a lay person, usually a parent, occasionally self administered, and rarely a teacher. This is in contrast to internationally, where a larger proportion was treated by professionals, likely due to the local under-recognition of the severity of the underlying condition, different health seeking behaviours and access to health care in our setting, and low public and school awareness of anaphylaxis and its management. The majority of first medical attenders were non-allergy specialists. Adrenaline was rarely administered, by lay responders and professionals. This calls for intensification of education to schools and emergency department staff. Fewer of our participants required hospital admission, likely due to the comparatively higher proportion of less severe reactions reviewed. Application of prophylactic measures needs improvement, particularly issuing of adrenaline autoinjectors in the severely affected group of participants and referral for Medic Alert identification. Education to parents and patients also requires intensification, as even though there was a high rate of counseling and training, still 10% of

reactions went untreated in the acute situation, half of which were severe. Investigation into barriers to treatment is also suggested.

IMPLEMENTATION

A secondary benefit of our study was identifying patients who required optimization of treatment, risk reduction strategies, and follow-up plans, addressing this as we proceeded. These included teaching and empowering patients and parents regarding the condition and avoidance measures, re-iterating advice on emergency management plans, identifying and addressing any gaps in knowledge, and confirming and coordinating follow-up appointments at appropriate institutions.

Cooperative relations with our European colleagues at NORA were initiated, to contribute to the understanding of global anaphylaxis trends. We have also commenced collaborations between local institutions, in the form of discussions between the RCWMCH's Division of Asthma and Allergy, and the Department of Allergology and Clinical Immunology at Groote Schuur Hospital, to consider replicating this study in an identical adult population.

STRENGTHS AND LIMITATIONS

This is the first locally-based, internationally-standardized review of anaphylaxis patterns, allowing a basis for harmonized comparisons with global studies. The establishment of a dedicated hospital-based registry is instrumental to continue long-term analysis.

The recruitment process was systematic, as opposed to an opportunistic multi-centered approach, accounting for a lower threshold for inclusion locally. A tertiary setting for this study was appropriate, in keeping with recommended follow-up guidelines, but the potential for missing mismanaged unreferred potential participants exists. Analysis of trends over time was not possible due to the short study period. The study was also based at a single centre, resulting in a limited sample size. In addition some potential participants were lost-to-follow-up or excluded for other reasons.

We analysed no fatalities, although one occurred during our collection period. This was due to ethical review limitation: our study was approved for

consent and face-to-face interviews at routine follow-up only, with doctor's notes as support looking retrospectively at reactions, while the European Anaphylaxis Registry involved taking consent at a first visit and collecting data from folder reviews pro- and retrospectively for the study time demarcated. The reliance on parental memory might be biased, but the review of the associated hospital records ameliorates this.

Additional benefits of the study were the identification and recall of patients who defaulted treatment, and optimization of care if management was deficient. The established electronic database serves as a tool for future data collection and review of local trends over time, as well as to facilitate comparative studies. Discussions were initiated locally and internationally to facilitate collaboration on future research projects.

CONCLUSION

This is the first comprehensive descriptive review of local anaphylactic trends. In comparison to identically conducted European studies, certain discrepancies would benefit from further investigation: particularly the propensity for allergic reactions in the coloured population, as well as our much higher rate of association with other allergic conditions compared to international patterns. An analysis of our baseline comorbid disorders would also assist in putting the review in context, and a review of barriers to care would assist with patient compliance. This further serves as a motivation for more locally-based, internationally-standardized anaphylaxis registries and research. Intensification of educational efforts to patients, parents, schools, and medical teams is strongly advised.

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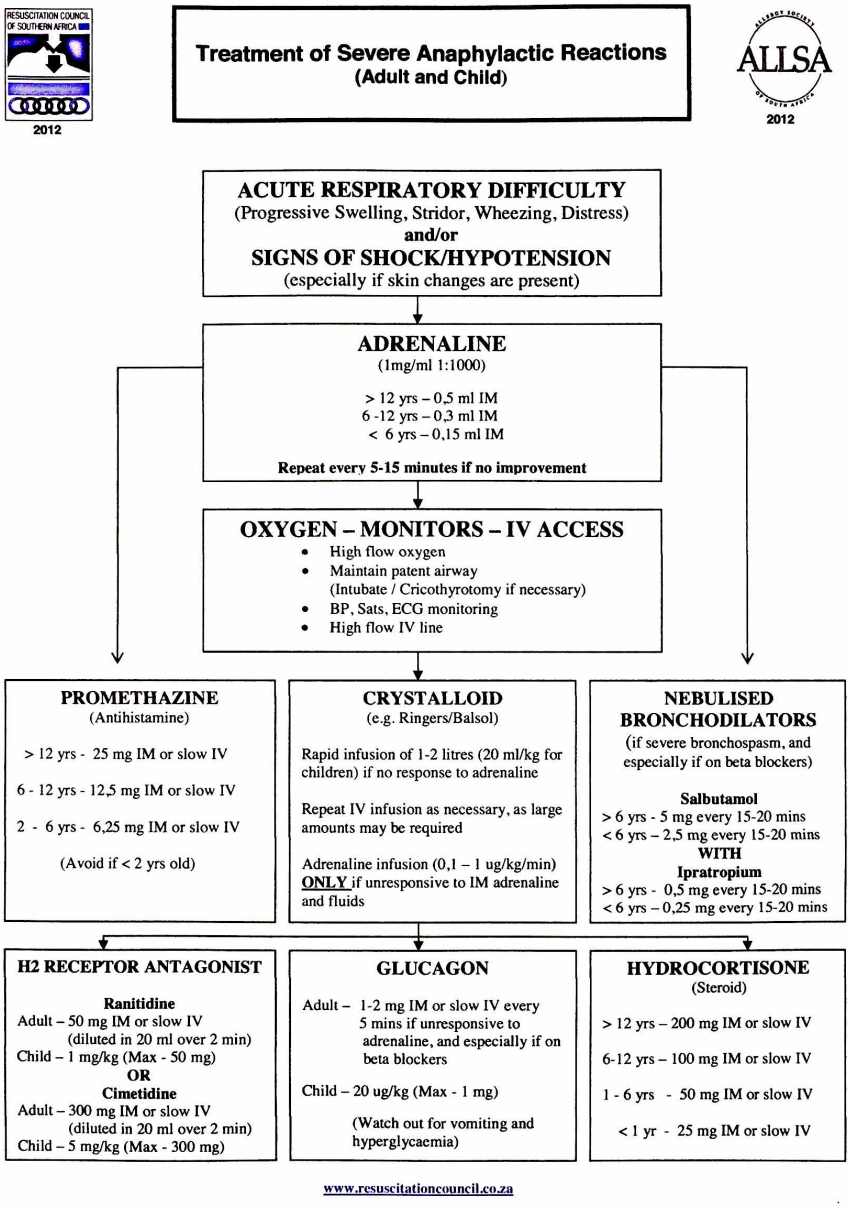
APPENDIX A: ALLSA ALGORITHM

FOR EMERGENCY ANAPHYLAXIS MANAGEMENT[11]



APPENDIX B:

INFORMED CONSENT: INFORMATION DOCUMENT

[Available in English, Afrikaans and Xhosa, to be interpreted via hospital translational services for other languages as necessary.]

PROJECT TITLE:

SEVERE ALLERGIC REACTIONS AT A TERTIARY PAEDIATRIC SERVICE 2014 – 2016

PRINCIPLE INVESTIGATOR:
Dr Sa-eeda Chippendale (0216585111)

THE AIM OF THIS LEAFLET:

- **To summarize the study we are planning**
- **To explain the details of how you and your child can participate, and what to expect**
- **Our plans for the results**
- **You and your child have the right to refuse to participate, or agree to take part now and refuse later**
- **Ask any questions to assist us to help you or your child understand better**
- **Your participation is voluntary**

DECRIPTION OF RESEARCH

PURPOSE

This research study is looking at all children presenting to Red Cross Hospital from 2014 with severe allergic reactions. We are asking you or your child to participate in providing us with information to better understand this condition, and potentially improve patient care for you, your child and other children.

BACKGROUND INFORMATION

Anaphylaxis is a serious, potentially life-threatening condition. There are no South African studies on how this affects our communities, and by participating in this study, you and your child are assisting us to gain valuable insights into this severe disorder. The aim is to utilize this knowledge to potentially optimize you, your child, and future children's care.

PROCEDURES

If you or your child decide to participate, we request that the answering of a simple questionnaire, set up by our colleagues in Europe.

SUMMARY OF QUESTIONNAIRE

We will ask about you and your child's demographics (age, gender, racial profile), the symptoms of the event, if there has been previous episodes and advice, any associated medical conditions, triggering factors, treatment received, and management since then.

DURATION

The questionnaire would be a 30-minute interview, while the study will be continued until 2016.

RISKS

None identified

BENEFITS

There will be no immediate benefit associated with taking part in the study.

COMPENSATION

The survey will be done face-to-face at the Allergy Clinic, at the same time as you or your child's scheduled clinical review, and you will incur no expense. There will be no compensation financially for the time you spend on the survey.

CONFIDENTIALITY

You or your child's details will be collected, but stored separate to the questionnaires. You and your child's answers will be collected with other children's and kept anonymous. All of our reports will have none of your names attached. Privacy of personal information will be an utmost concern, with only the captured statistical data (measurements related to the study) used in the write up of this report.

VOLUNTARY PARTICIPATION

You and your child's participation is voluntary. By choosing to assist, or not, you and your child's relations with the Red Cross Children's Hospital, its personnel, and associated institutions, will not be affected. We still offer your child further training and education, optimization of your medication, and clarification of follow-up at an appropriate institution. You or your child's participation can be withdrawn at any time. Both of your contributions to understanding this important condition are highly appreciated.

FUTURE USE OF INFORMATION

The answers you and your child provide will be collected anonymously and analysed by our computer. The reports, not your personal information, will be utilized at our Allergy Clinic by the doctors looking

after you and your child, and with our colleagues at Anaphylaxie: a European conglomerate looking at similar studies internationally. Stringent measures are in place to protect your personal details, and these will not be distributed.

CONTACT DETAILS

Feel free to contact us if there are any questions regarding consent, this study, the database, or Anaphylaxie: the principal investigators Dr Chippendale and Prof Levin at Red Cross Hospital (0216585111). If you feel the need to discuss you or your child's rights as a research participant and your treatment by us with someone other than the research team, contact the UCT Human Research and Ethics Committee at 0214066338.

INFORMED CONSENT: PATIENT ASSENT (7-12 YEARS)

Hello! We would like to speak to you and your parents about the time you had your allergic reaction.

Your doctors are doing a research project, where we ask children and parents like yourself a few questions, to find out more about your condition and the best way to treat it.

By answering a few questions, you can help us understand your illness better, and possibly help us with other children like you.

We will keep your details private, but will share your answers with some other doctors also looking after people with this condition.

You can say "No", and your treatment at Red Cross Hospital will still go on like normal.

☐ **Yes, I'm happy to answer some questions**

☐ **No, I'd prefer not to be part of this**

NAME: _____

DATE: _____

INFORMED CONSENT: PATIENT CONSENT (>12 YEARS)

If you agree with the following statements, please sign below.

- ☐ I understand about the research, have been allowed to ask questions and all of my questions have been answered.
- ☐ I agree to participate in the study.
- ☐ I agree for the information gathered during the study to be collected and used in a database at Red Cross Hospital Allergy Clinic.
- ☐ I can be contacted again when I reach the age of 18 for me to decide again whether I still agree for my information to be kept in the database.

_____	_____
Name of Research Participant	Research Participant's Signature
_____	_____
Researcher	Researcher Signature
_____	_____
Witness	Witness Signature
_____	_____
Place	Date

If you'd prefer not to take part, please do not sign, and just tick this box:

- ☐ No, I'd prefer not to take part in this study.

INFORMED CONSENT: PARENTAL CONSENT

AUTHORIZATION

Me and my child fully understand the information provided, and my questions have been answered satisfactorily.

- ☐ I hereby give consent to participate in the study.
- ☐ I also consent for the findings of this study pertaining to myself or my child, to be collected and utilized in a database at Red Cross Hospital Allergy Clinic.
- ☐ In addition, my child can be contacted for re-consideration of participation in this study, and inclusion in the database, at the age of 18.

Name of Parent/Guardian, Relationship to Patient	Parent/Guardian's Signature
Researcher	Researcher Signature
Witness	Witness Signature
Place	Date

APPENDIX C: QUESTIONNAIRE

Questionnaire for Anaphylaxis

ANAPHYLAXIE.net

Patient

Information are automatically encrypted.

1 | Encrypted patientdata. *

2 | Name: * (in case of compound name only the first name is used) *

3 | Surname: * (without academic title, in case of compound name only the first name is used)*

4 | Date of birth: * (DD.MM.YYYY) *

5 | Gender: *

- ◯ female
- ◯ male

5a| Race (as per STATSSA)[89]

- ☐ African
- ☐ White
- ☐ Coloured
- ☐ Indian or other Asian
- ☐ Other/Unspecified

6 | Date (of the reaction): * (DD.MM.YYYY) *

Should the exact date of the reaction not be known, please insert the day as 00 (for example 00.07.2006)

7 | Date of the first visit in the centre: * (DD.MM.YYYY) *

1) Information about the anaphylactic reaction

1.1 Which symptoms occurred?

8 | 1.1.1. Skin and mucosal symptoms *

- ☐ not specified
- ☐ no skin or mucosal symptoms
- ☐ angioedema / laryngeal edema
- ☐ urticaria
- ☐ pruritus/ itch
- ☐ erythema/ flush
- ☐ conjunctivitis

9 | 1.1.2 Gastrointestinal symptoms *

- ☐ not specified
- ☐ no gastrointestinal symptoms
- ☐ abdominal pain / cramps
- ☐ abdominal distention
- ☐ diarrhoea
- ☐ dysphagia
- ☐ vomiting
- ☐ incontinence
- ☐ nausea

10 | 1.1.3 Respiratory symptoms*

- ☐ not specified
- ☐ no respiratory symptoms
- ☐ asthma exacerbation
- ☐ chest tightness
- ☐ cough
- ☐ respiratory arrest
- ☐ dyspnea/ shortness of breath
- ☐ change in voice
- ☐ stridor (inspiratory)"
- ☐ throat tightness
- ☐ rhinitis

11 | 1.1.4 Cardiovascular symptoms *

- ☐ not specified
- ☐ no cardiovascular symptoms
- ☐ loss of consciousness
- ☐ hypotension (collapse)
- ☐ cardiac arrest
- ☐ dizziness
- ☐ tachycardia
- ☐ reduction of alertness
- ☐ palpitations/ cardiac arrhythmia
- ☐ chest pain/ angina

12 | 1.1.5 other symptoms *

- ☐ dysarthria
- ☐ dysphonia
- ☐ hotness, sweating, trembling
- ☐ tingling/burning of the hands/feet, paresthesia
- ☐ sight disorder
- ☐ agony
- ☐ cyanosis, pallor

13 | 1.2 How long was the time between allergen exposure and onset of symptoms? *

- ◯ don't know
- ◯ 00 – 10 Minutes
- ◯ 11 - 30 Minutes
- ◯ 31 - 60 Minutes
- ◯ 61 - 120 Minutes
- ◯ 121 – 240 Minutes (2 – 4 hours)
- ◯ more than 240 Minutes

14 | 1.3.Did a biphasic reaction occur? *

Biphasic reaction = After initial improvement, subsequent recurrence of same, or appearance of new symptoms.

- ◯ yes
- ◯ no
- ◯ don't know

15 | 1.3.1 If so when did symptoms reoccur? *

- ◯ don't know
- ◯ 4 – 12 hours after initial symptoms
- ◯ 12 – 24 hours
- ◯ more than 24 hours

16 | 1.4. Was the reaction fatal? *

- ◯ yes
- ◯ no

17 | 1.4.1 If yes please, give the time between allergen exposure and death *

- ◯ don't know
- ◯ 0 – 10 mins
- ◯ 11 – 30 mins
- ◯ 31 – 60 mins
- ◯ 61 – 120 mins
- ◯ more than 120 mins [ ]

18 | 1.4.2 If yes, was treatment commenced prior to arrest? *

- ◯ no
- ◯ yes
- ◯ don't know

19 | 1.4.3 If yes, was adrenaline used prior to arrest? *

- ◯ no
- ◯ yes
- ◯ don't know

1.5 Where was the patient at the time of the exposure to the allergen?

20 | 1.5.1 In which country did the reaction occur? *

- ◯ don't know
- ◯ home country
- ◯ foreign country [ ]

21 | 1.5.2 Location of the patient at the time of exposure to the allergen? *

- ◯ don't know
- ◯ place of work
- ◯ school, kindergarten
- ◯ medical practice, hospital
- ◯ garden, park, countryside etc
- ◯ restaurant, cafeteria, takeaway, hotel
- ◯ urban public place (street, cinema, etc.)
- ◯ public transport including aeroplanes
- ◯ relative's or friend's home
- ◯ dentist
- ◯ home
- ◯ other [ ]

22 | 1.6. Has the patient ever previously reacted to the same allergen? *

- ◯ yes
- ◯ no
- ◯ don't know

If yes, please answer the following questions:

23 | 1.6.1 How many times has this allergen caused a reaction? *

- ◯ don't know
- ◯ 2 times
- ◯ 3 times
- ◯ more 3 times

24 | 1.6.2.1 Has the patient ever had more severe reactions? *

- ◯ yes
- ◯ no
- ◯ don't know

25 | 1.6.2.2 Has the patient ever had milder reactions? *

- ◯ yes
- ◯ no
- ◯ don't know

26 | 1.6.3 Which organs were affected during previous reaction(s)? *

- ☐ don't know
- ☐ gastrointestinal tract
- ☐ skin
- ☐ cardiovascular system
- ☐ respiratory tract

2) Diagnostic testing

27 | 2.1 Was the eliciting allergen confirmed by diagnostic test, before or since the reaction?*

- ◯ no
- ◯ Yes, already before the registered reaction here
- ◯ Yes, for the first time since the registered reaction here/
- ◯ don't know

28 | 2.1.1 If yes, which tests *

	positive	negative	not done
skin test (SPT)	◯	◯	◯
provocation challenge (eg. oral food challenge, drug challenge)	◯	◯	◯
specific IgE (total extract)	◯	◯	◯
specific IgE (recombinant allergen)	◯	◯	◯
intradermal test	◯	◯	◯
basophil activation test	◯	◯	◯
CAST (cellular antigen stimulation test)	◯	◯	◯
IgG4 (venom exposition marker)	◯	◯	◯
other	◯	◯	◯

29 | 2.1.2.Was tryptase determined during the allergological work up? (outside the episode) *

- ◯ yes
- ◯ no
- ◯ don't know

30 | If yes, please specify the value

Format: 00,00

31 | 2.2 Patient did not attend the clinic again, therefore no further diagnostic tests were performed.

(In this case, please tick the field!)

- ☐ yes

2.3 Allergy diagnosis and advice prior to reaction

33 | 2.3.1 Did the patient know that he was allergic to the eliciting allergen prior to this reaction? *

- ◯ yes
- ◯ no
- ◯ don´t know

If yes, please answer the following questions:

34 | 2.3.1.1 If yes, had he received a diagnosis from *

- ◯ don't know
- ◯ primary medical practitioner
- ◯ hospital medical practitioner (non-allergy specialist)
- ◯ specialist Allergy Practitioner
- ◯ patient (self-diagnosis);
- ◯ complementary Medicine
- ◯ other

35 | 2.3.2 Has the patient received advice regarding avoidance of the allergen? *

- ◯ yes
- ◯ no
- ◯ don´t know

36 | 2.3.2.1 If yes, has the patient received advice from: *

- ◯ don't know
- ◯ primary medical practitioner
- ◯ hospital medical practitioner (non-allergy specialist)
- ◯ specialist Allergy Practitioner
- ◯ complementary Medicine
- ◯ dietitian
- ◯ allergy Support organisations
- ◯ other

37 | 2.3.3 Has the patient received advice regarding emergency management? *

- ◯ yes
- ◯ no
- ◯ don´t know

38 | 2.3.3.1 If yes, has the patient received advice from *

- ◯ don't know
- ◯ primary medical practitioner
- ◯ hospital medical practitioner (non-allergy specialist)
- ◯ specialist Allergy Practitioner
- ◯ complementary Medicine
- ◯ specialised Nurse
- ◯ allergy Support organisations
- ◯ other

3) The eliciting factors

39 | 3.1 Is the eliciting factor known? *

- ◯ yes
- ◯ no
- ◯ reasonable suspicion

Please select the elicitor from the following categories.

If "reasonable suspicion" is chosen, 3 eliciting factors can be selected.

If "Yes" is chosen, only 1 eliciting factor can be selected.

40 | 3.2) Food

3.2.10 Additional questions to food

41 | 3.2.10 What type of food was eaten? *

- ☐ non-prepacked
- ☐ pre-packed
- ☐ unknown

42 | 3.2.10.1 If non-prepacked: where was it bought? *

- ☐ catering/ take-away
- ☐ supermarket service counter, e.g. deli, bakery
- ☐ delicatessen
- ☐ bakery
- ☐ butcher
- ☐ fishmonger
- ☐ buffet
- ☐ other
- ☐ not known

43 | If pre-packed product - Was the brand known? If so please name. *

44 | If pre-packed product - Was the elicitor labelled on the packaging?*

- ◯ yes, in the list of ingredients
- ◯ yes, in a 'contains' / allergy advice box
- ◯ yes, in "the may contain...." advice box
- ◯ yes, in the list of ingredients and in a "contains"/allergy advice box
- ◯ no
- ◯ not known

45 | 3.2.11) Amount of the allergen causing the reaction? *

- ◯ < 1 teaspoon
- ◯ 1 teaspoon
- ◯ 1 tablespoon
- ◯ ½ cup
- ◯ 1 cup
- ◯ 1 plate
- ◯ don´t know

46 | 3.3 Drugs

If a vaccine is the cause, please answer the following question:

47 | Is the patient hen´s egg allergic? *

- ◯ yes
- ◯ no
- ◯ don´t know

48 | 3.3.13. If drugs– Name of the drug: used

49 | 3.4) Insect stings:

50 | 3.5) Latex:

- ◯ no
- ◯ yes
- ◯ suspicion of

51 | 3.5.1 Was the reaction caused by *

- ◯ wearing latex gloves, e.g healthcare practitioner
- ◯ being treated by people wearing latex gloves
- ◯ eating food containing latex from packaging or from food handlers wearing latex gloves
- ◯ exposure to latex via consumer products, e.g. balloons, condoms
- ◯ other: [ ]

52 | 3.6) Specific immunotherapy (SIT):

- ◯ SCIT
- ◯ SLIT
- ◯ OIT

53 | Additional Information for the specific immunotherapy

Name of the product:	
Name of the company:	
Which dose rate (amount of allergens)?	
Which allergen?	

54 | 3.6.1 Where was the SIT administered?*

- ◯ primary care
- ◯ hospital
- ◯ home
- ◯ other:

55 | 3.6.2 Where did the reaction happen? *

- ◯ in setting of administration
- ◯ following departure from administration setting

56 | 3.7) Exercise:

(Does the patient have food- dependent exercise induced anaphylaxis? yes/no if yes, further information is asked in 4.2.1.)

- ◯ yes
- ◯ no

57 | 3.8 Other eliciting factors:

[ ]

4) Exacerbating factors and diseases

58 | 4.1 Does the patient have concomitant diseases?

	previous history	current history
don´t know	☐	☐
none	☐	☐
hayfever/ allergic rhinitis	☐	☐
asthma	☐	☐
atopic Dermatitis/ eczema	☐	☐
diabetes mellitus	☐	☐
food-allergy	☐	☐
uticaria	☐	☐
cardiovascular disease	☐	☐
infection	☐	☐
malignant disease	☐	☐
mastocytosis	☐	☐
thyroid disease	☐	☐
polyposis nasi	☐	☐
other	☐	☐

59 | 4.2 Co-factors / Exacerbating factors

Have the following conditions been relevant fort the patient at the reaction?

60 | 4.2. 1 Physical Exercise: *

- ○ mild eg. walking
- ○ moderate eg. vigorous housework or gardening
- ○ vigorous eg. running, heavy manual work, competitive sport
- ○ don't know
- ○ no exercise

61 | 4.2. 2 Psychological stress: *

- ○ unlikely
- ○ likely

62 | 4.2.3 Medication: *

- ☐ none
- ☐ don´t know
- ☐ ACE-inhibitor
- ☐ ASA/ aspirin
- ☐ AT-2-antagonist
- ☐ Beta-blocker
- ☐ Ca-antagonists
- ☐ diuretics
- ☐ proton pump inhibitors
- ☐ statins
- ☐ thyroxine
- ☐ other:

63 | 4.2.4) Menstruation:*

- ◯ no
- ◯ yes
- ◯ don't know

64 | 4.2.5) Alcohol: *

- ◯ no
- ◯ yes
- ◯ don't know

65 | 4.2.6 Other cofactors:

5) Treatment

66 | 5.1. Who performed the FIRST LINE treatment?

(Definition of first line treatment: emergency, first aid until stabilisation achieved, or if that is not achieved, until advanced resuscitation is commenced.)*

- ◯ solely lay
- ◯ solely professional
- ◯ first lay followed by professional
- ◯ no treatment
- ◯ don't know

67 | 5.1.1. If lay – which person? *

- ◯ self-administered with emergency drugs
- ◯ family member with emergency drugs
- ◯ teacher with emergency drugs
- ◯ nursery teacher with emergency drugs
- ◯ other person with emergency drugs

68 | 5.1.2. if professional – which person? *

- ◯ allergy specialist
- ◯ non-allergy specialist e.g. anaesthetist
- ◯ emergency doctor
- ◯ general practitioner
- ◯ emergency healthcare professional e.g. paramedic, specialist nurse
- ◯ other

5.2. Which drugs were given for the first line treatment?

69 | 5.2.1 By lay person or self: *

- [ ] adrenalin-autoinjector
- [ ] beta2-mimetics eg. salbutamol
- [ ] antihistamine
- [ ] corticosteroids
- [ ] other:

70 | 5.2.2 By a professional: *

Please enter in the open field the dose of the administered drug

- [ ] adrenalin i.m.
- [ ] adrenalin i.v.
- [ ] adrenalin inhalative
- [ ] antihistamines i.v.
- [ ] antihistamines oral
- [ ] beta2-mimetics inhalativ
- [ ] beta2-mimetics i.v.
- [ ] beta2-mimetics oral
- [ ] dopamine
- [ ] glucagon
- [ ] corticosteroids rectal
- [ ] corticosteroids i.v.
- [ ] corticosteroids oral
- [ ] methylene blue
- [ ] O2
- [ ] theophylline i.v.
- [ ] theophylline oral
- [ ] none
- [ ] not known
- [ ] other:

71 | 5.3 Was a second dose of IM adrenaline administered? *

- ○ yes
- ○ no
- ○ don't know

72 | If so, who administered it? *

- ○ lay / self
- ○ professional

73 | How long after the first dose? *

(in minutes)

74 | 5.4 If lay person or patient itself did not use any emergency drugs – what was the situation?

	prescribed, available, but not used	prescribed, but not available,	not prescribed
adrenalin-autoinjector	◯	◯	◯
beta2-mimetics eg. salbutamol	◯	◯	◯
antihistamine	◯	◯	◯
corticosteroids	◯	◯	◯
other:	◯	◯	◯

75 | 5.5. Was a SECOND LINE treatment done during the episode?

(Definition of second line: treatment following stabilisation to prevent biphasic or secondary events, or in the event of lack of response to first line treatment.) *

If yes, please answer the following questions:

◯ yes
◯ no
◯ don't know

76 | 5.5.1 If yes, who performed the SECOND LINE treatment? *

◯ allergy Specialist
◯ non-allergy specialist e.g. anaesthetist
◯ emergency doctor
◯ general practitioner
◯ emergency healthcare professional e.g. paramedic, specialist nurse
◯ other person

77 | 5.5.2. Which drugs were administered for the second line treatment? *

Please enter in the open field the dose of the administered drug

- ☐ adrenalin i.m
- ☐ adrenalin i.v.
- ☐ adrenalin inhalativ
- ☐ antihistamines i.v.
- ☐ antihistamines oral
- ☐ beta2-mimetics inhalativ
- ☐ beta2-mimetics i.v.
- ☐ beta2-mimetics oral
- ☐ dopamine
- ☐ glucagon
- ☐ corticosteroids rektal
- ☐ corticosteroids i.v.
- ☐ corticosteroids oral
- ☐ methylene blue
- ☐ O2
- ☐ theophylline i.v
- ☐ theophylline oral
- ☐ none
- ☐ not known
- ☐ other

5.6.1 Was the patient admitted to the hospital because of the anaphylactic reaction? *

- ○ yes
- ○ no
- ○ unknown

5.6.2 Was the patient treated in intensive care because of the anaphylactic reaction? *

- ○ yes
- ○ no
- ○ unknwon

6) Prophylaxis

78 | 6.1 What prophylactic measures have been instigated following the episode?

If this is unknown put a check mark here.

- ☐ don´t know

79 | *

	already in place prior to reaction	at the emergency department/ primary care prior to discharge	in primary care during a follow-up visit	in specialist centre during a follow-up visit	nothing
counselling about avoidance of the trigger	☐	☐	☐	☐	☐
prescription of emergency drugs	☐	☐	☐	☐	☐
training in emergency management plan (inc drug training)	☐	☐	☐	☐	☐
specific Immunotherapy	☐	☐	☐	☐	☐
others	☐	☐	☐	☐	☐

80 | 6.2 What kind of emergency drugs were prescribed following recovery from the reaction?

(If this is unknown, put a check mark here.)

☐ don´t know

81 | *

	already in place prior to reaction	at the emergency department/ primary care prior to discharge	in primary care during a follow-up visit	in specialist centre during a follow-up visit	nothing
adrenaline autoinjector	☐	☐	☐	☐	☐
adrenaline inhaler	☐	☐	☐	☐	☐
antihistamines	☐	☐	☐	☐	☐
beta2-mimetics	☐	☐	☐	☐	☐
corticosteroids	☐	☐	☐	☐	☐
others>	☐	☐	☐	☐	☐

82 | Other important comments not covered in the questionnaire:

APPENDIX D: APPROVAL FORMS

1. UCT SCAH Departmental Reseach Committee Approval

UNIVERSITY OF CAPE TOWN
IYUNIVESITHI YASEKAPA · UNIVERSITEIT VAN KAAPSTAD

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

Form FHS013: New protocol application form – section A

Researchers must ensure that they use the current version of the application form on **UCT Administrative Forms** web page.

SCAH DRC 862/15

Note: Applicants for **databases**, **registries** or **repositories** should only fill out form FHS020.

30 APR 2015

1. General information

Protocol title	SEVERE ALLERGIC REACTIONS AT A TERTIARY PAEDIATRIC ALLERGY SERVICE 2013-15			
Protocol number (if applicable)				
Is this a sub-study linked to an existing/main study?	☐ Yes	☒ No	If yes, please provide the HREC ref no. of the existing/main study	

2. Investigator(s) profile

Note:
- For all postgraduate student research the **main** supervisor must be listed as PI on this form.
- For all undergraduate student research please **only** complete the FHS021 form and not this form.

2.1 UCT's principal investigator (PI)

Title, first name, surname	PROF MICHAEL LEVIN			
Department/Division	DIVISION OF ALLERGY, DEPARTMENT OF PAEDIATRICS AND CHILD HEALTH			
Phone	0216585305			
Email address	MICHAEL.LEVIN@UCT.AC.ZA			
Department /Office Internal Mail Address for Correspondence	ROOM 516, ICH BUILDING RED CROSS HOSPITAL			
Registration with HPCSA (tick ✓)	☒ Yes	☐ No	Registration #	MP0439398

Note:
- If a non-medically trained PI is overseeing research which involves medical procedures, the application must include a medical doctor registered with the HPCSA as a co-investigator.
- The research must have a UCT-based principal investigator, co-investigator or supervisor.

2.2 Co-investigator(s) Note: Staff and students involved in the research must be listed as co-investigators

Title, first name, surname	Department/Division	E-mail
DR. SA-EEDA CHIPPENDALE	REGISTRAR, DEPT OF PAEDIATRICS	SAEEDA357@YAHOO.COM

2.3 Is this protocol for degree purposes? (tick ✓)	
☐ No	☒ Yes
If yes, please specify:	
Type of degree	MMed (Paediatrics)
Student's name and e-mail	SAFEDA CHIPPENDALE - SAFEDA357@YAHOO.COM

2.4 Supervisor(s)		
Title, first name, surname	Department and University	E-mail
PROF MICHAEL LEVIN	ALLERGY, DEPT OF PAEDS, UCT	MICHAEL.LEVIN@UCT.AC.ZA

2.5 How many of the following does the PI or supervisor currently oversee? (Total number for all research projects)			
Open research studies		Sites (excluding this application)	
Co-investigators		Number of participants	

2.6 What is the PI's role in authoring this protocol? (tick ✓)	
Primary author	
Collaborator	
Supervisor	✓
None (developed by sponsors)	

2.7 Are there any publication restrictions on the research?	
☒ No	☐ Yes
If yes, please describe and justify:	

2.8 Does the protocol comply with UCT's intellectual property rights policy? (tick ✓)	
☒ Yes	☐ No
If no, please justify:	

3. Protocol profile

3.1 Has this protocol been submitted to another Human Research Ethics Committee? (tick ✓)			
☒ No		☐ Yes	
If yes, please complete:	Name of Institution		Outcome

3.2 To your knowledge, has this protocol been rejected by another HREC? (tick ✓)		
☒ No	☐ Don't know	☐ Yes
If yes, please provide the reasons:		

3.3 Is this application similar or related to research previously approved by this Committee? (e.g. a sub-study, follow-up study, earlier phase trial) (tick ✓)		
☒ No		☐ Yes
If yes, please complete:	HREC REF no.	Project title and update, i.e. ongoing, completed etc. (Please add brief description in synopsis)

3.4 Does this protocol comply with the Helsinki Declaration of 2013? (tick ✓)	
☐ No	☒ Yes
If no, please explain with full justification:	

3.5 Does the protocol provide insurance for research-related adverse events (tick ✓)		
☒ NA (e.g. minimal risk research, medical record review)	☐ No	☐ Yes
If yes, please describe:		
ABPI-compliant corporate insurance policy		
UCT's no-fault insurance policy Note: Please include the UCT No fault Insurance Clause on your Consent Form		
Other. Please specify		

4 Funding and grant information (with effect from 1 January 2013)

4.1 Funding source	(tick ✓ at least one)	Ethics Review Levy – cost including vat
UCT (e.g. departmental funding / student research)	X	R0
Grant Funding Organizations (e.g. MRC, NRF, CANSA,)		R0
Federally funded / Foundation sponsored / Private Institutions (**BELOW R1m**)		R6 099
Federally funded / Foundation sponsored / Private Institutions (**ABOVE R1m**)		R12 198
Pharmaceutical / Industry Driven company sponsors an investigator to conduct a new research project into Traditional or Complementary Medicine or Nutriceuticals		R12 198
Pharmaceutical / Industry Driven company sponsors an investigator to conduct a new research project		R24 396
Pharmaceutical / Industry Driven Additional Clinical Site / Extension study		R12 198
No funding/sponsor		→ skip to Q. 5

Note: the HREC does not have the authority to waive the ethics review levy. If a waiver is required, please contact Mr Salie Nassiep, the Research Management Accountant in the Faculty of Health Sciences (021 406 6409) email: salie.nassiep@uct.ac.za

4.2 What is the total sponsorship/funding for this protocol?	

4.3 Into what entity will the funding be paid?	

4.4 Ethics review levy (Clinical & Industry-sponsored research only)	
For invoicing purposes, please provide:	
Sponsor's name	
Contact person	
Address	
Telephone number	
Email Address	

4.5 Where applicable, has the PI negotiated an agreement with the hospital or other health or laboratory services to cover the costs of interventions/ procedures/ investigations performed solely for research purposes? (e.g. extra MRIs, CT scans, diagnostic tests, prolonged hospitalisation, use of non-research staff to collect research-related data or perform research-related procedures) **(tick ✓)**

☒ NA	☐ Yes	☐ No

If no, please explain how research costs will be recovered

Note: a summary budget must be attached in the appendices.

5. Characteristics of the protocol

5.1 Category of research Please select an appropriate category for your protocol. If the protocol falls in more than one category please designate a primary and secondary category by entering a '1' and a '2'.	
Medical intervention/ clinical trial (e.g. medicines, traditional or complementary medicines, nutriceuticals, devices or innovations)	
Behavioural/ psychosocial interventions (e.g. comparison of counselling programmes)	
Epidemiology/ observational study (e.g. survey, prevalence, case control, cohort studies)	X
Quality improvement	X
Testing new technologies	
Medical record review, audit	X
Establishment of a specimen repository, medical data base/ registry	X
Clinical laboratory studies	
Clinical laboratory studies (DNA related)	
Qualitative research (e.g. focus groups, in-depth interviewing, ethnography)	
Pilot study	
Other. Please describe:	

5.2 Category of participants	☐ Adults	☒ Minors (<18 years). Please specify age range: 0-13 years

5.3 Estimated number of participants	75 - 100

5.4 Estimated duration of the study	3 YEARS

5.5 Location(s) of the study: (Please supply name of the Research Unit / Site and/or Hospital/Institution and particular department – if applicable)
DIVISION OF ALLERGY, DEPT OF PAEDIATRICS AND CHILD HEALTH, RED CROSS CHILDREN'S HOSPITAL

5.6 Where are you recruiting from?
RED CROSS HOSPITAL'S CLINICAL SUMMARY SYSTEM AND RECORDS, AND PHARMACY DEPARTMENT

5.7 Which authority will be approached for institutional approval?	MEDICAL SUPERINTENDANT DR MINTY

Note:

If including UCT staff: Please obtain permission from Ms. Miriam Hoosain, the Executive Director of Human Resources, when including UCT staff as research participants. (This is a University-wide requirement): Use forms HR194 and HR190

If including UCT students: Please obtain permission from Dr Moonira Khan, the Executive Director, Department of Student Affairs when including students as research participants. (This is a University-wide requirement): Use form DSA 100

5.8 Will non-English speaking participants be enrolled in the study? (tick ✓)		
☐ NA	☐ No	☒ Yes

If yes, please tick ✓ what measures will be used to promote participants' and families' understanding:

Written translation of consent/ assent forms into Afrikaans	X
Written translation of consent/ assent forms into Xhosa	X
Use of trained translator(s)/ interpreter(s)	
Other. Please specify below and describe how the investigators intend to explain the study to potential participants and ensure their understanding:	

5.9 What measures will be taken to protect confidentiality (tick ✓)	
Paper-based records will be kept in a secure location and only accessible to personnel involved in the study	X
Computer-based records will only be available to personnel involved in the study through the use of access privileges and passwords	X
Personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information	
Personal identifiers will be removed from research-related information	X
Encryption	
Audio and/ or video recordings will be transcribed and then destroyed to eliminate identification of participants	
Use of pseudonyms	
Participants in focus groups will be advised that confidentiality cannot be assured	
Other. Please specify:	

6. Clinical trials

This section must be completed only if the research involves a clinical trial of drugs/ medicines, herbal, complementary or indigenous therapies; therapeutic devices; an innovative therapy or intervention; off-label use or a departure from standard treatment or care. The SA GCP Guidelines (2006) define a clinical trial as any investigation in human participants intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s) and/or to study absorption, distribution, metabolism and excretion of an investigational product(s) with the objective of ascertaining its safety and/or efficacy.		
Is this protocol a clinical trial (tick ✓):	☐ Yes	☒ No (If no, please go to Q.7)

6.1 Is the product registered with the Medicines Control Council (MCC)? (tick ✓)	☐ Yes	☐ No
If yes, please provide the registration number		
If no, is the MCC's letter for use of an unregistered medicine attached?	☐ Yes ☐ No ☐ Application submitted	
If registered, will the product be studied for an **indication** different to that approved in the SA package insert?	☐ Yes	☐ No
If registered, will the product be studied using a **dose** different to that approved in the SA package insert?	☐ Yes	☐ No
If registered, will the product be studied using a **formulation** different to that approved in the SA package insert?	☐ Yes	☐ No
If registered, will the product be studied using **a route of administration** different to that approved in the SA package insert?	☐ Yes	☐ No

Note: If yes to any of the above, MCC approval is required.

6.2 Does the study involve an FDA-monitored	☐ Yes	☐ No

6.3 Is this trial registered with the South African Clinical Trial Register?	☐ Yes	☐ No
If yes, please provide the registration number		
If no, application submitted?	☐ Yes	☐ No
If no application submitted, please justify.		

6.4 Is this trial registered with the Pan African Clinical Trials Registry? (www.pactr.org)	☐ Yes	☐ No
If yes, please provide the registration number		
If no, application submitted	☐ Yes	☐ No

6.5 Does this trial comply with the Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa, 2nd Edition, 2006? (tick ✓)	☐ Yes	☐ No
If no, please justify		

6.6 Is the PI covered by professional liability insurance? (tick ✓)	☐ Yes	☐ No
If yes, please provide Medical Protection number		

7. Statement of conflict of interest

The PI is expected to declare any existing or potential conflict of interest that may affect the scientific integrity and ethical conduct of this research. For purposes of this section, 'immediate family' means the PI's spouse or domestic partner and dependent children. **Please tick ✓ all that apply.**	
7.1 No conflict of interest declared:	
I, or any member of my immediate family, **do not** have any interest related to this research (e.g. financial interest in the sponsor of the research or intervention being tested.)	X
I, or any member of my immediate family, **do not** have a proprietary interest in the product being tested in this research (e.g. patent, trademark, copyright, licensing agreement).	X
I, or any member of my immediate family, **do not** have any relationships related to this research (e.g. board membership, consultative, executive, employment) or any entity with an ownership interest in the research other than the relationship of sponsor-investigator.	X

7.2 Conflict of interest declared:	
As Principal Investigator of this research **I am aware of a potential conflict of interest**. Please describe and provide a plan to manage the conflict of interest in the space below:	

8. Declarations and Signatures

This application will not be processed unless all the required declarations and signatures are completed according to the Committee's Standard Operating Procedures. (SOP)

8.1 Head of Department or Division

My signature confirms that:

i. The researcher(s)/student(s)/supervisor(s) have the skills, training, experience and time to undertake this research.
ii. There are adequate resources (e.g. equipment, space, support services) to perform this research.

Signature of Head		Date	2/7/15.
Print name	MCEWAN.		

Note: Where the PI is also Head of Department, confirmation must be obtained from an authorised designee. PIs may not approve their own research.

8.2 Chairperson of the Departmental Research Committee (DRC)

My signature confirms that:

i. This research has undergone peer review by a person(s) experienced in the field of study
ii. This research is well-designed and scientifically sound.
iii. Where relevant, all methodological issues have been resolved to the satisfaction of the peer reviewer(s)
iv. If conducted according to the protocol, this research is expected to yield valid and useful information

PROF H. ZAR
Chairman
Committee
School of Child & Adolescent He
Research Committee

Signature of Chairperson		Date	15/06/2015
Print name	Brenda Morrow		

Note: Where the PI is also the Chairperson of the DRC, confirmation must be obtained from an authorised designee. PIs may not approve their own research.

8.3 Principal Investigator

My signature confirms that.

i. Information in this application is true and accurate.
ii. I will begin the research only after HREC approval is obtained.
iii. I accept full responsibility for the conduct of this research and the protection of participants' rights and welfare
iv. I will conduct the research according to all ethical, regulatory and legal requirements stipulated in the HREC's Standard Operating Procedures.
v. I will provide progress reports to the HREC as requested, including a final closing report at the end of the research.
vi. I will notify the HREC in writing if any change to the research is proposed and await approval before proceeding with the proposed change except when urgently necessary to protect participants' safety.
vii. I will notify the HREC in writing immediately if any adverse event or unanticipated problem occurs during the research.
viii. I will allow an audit of my research if requested by the HREC
ix. I have the time, training, experience and resources to oversee this research.

Signature of Principal Investigator		Date	30/4/15.
Print name	Levin		

8.4 Student supervisor (if research is for a degree)

My signature confirms that:

i. The student researcher has adequate training and resources to complete the research in the allocated timeframe.
ii. The research has scholarly merit.
iii. The level of risk inherent in the study is commensurate with the student researcher's experience and the extent of oversight that I will provide.
iv. I have time, training, experience and resources to oversee this research.
v. I will meet the student on a regular basis to monitor progress and address any problems that may arise during the study.
vi. I will ensure that the research undergoes continuing review as required by the HREC, including annual progress reports, protocol amendments and a final closing report at the end of the research.
vii. If applicable, I will ensure that I report unanticipated problems or serious adverse events to the HREC.
viii. I will arrange for an alternative faculty supervisor to take responsibility for this research during periods of absence such as sabbatical or annual leave.

Signature of Supervisor		Date	30/4/15.
Print name:	Levin		

Note: The supervisor and student researcher are jointly responsible for the ethical conduct of this research from inception to dissemination of findings.

8.5 Student (if research is for a degree)

My signature confirms that:

i. Information in this application is true and accurate.
ii. I will begin the research only after HREC approval is obtained.
iii. I accept full responsibility for the conduct of this research and the protection of participants' rights and welfare.
iv. I will conduct the research according to all ethical, regulatory and legal requirements as stipulated in the HREC's Standard Operating Procedures.

Signature of Student		Date	30/04/2015
Print name	SA-EEDA CHIFENDALE		

Note: With undergraduate research where there are a group of students assigned to the research project, all students are required to sign below, confirming the points listed under Section 8.5 (above):

Name & signature of additional Student		Date	
Name & signature of additional Student		Date	
Name & signature of additional Student		Date	
Name & signature of additional Student		Date	
Name & signature of additional Student		Date	

New protocol submission checklist

Please ensure that all the applicable sections are fully completed and included in the submission. Missing information will delay the review process as the application will be returned to the PI. Sections A-C must be included. Instructions for submission of new applications are posted on the HREC website.

Note: There are two categories for submissions of studies. Please note that upon receipt of the study and based on the severity or minority of risk to participants the decision to expedite a study will be for the discretion of the Chair & Deputy Chair of the committee.

Category 1: For Pharmaceutical / Grant / Donor Sponsored Clinical Trials involving Drugs / Devices

Instruction for full committee review:

- Please submit 3 hard copies of your submission pack for full committee approval.
- Please prepare your submission pack in the order specified below.
- Please separately add 32 copies of the PI Generated Synopsis & Sponsor's Synopsis (all copies to be stapled)
- Please separately add 32 copies of the Informed Consent Forms (all copies to be stapled)

Category 2: For Expedited Studies

Protocols may be reviewed using an expedited review process if they meet the following criteria [45 CFR 46.110(b)(1)]:
a. Research poses no more than minimal risk to subjects; AND
b. Research for which each of the procedures falls within one of the following expedited review categories outlined by the Office for Human Research Protections (OHRP) [45 CFR 46.110] and the Food and Drug Administration (FDA) [21 CFR 56.110]: Eligibility for Expedited Review of US Federally-funded Research – Pointers for Researchers.

Instruction for expedited review:

- Please submit 2 hard copies of your submission pack for review.
- Please prepare your submission pack in the order specified below.
- Please motivate fully for an expedited review using the eligibility criteria above
- Please note that after receiving your submission, the HREC Chairperson or designee might determine that your study falls in more than minimal risk to subjects and does require full committee review; the HREC Office will request additional copies of the documents for circulation among Committee members before the next HREC meeting.

Note: For our scanning purposes we request that you please refrain from binding the documents. Please use binder clips, paper clips and staples. Please avoid using ring binders.

Please pack 3 copies for category 1 and 2 copies for category 2 in the order specified below: Note: **Submissions will be sent back when insufficient copies are provided.**		
For Full Committee Review (3 copies) Category 1		**For Expedited Review (2 copies) Category 2**
1. Completed Protocol Application Form		1. Completed Protocol Application Form
2. PI Generated Synopsis (see FHS014)		2. PI Generated Synopsis (see FHS014)
3. Sponsor's Synopsis (if applicable)		3. Motivation for Expedited Review
4. Research Protocol (see FHS015hlp)		4. Research Protocol (see FHS015hlp)
Appendices (as applicable)		Appendices (as applicable)
5. Consent and assent forms (English versions)		5. Consent and assent forms (English versions)
6. Sponsor's Protocol		6. NIH or other US federal grant application (if PI is primary awardee)
7. NIH or other US federal grant application (if PI is primary awardee)		7. Surveys, questionnaires, interview schedules
8. If an application has been submitted to the MCC, a copy of Section 13 (Ethical Issues) extracted from the CTF1 application form		8. Recruitment materials: advertisements, flyers, posters
9. Surveys, questionnaires, interview schedules		9. Materials for participants: diaries, patient identification cards
10. Recruitment materials: advertisements, flyers, posters		10. Letters of authorisation from institutions such as hospitals, clinics and schools
11. Materials for participants: diaries, patient identification cards		11. Budget summary
12. Letters of authorisation from institutions such as hospitals, clinics and schools		12. Other relevant documentation
13. A summary of Phase III efficacy and safety data if this is an application for an open label or extension study		
14. Budget summary		
15. MCC letter of approval, if available		
16. Investigator's brochure and package inserts		
17. In the case of clinical trials, PI's declaration, CVs and GCP certificates for PI and co-investigators		
18. Other relevant documentation		

Note: Clearly list all documents with version numbers and dates on the cover letter.

Please submit the completed form together with the supporting documents by hand delivery or registered mail to	**FHS Human Research Ethics Admin Office** **c/o Mrs Lamees Emjedi** **Address:** Human Research Ethics Committee E 52, Room 24, Old Main Building, Groote Schuur Hospital, Observatory Telephone: 27 21 406 6492 Fax: 27 21 406 6411 Electronic copy of your submission to be made available only on request from the HREC Office **Email contacts:** • Administrators: shuretta.thomas@uct.ac.za **and** nosi.tsama@uct.ac.za • Invoice queries: Senior Secretary: sumayah.ariefdien@uct.ac.za Website: http://www.health.uct.ac.za/fhs/research/humanethics/forms/

2. HREC Original Approval

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

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
Email: sumayah.ariefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

11 December 2015

HREC REF: 510/2015

Prof M Levin
Division of Allergy
Paediatrics & Child Health
Red Cross War Memorial Children's Hospital
Rondebosch

Dear Prof Levin

PROJECT TITLE: SEVERE ALLERGIC REACTIONS AT A TERTIARY PAEDIATRIC ALLERGY SERVICE 2013-2015 (Mmed candidate- Dr S Chippendale)

Thank you for your response letter dated 09 December 2015, addressing the issues raised by the Human Research Ethics Committee (HREC).

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 January 2017.

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 following student:- Dr S Chippendale is also involved in this project.

Please quote the HREC reference no in all your correspondence.

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

Yours sincerely

T Burgess

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research

Hrec/ref:510/2015

Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

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

Hrec/ref 510/2015

3. HREC Updated Approval

UNIVERSITY OF CAPE TOWN

24 MAR 2017

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938) This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30 3 2018
☐ Not approved	See attached comments		
Signature Chairperson of the HREC	ff Tburgess	Date Signed	27/03/2017

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	24/03/2017		
HREC REF Number	510/2015	Current Ethics Approval was granted until	30 JAN 2017
Protocol title	SEVERE ALLERGIC REACTIONS AT A TERTIARY PAEDIATRIC ALLERGY SERVICE 20		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?	☐ Yes ☑ No		
If yes, could you please provide the HREC Ref's for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	PROF MICHAEL LEVIN		
Department / Office Internal Mail Address	ROOM 516, ICH BUILDING, RED CROSS HOSPITAL MICHAEL.LEVIN@UCT.AC.ZA		

1.1 Does this protocol receive US Federal funding?	☐ Yes	☒ No
1.2 If the study receives US Federal Funding, does the annual report require full committee approval?	☐ Yes	☒ No
1.3 Has sponsorship of this study changed? If yes, please attach a revised summary of the budget.	☐ Yes	☒ No

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

2. List of documentation for approval

3. Protocol status (tick ✓)

☒	Open to enrolment
☐	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
☐	Main study is complete but sub-study research-related activities are ongoing
☐	Study is closed → Please submit a Study Closure Form (FHS010)

4. Enrolment

Number of participants enrolled to date	85
Number of participants enrolled, since last HREC Progress report (continuing review)	/
Additional number of participants still required	72

5. Refusals

Total number of refusals (participants invited to join the study, but refused to take part)	3

6. Cumulative summary of participants

Total number of participants who provided consent	85
Number of participants determined to be ineligible (i.e. after screening)	49
Number of participants currently active on the study	85
Number of participants completed study (without events leading to withdrawal)	85
Number of participants withdrawn at participants' request (i.e. changed their mind)	0
Number of participants withdrawn by PI due to toxicity or adverse events	0
Number of participants withdrawn by PI for other reasons (e.g. pregnancy, poor compliance)	14
Number of participants lost to follow-up. Please comment below on reasons for loss of follow-up.	17
• Missed appointments. Folders collected & called to school majority, unable to contact track (wrong contact number or [illegible]) • 6 patients transferred out to other services closer to home: George, Atlantis, [illegible]	
Number of participants no longer taking part for reasons not listed above. Please provide reasons below:	
/	

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

7. Progress of study

Please provide a brief summary of the research to date including the overall progress and the progress since the last annual report as well as any relevant comments/issues you would like to report to the HREC:
• Using Clinicom (192), pharmacy records (97) and allergy clinic referrals (6), 295 patients were identified for our study - On folder reviews 72 of these were excluded based on incorrect diagnosis, outgrown before study period, no reaction in time frame, and transfers out. • 85 patients were interviewed with their parents and recruited with informed consent to our study in the period Aug – Oct 2016 . A further 72 patients have been identified for interviews later this year • Our database for capturing results is in the development phase, with mock run of hypothetical data being utilised at present, to be finalised and ready for use soon. Delay in submission of annual report: Dr Coffeeonde (involved student) booked off for many weeks for health reasons. then had Exam exams ~~[illegible]~~

8. Protocol violations and exceptions (tick ✓ all that apply)

☒	No prior violations or exceptions have occurred since the original approval
☐	Prior violations or exceptions have been reported since the last review and have already been acknowledged or approved
☐	Unreported minor violations that have occurred since the last review, as well as significant deviations not yet reported, are attached for review

9. Amendments (tick ✓ all that apply)

✓	No prior amendments have been made since the original approval
☐	Prior amendments have been reported since the last review and have already been approved
☒ (mistake)	New protocol changes/ amendments are requested as part of this continuing review (See note below)

Note: If new protocol changes are being requested in this review, please complete an amendment form (FHS006).
Specific changes in the amended protocol and consent/assent forms must be **bolded**, *italicised* or tracked and all changes must include a rationale.

10. Adverse events

10.1 Please provide below or attach a narrative summary of serious adverse events and/ or unanticipated problems since the last progress report. Please indicate changes made to the protocol and informed consent document(s) as a result (if not already reported to the HREC). Please comment on whether causality to any study procedure or intervention could be established.
MINOR changes · Poor patient recall for years 2013 - 2015 · data, as described in the approved protocol, looking at all of Red Cross Hospital not just allergy [illegible] Proposed alteration to title: SEVERE ALLERGIC REACTIONS AT A TERTIARY PAEDIATRIC ALLERGY SERVICE 2013 - 20[illegible] to: SEVERE ALLERGIC REACTIONS AT A TERTIARY PAEDIATRIC SERVICE 2011 - 2016 [illegible] to document FHS006 [illegible] from FHS006 not necessary? Completed form included anyway]

10.2 Have participants received appropriate treatment/ follow-up/ referral when indicated (e.g. in the case of abnormal or incidental clinical findings, distress or anxiety)?		
☒ Yes	☐ No	☐ Not applicable
If yes, please describe:		
13 patients were found to meet inclusion criteria to our study, but had no follow-up arranged. We have since booked Allergy specialist review and further management		

11. Summary of Monitoring and Audit Activities (tick ✓)

11.1 Was this study monitored or audited by an external agency (e.g. MCC, FDA)?		
☐ Yes	☒ No	☐ Not applicable

11.2 Did a Data and Safety Monitoring Board publish a report?		
☐ Yes	☒ No	☐ Not applicable

11.3 If yes, please identify the agency and attach a summary of the findings.					
Agency Name		Report attached	☐ Yes	☐ No	☒ Not applicable
		DSMB report attached	☐ Yes	☐ No	☒ Not applicable

11.4 Has there been any agency, institutional or other inquiry into non-compliance in this study, or any finding of non-compliance concerning a member of the research team?	
☐ Yes	☒ No
If yes, please explain:	

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

12. Level of risk (tick ✓)

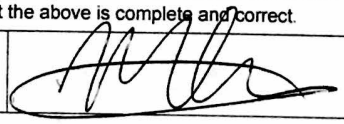
12.1 In light of your experience of this research, please indicate whether the level of risk to participants has:	
☐	Increased
☐	Decreased
☒	Shown no change
If there has been a change, please explain:	
Not Applicable	

12.2 Please provide a narrative summary of recent relevant literature that may have a bearing on the level of risk
Not Applicable

13. Statement of conflict of interest

Has there been any change in the conflict of interest status of this protocol since the original approval? (tick ✓)	
☐ Yes	☒ No
If yes, please explain and if necessary attach a revised conflict of interest statement (Section #7 in the New Protocol Application Form FHS013):	

14. Signature

My signature certifies that the above is complete and correct.			
Signature of PI		Date	22/3/17

4. HREC Topic Amendment Approval:

   Severe Allergic Reactions at a Tertiary Paediatric Allergy Service 2013 – 2015

   to

   Severe Allergic Reactions at a Tertiary Paediatric Service 2014 - 2016

UNIVERSITY OF CAPE TOWN

24 MAR 2017

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

Form FHS006: Protocol Amendment

HREC office use only (FWA00001637; IRB00001938)			
☑ Approved	☑ Type of review: Expedited	☐ Full committee	
This serves as notification that all changes and documentation described below are approved.			
Signature Chairperson of the HREC	ff Thurgess	Date	27/03/2017

Note: All major amendments must include a local **PI Synopsis** justifying the changes for the amendment. Please note that incomplete amendment submissions will not be reviewed.

Comments from the HREC to the Principal Investigator:
Note: The approval of this protocol amendment does not grant annual approval. Please complete the FHS016 / FHS017 form for annual approval at least one month before study expiration.

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	24/03/2017		
HREC REF Number	510/2015		
Protocol title	SEVERE ALLERGIC REACTIONS AT A TERTIARY PAEDIATRIC ALLERGY SERVICE OF 2014		
Protocol number (if applicable)			
Principal Investigator	PROF MICHAEL LEVIN		
Department / Office Internal Mail Address	ROOM 5TL, ICH BUILDING, RED CROSS HOSPITAL MICHAEL.LEVIN@UCT.AC.ZA		
1.1 Is this a major or a minor amendment? (see FHS006hlp) Major (tick box) Minor (tick box)		☐ Major	☒ Minor
1.2 Does this protocol receive US Federal funding?		☐ Yes	☒ No
1.3 If the amendment is a major amendment and receives US Federal Funding, does the amendment require full committee approval?		☐ Yes	☒ No

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. This page will be detached, signed and returned to the PI as notification of approval. Please add extra pages if necessary.
Title only: SEVERE ALLERGIC REACTIONS AT A TERTIARY PAEDIATRIC ALLERGY SERVICE 2013 2015 to SEVERE ALLERGIC REACTIONS AT A TERTIARY PAEDIATRIC SERVICE 2014 - 2015

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) , data based
☐	Drug/device (composition, amount, schedule, route of administration, combination with other drugs/devices, safety information)
☐	Data collection/ analysis
☐	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)
☐	Consent form and information sheet
☐	Recruitment materials (e.g. advertisements)
☐	Administrative (e.g. change in sponsor's name, change in contact information)
☐	Other. Please specify:

4.1 In your opinion, will there be any **increase** in risk, discomfort or inconvenience to participants?	☐ Yes	☒ No
If yes, please provide a detailed justification/explanation:		

4.2 What follow-up action do you propose for participants who are already enrolled in the study?	
☐	Inform current participants as soon as possible
☐	Re-consent current participants with revised consent/assent forms (append)
☒	No action required
☐	Other. Please describe:

5. Detailed description of the change(s)

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

i. Old wording (e.g. ~~strikethrough~~ text, CHANGED FROM and CHANGED TO)

ii. New wording (e.g. *italicized*, **bold**, tracked)

iii. Detailed rationale/ justification/ explanation for each change

6. 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		Date	22/3/17

5. RCWMCH Institutional Approval

Western Cape Government
Health

Dr AS Booysen
Manager: Medical Services
Email: Tony.Booysen@Westerncape.gov.za
Tel: +27 21 658 5788 fax: +27 21 658 5166

Dr S Chippendale
Red Cross War Memorial Children's Hospital

Dear Dr S Chippendale

APPROVAL OF RESEARCH

PROJECT TITLE: SEVERE ALLERGIC REACTIONS AT A PAEDIATRIC TERTIARY SERVICE 2013-2015

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,

Dr AS Booysen
Manager: Medical Services
Date: 13.01.16

APPENDIX E: SAMJ INSTRUCTIONS TO AUTHORS

ISSN 0256-9574 *printed version*
ISSN 2078-5135 *online version*

INSTRUCTIONS TO AUTHORS

Scope and policies

The *SAMJ* is a monthly, peer-reviewed, internationally indexed, general medical journal publishing leading research impacting clinical care in Africa. The Journal is not limited to articles that have 'general medical content', but is intending to capture the spectrum of medical and health sciences, grouped by relevance to the country's burden of disease. This will include research in the social sciences and economics that is relevant to the medical issues around our burden of disease.

The journal carries research articles and letters, editorials, clinical practice and other medical articles and personal opinion, South African health-related news, obituaries, general correspondence, and classified advertisements (refer to the section policies for further information).

Conflict 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.

Manuscripts 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 or RTF document 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)'.
- 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. n not u for micro, a not a for alpha, b 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

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 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) woud 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)'.

Manuscripts submission

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.

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.
3. The text complies with the stylistic and bibliographic requirements in **Author Guidelines**.
4. The manuscript is in Microsoft Word or RTF 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 (preferably TIFF or PNG). 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) and PubMed ID (PMID)/PubMed Central ID (PMCID).
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).