



## ***Protocol for the AustralAsian Severe Asthma Network***

### **Severe Asthma Web-based Database & Research Register**

#### **1. Title**

Severe Asthma Web-based Database [SAWD] & Research Register

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#### **2. Synopsis**

The Severe Asthma Network (SAN) is a multicentre clinical research network that will:

- collect and report on data from people with severe asthma,
- facilitate clinical research in this population, and
- seek to improve clinical practice for this condition.

The Network will provide a mechanism for sharing information which will help researchers and clinicians to better understand severe asthma and develop optimised clinical management strategies. The Network will collect data relating to patients who are diagnosed as Severe Refractory Asthma (SA) and who are recruited from participating sites across Australia, China, and New Zealand. All information collected from affiliate sites will be securely stored in the main data repository. Access to the database will be restricted to authorised users.

This protocol describes the Severe Asthma Web-based Database [SAWD], a multicentre cross-sectional study of the characteristics of severe asthma, in particular based around asthma phenotypes, and a prospective cohort study of the outcomes and future risks of phenotypes of severe asthma. A severe asthma Research Register will be linked to this, enabling individuals with severe asthma to join a register for contact regarding participation in future studies.

#### **3. Definition of Severe Asthma**

The World Health Organisation consultation on severe asthma has developed a uniform definition for severe asthma [Bousquet 2010].

Severe asthma is defined as: *‘Uncontrolled asthma which can result in risk of frequent severe exacerbations (or death) and/or adverse reactions to medications and/or chronic morbidity (including impaired lung function or reduced lung growth in children).’*

Severe asthma includes 3 groups, each carrying different health care messages and challenges. The first 2 groups are untreated severe asthma and difficult-to-treat severe asthma. The third group, *Severe Refractory Asthma*, which is the initial focus of the Severe Asthma Network, is defined as:

*Severe Refractory Asthma: This group includes asthma for which control is not achieved despite the highest level of recommended treatment [refractory asthma and*

*corticosteroid-resistant asthma], and asthma for which control can be maintained only with the highest level of recommended treatment.*

The defining characteristics for this group are as follows:

- 1) Confirmed Asthma diagnosis
- 2) Using Maximum therapy [Inhaled high dose of corticosteroid and 2<sup>nd</sup> controller]
- 3) Uncontrolled asthma [currently, or on reduction in maximal therapy], which constitutes any ONE or more of :
  - a) Poor symptom control
  - b) Frequent and/or very severe exacerbations
  - c) Airflow obstruction
- 4) Optimised management skills
- 5) Triggers and relevant co-morbidity have been assessed and managed

#### **4. Abbreviations**

ACA:	Asthma Control Assessment
ACQ:	Asthma Control Questionnaire
ACT:	Asthma Control Test
AHR:	Airway hyper-responsiveness
AE :	Adverse Event
AQLQ(S):	Asthma Quality of Life Questionnaire (Standardised) for 12+ years
BDR:	Bronchodilator Response
CS:	Corticosteroid
CRF:	Case Report Form
FEV <sub>1</sub> :	Forced expiratory volume in 1 second
FeNO:	Fractional exhaled nitric oxide
FVC:	Forced vital capacity
GINA:	Global Initiative for Asthma
HADS:	Hospital Anxiety and Depression Scale
HMRI:	Hunter Medical Research Institute
HRCT:	High resolution computed tomography
ICS:	Inhaled corticosteroid
ICU:	Intensive Care Unit
JHH:	John Hunter Hospital
LABA:	Long-acting beta2 agonist
LT:	Leukotriene
NAEPP:	National Asthma Education and Prevention Program
OCS:	Oral corticosteroid
RAST:	Radioallergosorbent test
REDCap:	Research Electronic Data Capture
SA:	Severe Asthma
SABA:	Short-acting beta2 agonist
SAE:	Serious Adverse Event
SAN/ASAN:	Australasian Severe Asthma Network
SAWD:	Severe Asthma Web-based Database
VAO:	Variable Airflow Obstruction
VC:	Vital Capacity
WAP:	Written asthma action plan
WHO:	World Health Organisation
WIMR:	Woolcock Institute of Medical Research
WPAI:GH:	Work Productivity and Activity Impairment Questionnaire: General Health V2.0

## 5. Introduction

**Illness Burden:** Severe Asthma is responsible for a disproportionate illness and economic burden to our community [Sullivan 2007]. There is a high prevalence of Asthma in our region and people with severe asthma require high levels of healthcare to manage their illness. While no surveys have yet been conducted using the new WHO definition, prevalence surveys in many different countries have identified that between 11% and 32% of people with asthma have severe persistent asthma, based on symptom frequency. Most of these people (approximately 80%) would be considered to have WHO-defined Severe Untreated Asthma, as they were not using any preventer treatment [Rabe 2004]. In Australia, 13% of adults with asthma who had symptoms every day/most days, had taken reliever medication in the last month, and were not using preventer medication [Marks 2007], and could therefore be considered to have Severe Untreated Asthma. A precise estimate of the prevalence of WHO-defined difficult-to-treat severe asthma and treatment resistant severe asthma is not known. However, a common criterion for these types of severe asthma is the use of high-intensity preventer therapy, and these patients would be included in the 7% of Australian adults dispensed any inhaled corticosteroid in 2009, who were dispensed the most potent formulation of ICS or ICS/LABA (e.g. Seretide 500/50 or 250/25) seven or more times a year [ACAM, Asthma in Australia 2011]. A Canadian pharmacoepidemiologic study identified a prevalence of severe asthma at 14%, with approximately 98% of these having uncontrolled severe asthma, [Firoozi 2007].

Improving data collection (through improved health surveys, and through detailed studies such as via the Severe Asthma Network) is essential to improve our knowledge about the prevalence of severe asthma as defined by the WHO, and its implications for patients and for health resource utilisation in Australia and other countries.

Severe Refractory Asthma is, by definition, persistent disease despite current optimal therapy, and consequently, there is a need for better treatment for severe asthma. People with this form of severe asthma experience a high illness burden from poorly controlled disease, frequent exacerbations leading to hospitalisation and loss of productive time at work, side-effects from pharmacotherapy [eg long term oral corticosteroids], and substantial co-morbidity. In a prospective study, it was observed that poor control in severe asthma was persistent and responsible for more than double the illness costs of controlled asthma [Sullivan 2007].

**Severe Asthma Network:** Several studies have identified that there is significant heterogeneity in the phenotypic characteristics of severe asthma and also substantial variation in the clinical management of people with severe asthma. A useful approach to these problems has been the development of clinical research networks and registers of patients with severe asthma. As noted by the World Health Organisation, ‘Severe asthma registries provide a foundation to generate a greater understanding of public health need, and to define phenotypic heterogeneity.’ [Bousquet 2010]. Severe asthma networks exist in North America and Europe. We believe a similar approach will be useful in our region and the Australasian Severe Asthma Network has been initiated to address this need.

The Severe Asthma Network in Australasia will facilitate clinical research excellence in Severe Asthma to help manage this problem more effectively and to identify

optimal clinical management strategies. The network will also work collaboratively with international networks and experts around the world to promote understanding of this condition and improve its management. The networks in North America and Europe have demonstrated the potential for collaboration in this area.

The focus of the Severe Asthma Network is on better understanding of Severe Asthma, and developing the most effective clinical management strategies for Severe Asthma. To achieve this, it will be necessary to collect and securely store information about patients who suffer from severe persistent asthma, and to collate and report this information. The network will provide opportunities to facilitate ethically approved research into severe asthma, as well as the potential to monitor the care of Severe Asthma in our region.

The Severe Asthma Network will have the following initial components:

- 1) **Characterisation of Severe Asthma:** A cross-sectional characterisation study to describe the heterogeneity of severe asthma within and between regions, focussing on asthma phenotypic characterisation (*via* ‘SAWD’).
- 2) **Severe Asthma Research Register:** A register of patients with severe asthma who are willing to be contacted for participation in research studies (*via the* ‘Research Register’).
- 3) **Severe Asthma Heterogeneity and Future Risk:** A prospective cohort study to prospectively identify factors associated with future risk of exacerbations, asthma control, and adverse effects in severe asthma, focussing on asthma phenotypic characterisation, and the association between phenotypes and future risk (*via* ‘SAWD’).
- 4) **Severe Asthma Clinical Discussion group:** a web-based discussion group.

## 6. Objective

- 1) To identify phenotypic characteristics of severe refractory asthma
- 2) To identify future risks associated with each phenotype

## 7. Study Design

- 1) Characterisation
  - a) *Design:* cross-sectional analytical study
  - b) *Participants:* adults with severe refractory asthma
  - c) *Comparison group:* adults with non-severe asthma
  - d) *Assessments:* 1-2 assessment visits
  - e) *Analysis:* Summary statistics to characterise baseline variables. Between centre comparison using multivariate statistical analysis techniques appropriate for data distribution. Cluster or related techniques using unbiased approaches for phenotype identification.
  - f) *Sample size:* each centre to recruit 20 participants with severe refractory asthma and 20 controlled non-severe asthma participants.
- 2) Future Risk
  - a) *Design:* prospective cohort study
  - b) *Participants:* severe refractory asthma
  - c) *Comparison group:* adults with non-severe asthma
  - d) *Assessments:* each 6 months for 2 years; contact via phone (optional face-to-face visits, if required)

- e) *Analysis*: Summary statistics to characterise baseline variables. Between centre comparison using multivariate statistical analysis techniques appropriate for data distribution. Multiple regression to assess relationship between selected baseline variables and key outcomes (exacerbations, loss of lung function, asthma control). Cluster or related techniques using unbiased approaches for prognostic categories of phenotypes.
- f) *Sample size*: each centre to recruit 20 participants with severe refractory asthma and 20 controlled non-severe asthma participants

## 8. Inclusion criteria

### **SEVERE REFRACTORY ASTHMA**

- 1) Able to provide informed written consent
- 2) Adults ( $\geq 18$  years of age)
- 3) Confirmed asthma diagnosis with confirmed variable airflow obstruction (VAO) at screening visit or documented within the past 10 years

♦ **Bronchodilator response (BDR) > 200mL and/or > 12%** (post-bronchodilator FEV<sub>1</sub> following administration of 400µg salbutamol, pMDI with spacer; after 10 minutes)

$$\% \text{ improvement} = \frac{\text{FEV}_1 \text{ post bronchodilator} - \text{FEV}_1 \text{ baseline}}{\text{FEV}_1 \text{ baseline}} \times 100$$

♦ **Airway hyper-responsiveness (AHR)** in response to any standard challenge agent eg methacholine, histamine, hypertonic saline, mannitol, adenosine monophosphate, exercise

♦ **Peak flow variability > 12%** when monitored over at least 1 week

$$\% \text{ variability} = \frac{(\text{max PEF} - \text{min PEF})}{\text{min PEF}} \times 100$$

♦ **FEV<sub>1</sub> variability > 12%** (between two FEV<sub>1</sub> values measured within 2 months of each other)

*If no documented evidence is available prior to screening visit, then **challenge** or test for BDR **at visit 1***

- 4) Optimised management skills  
(Inhaler technique, education, adherence, written asthma action plan)
- 5) Triggers and relevant co-morbidity have been assessed and managed
- 6) Uncontrolled asthma and treatment requirements as defined below.

**Severe Asthma (SA) definition:**

*The definition of severe asthma that will be used for this study is: **severe refractory asthma**, defined as: **asthma for which control is not achieved despite the highest level of recommended treatment [refractory asthma and corticosteroid-resistant asthma], and asthma for which control can be maintained only with the highest level of recommended treatment.***

<b>Severe Asthma Diagnosis</b>	
<b>Confirmed Asthma Diagnosis</b>	Variable airflow obstruction(VAO) with optimised asthma management skills and managed triggers and co-morbidities
+	
<b>Maximal ICS Therapy with 2<sup>nd</sup> Controller</b>	> 1000µg BDP (Beclomethasone) Equivalent ( <i>as in Table 1</i> ), AND 2 <sup>nd</sup> controller can be long acting beta agonist [eg salmeterol eformoterol], OR long acting anitmuscarinic [eg tiotropium] OR oral prednisone ≥50% of the previous year OR montelukast OR theophylline
+	
<b>Poor asthma Control</b>	1 or more of the following: <ul style="list-style-type: none"> <li>i. <i>Poor symptom control:</i> ACQ consistently &gt;1.5, ACT &lt;20 (or “not well controlled” by NAEPP/GINA guidelines)</li> <li>ii. <i>Frequent severe exacerbations:</i> 2 or more bursts of systemic CSs (&gt;3 days each) in the previous year</li> <li>iii. <i>Serious exacerbations:</i> at least one hospitalization, ICU stay or mechanical ventilation in the previous year, or</li> <li>iv. <i>Persistent airflow limitation:</i> FEV<sub>1</sub> &lt; 80% predicted (in the face of reduced FEV<sub>1</sub>/FVC) following a withhold of short and long acting bronchodilators (ie. PRE-bronchodilator).</li> </ul>

**Table 1: High Dose ICS per day (requirement for Severe Asthma)**

<b>DRUG</b>	<b>HIGH DAILY DOSE (µg/day)</b>
<b>Combination ICS/LABA</b>	
<b>Symbicort</b> Turb/Rapihalder (budesonide/eformoterol)	<b>&gt; 800</b>
<b>Seretide</b> MDI/Accuhalder (fluticasone propionate/salmeterol)	<b>&gt; 500</b>
<b>Flutiform</b> Inhaler (fluticasone propionate/eformoterol)	<b>&gt; 500</b>
<b>Breo Ellipta</b> (fluticasone furoate/vilanterol)	<b>≥ 200</b>
<b>OR Corticosteroid</b> (+2 <sup>nd</sup> controller as below)*	
<b>Qvar</b> (beclomethasone dipropionate-hfa)	<b>&gt; 400</b>
<b>Pulmicort</b> (budesonide)	<b>&gt; 800</b>
<b>Alvesco</b> (ciclesonide)	<b>&gt; 320</b>
<b>AeroBid</b> (flunisolide)	<b>&gt; 2000</b>
<b>Flixotide</b> (fluticasone propionate)	<b>&gt; 500</b>
Mometasone furoate	<b>&gt; 440</b>
<b>* PLUS SECOND CONTROLLER:</b> any of the following; <b>Oxis, Serevent, Foradile, Onbrez, Spiriva, Bretaris, Seebri, Incruse, Austyn, Neulin, Theo-Dur, Slo-bid, Prednisolone</b> ≥50% of the previous year, <b>Singulair</b>	<i>n/a</i>

High ICS doses from [GINA 2014]

**NON-SEVERE ASTHMA (control group)**

- 1) Able to provide informed written consent
- 2) Adults (≥ 18 years of age)
- 3) Confirmed Asthma diagnosis (with confirmed VAO, as above)
- 4) Using maintenance inhaled controller therapy
- 5) Controlled: ACQ ≤ 1.5 or ACT ≥ 20
- 6) Stable disease with no respiratory infection, asthma exacerbation, or change in maintenance therapy in the 4 weeks preceding screening

*Asthma subtype for severe and non-severe asthma will be determined using induced sputum and analysis stratified by sputum eosinophils (≥ or < 3%).*

**9. Exclusion Criteria**

- 1) Pregnancy
- 2) Cognitive impairment preventing completion of data collection forms
- 3) People highly dependent on medical care
- 4) People with significant life limiting co-morbidity [will prevent participation in cohort study]
- 5) Primary diagnosis of lung disease other than asthma
- 6) Current lung cancer or other blood, lymphatic or solid organ malignancy
- 7) Inability to attend study visits
- 8) Current exacerbation at baseline visit (repeat screening when stable)

10. Assessments Schedule of visits/telephone calls and study procedures

Design	Visit Number (☎ - telephone follow-up/ optional face-to-face visit)	Optional Additional Investigations	1 <sup>c</sup>	1a <sup>d</sup>	2 ☎	3 ☎	4 ☎	5 ☎
	Months (month range for follow-up, timing between follow-ups <u>should not be</u> < 4 months or > 7 months) <sup>a</sup>	During 5 years prior to visit 1 <sup>b</sup>	0	Within 2 weeks of visit 1 - optional	6 (4-7)	12 (10-13)	18 (16-19)	24 (22-25)
		Optional	Screen	Screen	2-year follow-up period <sup>L</sup>			
	Visit duration, hrs		2.5		1	1	1	1
Questions	Informed consent <sup>e,f</sup>		✓					
	Medical assessment (unfamiliar participants only): symptom history, diagnosis establishment, treatment, physical exam if desired)		✓					
	Inclusion/Exclusion criteria		✓					
	Asthma history and triggers		✓					
	Medical History/Comorbidities		✓		✓	✓	✓	✓
	Smoking History		✓					
	Asthma treatment optimisation check		✓					
	Asthma medication use & adherence		✓		✓	✓	✓	✓
	Concomitant medication use		✓		✓	✓	✓	✓
	Allergy history		✓					
	AQLQ(S)		✓		✓	✓	✓	✓
	Asthma Control (ACQ6, ACT, ACA)		✓		✓	✓	✓	✓
	HADS		✓		✓	✓	✓	✓
	WPAI:GH		✓		✓	✓	✓	✓
	Review/Issue Exacerbation Calendar <sup>k</sup>		✓		✓	✓	✓	✓
	Exacerbations		✓		✓	✓	✓	✓
Review/Issue WAP (if applicable)		✓		✓	✓	✓	✓	
AEs		✓		✓	✓	✓	✓	
Procedures <sup>g</sup>	Height and Weight		✓		(✓)	(✓)	(✓)	(✓)
	Skin prick test <sup>h</sup>		✓	(✓)				
	FeNO (OPTIONAL)		✓		(✓)	(✓)	(✓)	(✓)
	Spirometry <sup>i</sup>		✓	(✓)	(✓)	(✓)	(✓)	(✓)
	AHR/challenge(if required)		✓					
	Sputum Induction (OPTIONAL)		✓	(✓)	(✓)	(✓)	(✓)	(✓)
Optional	Blood tests <sup>j</sup> (FBE, IgE, RAST, Biomarker)		✓	(✓)	(✓)	(✓)	(✓)	(✓)
	Polysomnography	(✓) <sup>b</sup>						
	24hr pH	(✓) <sup>b</sup>						
	HRCT chest	(✓) <sup>b</sup>						
	Sinus CT	(✓) <sup>b</sup>						
	Esophagoscopy	(✓) <sup>b</sup>						
Laryngoscopy	(✓) <sup>b</sup>							

**FOOT NOTES:**

<sup>a</sup> Visit/telephone follow-up timing may be altered to accommodate unexpected events/coincide with participant clinic appointments. Timing between follow-up visits/phone calls should fall within the stated month range and should not be less than 4 months or exceed 7 months.

<sup>b</sup> OPTIONAL additional investigations (eg. polysomnography, 24hr pH, HRCT chest, Sinus CT, esophagoscopy, laryngoscopy) may have been performed in some patients as part of clinical assessment of severe asthma and these results will be recorded in the database (SAWD). However, these tests do not form an official part of the research programme. Results from these investigations will be recorded if performed within 5 years prior to Visit 1.

<sup>c</sup> If deemed suitable by investigator (and with participants consent to retrieve existing medical information/search medical records), study information (questionnaires and procedure results) may be obtained from the individual's participation in a previous study (if within previous 6 months). **NB.** This date becomes the Visit 1 date and is to be used as the basis for the timing of follow-ups.

<sup>d</sup> Visit 1a: An optional second visit may be required to collect all screening data. If AHR assessment is required at visit 1 for documentation of VAO, only PRE-brochodilator spirometry will be performed. BDR can be assessed via PRE+POST-bronchodilator spirometry at visit 1a. A sputum induction may also be performed at visit 1a if the sputum sample obtained at visit 1 was not of adequate quality. Blood tests may be performed at visit 1a, if required due to time restrictions at visit 1.

<sup>e</sup> Consent must be obtained prior to any protocol procedures. The study information sheet must inform participant of requirements for withholding or stopping medications in preparation for entry into the study.

<sup>f</sup> A separate consent will be obtained from participants who would like to be included in the Severe Asthma Register (if interested in being contacted for future research). Participants may consent to the Severe Asthma Register but not to participation in the SAWD characterisation and future-risk study.

<sup>g</sup> Procedures may be performed, as required, during the follow-up period if a face-to-face visit is deemed necessary by the investigator and the participant agrees. Sputum induction is OPTIONAL depending on site and investigators advice.

<sup>h</sup> Existing results for skin prick test may be used (if documented within previous 10 years). RAST within 3 years may be cited in place of skin prick test.

<sup>i</sup> Spirometry results may be used if performed within 1 month of (or at) visit/follow-up date

<sup>j</sup> Available blood results (IgE, FBC, RAST) may be included if measured within 3 years prior to (or at) visit 1 during the study

<sup>k</sup> Exacerbation calendar issued to participants for recording exacerbations/medication changes between/during follow-up periods (*OPTIONAL: site/investigator discretion and per participant choice*)

<sup>L</sup> Follow-up Extension - *some selected sites* may perform 6-monthly follow-up for an additional 2 years (4 years total). Data collected will be the same as that performed during the initial 2 years.

### Screening Visit (Visit 1)

*Participants will be advised prior to visit to withhold asthma medications and antihistamines (see Tables 2 and 3).*

Written informed consent will be obtained.

*If deemed suitable by investigator (and with participants consent), study information (questionnaires and procedure results) may be obtained from the individual's participation in a previous study (if within previous 6 months). **NB.** This date becomes the Visit 1 date and is to be used as the basis for the timing of follow-ups.*

The following assessments and procedures will be performed:

- Inclusion/Exclusion criteria check
- Medical assessment
- Height and weight without shoes
- Skin prick tests with exposure to a range of common aeroallergens, including grasses, house dust mite, cat, dog and moulds (*see Table 3 for antihistamine withholding times*) (or existing results if documented within previous 10 years)
- Medications: asthma and concomitant.
- Asthma optimisation plan: eligible participants with severe asthma will be considered to be on optimal treatment if their current treatment matches treatment recommended in the inclusion criteria for Severe Refractory Asthma,) and Table 1.
- Medical history/comorbidities
- Allergy history
- Juniper Asthma Quality of Life Questionnaire (AQLQ(S)) with Standardised Activities [Juniper 1999]
- Asthma Control: Asthma Control Test (ACT), Juniper Asthma Control Questionnaire – 6 item (ACQ6) [Juniper 2005], Asthma Control Assessment (ACA), GINA Asthma control
- Hospital Anxiety and Depression Scale (HADS) questionnaire
- Work Productivity and Activity Impairment Questionnaire: General Health V2.0 (WPAI:GH) [Reilly 2009]
- History of variable airflow obstruction (VAO)
- FeNO (to be performed PRIOR to spirometry) *OPTIONAL procedure according to site and investigator advice*
- PRE+POST-bronchodilator spirometry (FEV<sub>1</sub> and FVC or slow VC). *Participants will be advised to withhold their asthma medication (times outlined in Table 2)*
- Sputum induction using 4.5% hypertonic saline, to determine airway inflammatory cell type. *OPTIONAL procedure according to site and investigator advice*
- For participants who do not have a documented history of VAO within the preceding 10 years, bronchial responsiveness testing may be performed, This may be performed in conjunction with sputum induction (*for bronchial responsiveness, medication withholding times as outlined in Tables 2 and 3*). NB. BDR will be assessed via Pre+POST-bronchodilator spirometry at visit 1a.
- Blood tests: full blood count, RAST and IgE (*via pathology*), (result may be included if obtained during previous 3 years or at visit), and (*optional*) biomarker analysis.

**Table 2: Withholding times for asthma medications prior to bronchial hyper-responsiveness assessment (saline challenge) and spirometry**

6 hours	12 hours	24 hours
Airomir	Austyn	Neulin SR
Asmol	Foradile	Slo-bid
Atrovent	Neulin	Theo-Dur
Atrovent Forte	Oxis	
Bricanyl	Seretide	
Combivent	Serevent	
Epaq	Singulair	
Intal	Spiriva	
Intal Forte	Symbicort	
Respolin		
Tilade		
Ventolin		

**Table 3: Withholding times for antihistamines prior to skin prick test and bronchial hyper-responsiveness assessment (saline challenge)**

5 Days	5 Day (continued)	6 weeks
Aller G	Panquil	Hismanal
Andrumin	Periactin	
Avil	Phenergan	
Avil Retard	Polaramine	
Benadryl	Sinutab	
Claratyne	Sudagesic	
Demazin	Teldane	
Disolyn	Telfast	
Dramamin	Vallergan	
Panadol Sinus	Zadine	
	Zyrtec	

**Screening Visit (Visit 1a)**

*Within 2 weeks of visit 1, participants will be advised prior to visit to withhold asthma medications (Table 2).*

If AHR is assessed at Visit 1, the following may be performed at Visit 1a:

- Assessment of BDR via PRE + POST-bronchodilator spirometry. *Participants will be advised to withhold their asthma medication (times outlined in Table 2)*

If the sputum sample obtained at Visit 1 is not of adequate quality, the following may be performed:

- Sputum induction using 4.5% hypertonic saline, to determine airway inflammatory cell type. *OPTIONAL procedure according to site and investigator advice.*

If timing is restricted at visit 1, the following may be performed at visit 1a:

- Skin Prick Test
- Blood tests
- Other questions/procedures as directed via the investigator.

### **Optional Additional Investigations**

Optional additional investigations may be performed during the 5 years prior to screening. These tests are part of clinical assessment for severe asthma for some patients and the results will be recorded in SAWD. However, these tests are not a part of the official research programme. Additional investigations include:

- Polysomnography
- 24hr pH monitoring
- HRCT chest
- Sinus CT

### **Follow-up telephone contact (☎)/Face-to-face visits (2 – 5)**

Participants will be contacted by telephone or via face-to-face visit (if deemed necessary by the investigator and agreed to by the participant) every six months during the 2-year follow-up period. Participants will be asked about their asthma symptoms, medication use, exacerbations, new comorbidities and complete questionnaires (AQLQ, ACQ, ACT, HADS, WPAI:GH). Four telephone contacts or face-to-face visits are scheduled over the 2-year period. Procedures will be performed at face-to-face visits as advised by investigator. *Follow-up timing may be altered to accommodate unexpected events/coincide with participant clinic appointments. Timing between follow-up contact should fall within the stated month range (see assessment table) and should not be less than 4 months or exceed 7 months.*

### **Withdrawal Visit**

If a participant decides to withdraw from the study during follow-up, they may be asked to attend a withdrawal visit (if deemed necessary by investigator and subject to consent). During the visit, the participant may be asked questions about their current conditions as part of clinical information collection such as: asthma symptoms, exacerbations and the progression of treatment being received.

### **Follow-up Extension (*selected sites only*)**

*At some selected sites*, participants will be contacted by telephone or via face-to-face visit (if deemed necessary by the investigator and agreed to by the participant) every six months for an additional 2 years (ie. 4 years total). Participants will be asked about their asthma symptoms, medication use, exacerbations, new comorbidities and complete questionnaires (AQLQ, ACQ, ACT, HADS, WPAI:GH). Four additional telephone contacts or face-to-face visits are scheduled over the 3<sup>rd</sup> and 4<sup>th</sup> years. Procedures will be performed at face-to-face visits as advised by investigator. *Follow-up timing may be altered to accommodate unexpected events/coincide with participant clinic appointments. Timing between follow-up contact should fall within the stated month range (see assessment table) and should not be less than 4 months or exceed 7 months.*

## 11. Severe Asthma Web-based Database (SAWD)

### 1) Data collection method:

An electronic data collection platform, Research Electronic Data Capture (REDCap) [Harris 2009] will be the method used for this database. The authorised study personnel from each individual participating site will be responsible for data collection, editing, and also protecting the data being collected at their own site. Quality review/control will be the joint responsibility of individual sites and the central personnel [data custodian].

### 2) Data identifiability:

*Identifiable data:* data such as: name, IDs, sex, date of birth, address and phone numbers. These data will be accessed for specific purpose only e.g. identifying and or contact patient for follow up, data linkage, and only by approved personnel;

*Re-identifiable data:* Participants are assigned a unique ID code which appears on each CRF and is entered in the database. All data submitted to the database is linked to the unique ID code. The de-code list is NOT stored in the database and access is controlled by the data Custodian/site coordinators. Re-identification may be necessary to match a participant who needs to be contacted for follow up and/or continuation of the treatment, patient safety concerns or who needs specific treatment or treatment monitoring.

### 3) Data storage and security:

a) *Storage:* All data that are collected from different individual participating sites will be sent to the central repository via the webpage and securely stored in the main data repository/database at HMRI with a backup power supply installed and an off side backup system.

b) *Security:* we, the SAN have adopted the highest security measures for the database::

- The REDCap SAWD is stored and run from the HMRI data centre with all data both physically and virtually secured.
- The application security provides role based access and uses 256 bit grade encryption to protect the authentication details and all communication between clients and the servers will utilise HTTPS via SSL.
- HMRI data centre offers cold disaster recovery – if for some reason the infrastructure housing the application fails, HMRI provide an offsite fully operational replica of the system within the University of Newcastle Callaghan Campus data centre that can be turned on within moments. Backups are taken at 30 minute increments, stored to disk and tape and are housed onsite and offsite. Access to the server physically and virtually is limited to HMRI IT Services staff only.

- each web page has been encrypted which disallows any change to the web pages from either a user or a potential computer hacker
- any access to the database needs to be authorised
- any unauthorised data exporting (from the database) is blocked,

- the database is backed up on a daily basis
- patient clinical information is stored with demographics and other identifiers removed: please refer to “Data identifiability” and identifiable data (the database design) for further information. The de-code list is kept outside of the database and held by the Data Custodian;
- secure server within the HMRI’s IT section.
- An effective audit function as part of technical safeguards – the system audit log records all activities from the database which allows the administrator to track down access activities such as:
  - what activities (have been done)
  - where (which site)
  - when
  - by who (user)

7) Data access and usage:

A Data custodian will be appointed to manage requests for access to the data, ethical approvals and reports. The data custodian will report to the SAN steering committee and follow procedures detailed in the SAN manual. All requests will be required to meet ethical standards, and the process will be approved by participating ethics committee.

- a) *Access:* Any unauthorised access is prohibited to this database, the data and the Research Register, in other words, the data from the web-based database and Research Register is not for public access, and all access is strictly controlled by the SAN.
  - all access will comply with ethical standards and access processes will be approved by participating ethics committee. Access purpose will be strictly bound with clinical research and patient clinical management.
  - an access code (which is controlled by the SAN management) is required to be able to access the database and Research Register
  - ONLY authorised users (controlled by the SAN management) are able to access the database and Research Register and they may have different levels of access permission depending on their roles. All users must sign an agreement for access and data use. Usually, an authorised user from a participating site will have access permission to his/her own site ONLY however, the lead statistician and data monitors from the SAN may be granted full access permission to all sites database (from the main repository).
- b) *Usage:* The data from this database will be used for patient clinical management and approved clinical research. Any unapproved data usage will be prohibited. Utilising the data from the database will strictly comply with ethical standards.

8) Data custodian:

A data custodian will be appointed by the SAN management who will be responsible for:

- a) actively collaborating with the Governance body to ensure the data access request is properly reviewed by the Governance body (from the SAN) which means all requests will be required to meet ethical standards and approved by participating ethics committee(s)

- b) ensuring both the Governance body and individual participants are well informed for data access, access request and subsequent data usage.
- c) ensuring participants' rights are properly handled and their privacy is well protected under the Privacy Act 1988 e.g. necessary consent for accessing and or using patient information, patient information will not be released to any person or organisation without permission, patient demographic information is only used for specific and approved purpose, the patient data de-coding process is strictly controlled (permission, recording and reporting).
- d) controlling the “de-code” list as it is stored separately from patient clinical information within the Database repository in order to maintain the data in coded format.
- e) assisting approved data access by authorised users, e.g. study personnel from the SAN, the principle investigator of the SAN also potential data link process
- f) ensuring the security of patient data (from the data repository) is well maintained. That is, the security for patient data will not be compromised e.g. making sure each authorised access strictly follows the data protection guidelines from the SAN management and regularly monitoring the audit record (the ongoing record: who, when and where (IP address) to identify if there is suspicious access and preventing any security breach, and providing a summary of the audit record to the SAN management.
- g) ensuring the safety of the data repository by collaborating with IT personnel in maintaining the backup system to prevent any potential IT accident that may destroy or damage the main database.

## 12. Statistical Analysis

Summary statistics will be produced for the key variables contained within the database, such as asthma characteristics, and asthma treatment for baseline data. Relevant comparisons will be conducted between defined sub-groups and based on subject characteristic variables [eg. age, sex, treatment intensity, asthma duration, etc]. Subject to data availability, data linkage analysis may be conducted for selected outcome variables.

### Sample size

Additional sites as funding becomes available

JHH 40 x2 groups, n=80

China 9 sites x (20 severe asthma, 20 non-severe asthma)

Power 80%, alpha 5%

### Cross-sectional study

*Ho: Australia greater eosinophilic asthma than China*

Australia 40%, China 20%

- **Chinese severe asthma (n=81) and Australian severe asthma (n=81) would be required to detect the proposed difference with 80% power, alpha 5%.**

- Assuming Chinese (n=180) and Australian (n=180) with severe asthma included in the analysis, we would be able to detect the proposed difference with 98.7% power, alpha 5%.

*Ho: Severe asthma greater eosinophilic asthma than non-severe asthma*  
Severe 40%, non-severe 20%

- **Severe asthma (n=81) and non-severe asthma (n=81) would be required to detect the proposed difference with 80% power, alpha 5%.**

#### Future risk

Ho: Exacerbation rate for eosinophilic asthma greater than non-eosinophilic asthma

### **13. Publication policy**

The SAN management declares that any publication about the information that is derived from the database will be carefully assessed and approved by the management committee to ensure the information to be published is anonymous, which means only de-identified data will be used in any publication, even though all participants will be well informed about the forthcoming publication and an additional consent may be given by relevant participants if necessary.

It is expected that sufficient data accrual will have occurred by years 3 and 4 to permit data summary, overall analysis and preparation of the manuscript(s) for publication. The whole data set will be used to report on baseline characteristics, and future risk, in an anticipated 2 publications. Each site will have access to their own data and the whole data set in de-identified summary form. This will permit local comparisons to be made and may result in publication of local data. Principal investigators will be offered authorship of the main publication. PIs are able to propose analyses/author publications.

#### **Intellectual Property**

The existing agreements between Australian and Chinese governments regarding these issues will be adhered to. The statement below is taken from the Australia-China group missions website,

(<http://www.innovation.gov.au/Science/InternationalCollaboration/ACSRF/ProgramGuidelines/Pages/Section2.aspx>) and based on the *Memorandum of Understanding between the Department of Innovation, Industry, Science and Research of Australia and the Ministry of Science and Technology of the People's Republic of China on the management of the Australia-China Science and Research Fund*, signed at Shanghai on 2 August 2011.

‘Collaborative activities will protect intellectual property rights which relate to or arise from innovations developed under the joint research activities. The ascription and allocation of rights and interests regarding Intellectual Property Rights (IPRs) will occur on the basis of respective contribution and equitable interests.

The allocation of IPRs arising from the joint research activities will occur on the basis of a project management plan or collaboration arrangement developed jointly for each

project by its proponents. Contracts to protect IPRs will be signed in accordance with laws and regulations in force in Australia and China.

Intellectual property in these guidelines is defined in terms of Article 2 of the World Intellectual Property Organisation Convention signed in Stockholm on 14 July 1967. ‘

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**Appendices:**

- Appendix 1: Associated documents
- Appendix 2: Safety monitoring
- Appendix 3: Relevant Personnel/Contacts
- Appendix 4: Ethical considerations
- Appendix 5: The data collection process

## **Appendix 1: Associated Documents**

1. SAWD Study Information for Participants MASTER\*
2. SAWD Study Participant Consent Form MASTER\*
3. Register Information for Participants and Consent Form MASTER\*
4. Research Register enrolment details CRF\*
5. Asthma Control Questionnaire (6-item)
6. Asthma Quality of Life Questionnaire with Standardised Activities (Self Administered)
7. Asthma Control Test
8. Hospital Anxiety and Depression Scale
9. Work Productivity and Activity Impairment Questionnaire: General Health (V2.0)
10. SAWD Exacerbation Calendar\*
11. SAWD Exacerbation Calendar Instructions\*
12. SAWD REDCap Data Entry Guide\*

\* Document dates and version numbers not included as they are subject to amendment without variation to the clinical protocol.

## **Appendix 2**

### ***Safety monitoring***

Recorded adverse events (AEs) will be monitored and collated as required in study reports.

### ***Adverse events***

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study entry. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

If a site becomes aware of an AE associated with a product, it can be reported to the manufacturer according to their local standard practise for spontaneous AE reporting. A copy of the report should also be sent to the study coordinator.

### Appendix 3: Relevant Personnel/Contacts

#### Chief investigator:

**Professor Peter Gibson**

**T** +61 2 4042 0143 Direct

**F** +61 2 4042 0046

**M** +61 408 963 976

**E** [Peter.gibson@hnehealth.nsw.gov.au](mailto:Peter.gibson@hnehealth.nsw.gov.au)



#### Steering Committee:

*Chair:* Professor Matthew Peters

Professor Peter Gibson

Professor John Upham

Professor Paul Reynolds

Professor Philip Bardin

#### Project Manager & Data Custodian:

**Dr Erin Harvey**

**T** +61 2 4042 0099 Direct

**F** +61 2 4042 0046

**E** [erin.harvey@newcastle.edu.au](mailto:erin.harvey@newcastle.edu.au)

#### CEO, The Thoracic Society of Australia and New Zealand (TSANZ)

**T** +61 2 9222 6290 (general TSANZ)

#### Data Coordinating and Analysis Centre:

##### Woolcock Institute of Medical Research



Woolcock Institute of Medical Research

431 Glebe Point Road, Glebe NSW 2037 Australia

**T** +61 2 9114 0000 Reception

**W** [www.woolcock.org.au](http://www.woolcock.org.au)

#### Database location:

##### Hunter Medical Research Institute

Lot 1 Kookaburra Circuit,

New Lambton Heights NSW 2305 Australia

**T** +61 2 4042 0000

**W** [www.hmri.org.au/](http://www.hmri.org.au/)

## Appendix 4: Ethical Considerations

➤ *Risks/issues:*

- 1) Unnecessary consequences due to misuse / exposure of patient information (e.g. patient information is accessed by unauthorised people as a result of loss of access code from a study personnel, patient detail is mismatched). The preventative actions are:
  - a) ensure every user takes own responsibility to keep the access code safe and to report loss of access code and any unauthorised accessing as soon as detected;
  - b) all clinical information will be anonymous and the demographic (identifiable) information will be kept separately from the rest of patient information. Again, the de-code list will NOT be stored in the database and it is maintained by the data custodian,
  - c) different access permission is well controlled by the SAN management;
- 2) Access may become an issue if it is not handled properly. The preventative actions are:
  - a) unauthorised access to this database and Research Register is prohibited,
  - b) access activities are regularly monitored by the management,
  - c) authorised access will be strictly controlled by the management and,
  - d) any access request will be carefully reviewed in order to prevent any unwanted third party access (please refer to “data storage and security” for more information);
- 3) Data protection and enabling secure access is a significant issue when implementing such a system. Actions are:
  - a) there will be no special requirements for an individual external PC to access this database other than web browser access,
  - b) the data being entered into this database and Register from different sites is securely sent to the server and stored in the dedicated data repository and will be only accessed by authorised users with approved permission;
- 4) The trust between the staff and patient is key to the success of this database and Research Register. The SAN management and all participating sites will seek to build an effective relationship between staff and patient, actions are:
  - a) providing appropriate information and explanation to all participants (including our security measures)
  - b) seek participants consent for collecting their information for SAWD and/or the Research Register,
  - c) ensuring all staff/users to fulfil all security measures
  - d) fully comply with the Privacy Act,
  - e) facilitating complaints/feedback from participants and to ensure every complaint is taken seriously,
  - f) allowing participants to take part voluntarily and freely withdraw;
- 5) Holding all personal health information in a central database may be a risk in case of unauthorised access/use or damage to the central database. The preventative actions (along with those “data storage and security measures”) are such as:
  - a) The demographic information in the database will be kept separately from the rest of clinical information, and the de-code list will not be stored in the database,

- b) access to the database is strictly controlled by the SAN management even only the authorised personnel (with different levels of access permission) can access the database,
- c) unauthorised access is prohibited,
- d) any request for accessing will be carefully assessed and approved by the management in light of ethical standards and privacy guidelines also participants will be informed and even consent may be required if such access is not described in the original consent,
- e) the audit log will be monitored regularly,
- f) a backup database has been established to retrieve data in case an accident is occurred,
- g) a data custodian will be employed to implement all necessary measures in relation to data security, data protection, access and usage monitoring.

➤ *Potential benefits of the SAWD data repository*

- 1) The participant's asthma related information can be available for researchers and study personnel/clinicians within the SAN, and participants nominated medical officers to help them to better understand such asthma patients as a whole and support individual specific clinical management.;
- 2) the progress of patient's asthma condition can also be monitored and well documented in an efficient and consistent way within the database which could help researchers/clinicians to identify the optimal approach in managing severe asthma patients (pending participants agreement to provide the updated clinical information) ;
- 3) Provide a nationwide patient database that supports clinical researchers and helping to understand the magnitude of problem (for this type of asthma);
- 4) The database will ensure the patient care for SA is monitored in a consistent way and facilitate the standardised clinical process where necessary across network participating sites further, to provide an evidence of how these patients' severe asthma refractory to treatment can be managed as appropriate at the national level;
- 5) Provide a nationwide patient database which could help researchers/clinicians to recruit potential participants for suitable and approved clinical trials;
- 6) A nationwide patient database that could be an opportunity in providing additional information for parties which have potential interests, examples are such as:
  - A. provide scientific/statistical report that can facilitate decision making for government agencies (DoHA, Medicare Australia, TGA, PBS, WorkCover Australia, AIHW etc),
  - B. work with interested parties to identify ways that could effectively improve care for severe asthma patients,
  - C. support international collaborations in combating asthma in particular for severe asthma refractory to treatment

It is noted that in most of the above cases individual participants may not benefit directly from participation.

➤ *Voluntary Participation*

Participation in SAWD and joining the Research Register is voluntary. Participants are free to withdraw at any time without any reason. If a participant decides not to participate or join the Research Register this will not affect the current or future

management of his/her asthma. If at a later date he/she wishes to withdraw, he/she is free to do so.

We may ask the participant to attend a withdrawal visit (where necessary). During the visit we may ask questions about his/her current conditions as part of clinical information collection such as: asthma symptoms, exacerbations and the progression of the treatment being received subject to consent.

All information is kept strictly confidential and the participant's name will not appear in any reports. The results of the study (that a participant may be involved with) will be collated and communicated to the scientific community. They may also be compared to results from other studies.

➤ *Complaints arrangement/management*

All Participants will be given clear instructions for how they can lodge complaints if they have concerns about their rights and privacy as a participant in SAWD/member of the Research Register, or have a complaint about the manner in which their information is handled. The complaint may be given to the researcher/the study personnel, or, if an independent person is preferred, which is to

Dr Nicole Gerrand, Manager Research Ethics and Governance Unit, Hunter New England Human Research Ethics Committee, Hunter New England Local Health District, Locked Bag 1, New Lambton NSW 2305, telephone (02) 49214950, email hnehrec@hnehealth.nsw.gov.au. [OR SITE SPECIFIC ETHICS AS REQUIRED]

➤ *Personnel:*

Both the IT team and the SAN management team are responsible for designing and developing the database and Research Register and will continue to maintain these in conjunction with the support from network participating sites.

Authorised personnel from participating sites within the SAN may become authorised users with “limited” access permission i.e. only access to their own site patient database unless additional permission is given under special circumstance/purpose. All users have the responsibility for protecting the website and the information from the data repository.

➤ *Data quality, quality assurance, monitoring and safety*

There are robust quality assurance measures in place to ensure the data quality and integrity also, to ensure the data being collected is useful for clinical research and (patient) clinical management. More importantly, patient safety is not compromised when the information is used for the decision making process at the point of care. The following are the key quality assurance measures which the SAN has established:

- The data conventions and validation rules have been created for each data field (within the database)
- As part of data quality assurance for this database all personnel who are responsible for data entry will receive the SAWD REDCap Data Entry Guide and proper training prior to commencing the data entry process (this is to ensure that person is competent and complies with the rules and guidelines for data entry). Please note we recommend the data entry person are also familiar with medical terminology. An access code will be issued to the person who has passed the training (along with the approved permission for using the database) further, variety of ongoing technical support (e.g. phone or email support will also be available during the business hour when needed).

- Data collection and method: electronic data collection - the data entry process could be easily completed by those trained personnel along with the SAWD REDCap Data Entry Guide and technical support provided by the SAN. Please refer to the section of “data collection process” for more information.
  - A built-in drop down list or radio button will be used for as many data fields as possible to minimise free text field in each section/CRFs within the database, this is not only to make the job (data entry) easier but also to ensure the quality of data from the database, some examples are: radio buttons built in the field of “respiratory medications” which contains the values such as: “ongoing”, “ceased” and “dose changed”; checkboxes for the field of “test/procedure performed”.
  - A system auto check for many data fields are in place within the database to prevent entering of “dirty” data or incomplete data collection also to maintain the consistency. An error/warning message will instruct the editor how to correctly enter the required data for a data field e.g. the required date format (dd/mm/yyyy) will be displayed in the error/warning message when a date is erroneously entered; a message described which data field(s) is/are not yet completed when clicking the ‘Save record’ button) to complete the data entry for a section/CRF.
  - A dual review process (from either a participating site or wherever the data entry takes place) will be performed once the data entry is completed. The system will indicate the status of review (i.e. ‘Locked’) to ensure the data is safe to use. Any data being captured in the database is NOT ready for use until the review process is completed as part of safety measures.
  - A random audit check will also be carried out by the SAN management committee during a regular monitoring process to ensure the data entry process at individual site is monitored.
  - Once again all patient information stored in the database (for use) are anonymous. Please refer to the sections of “data storage and security” and “data access and usage” for relevant safety measures.
  - The SAN management has adopted the U (understandable) R (reproducible) U (understandable) principle when designing the database this is to ensure all data being collected for the database met this principle.
- *The types of data usage which may be applied to this database are:*
- studying patient clinical information for patient clinical management and approved clinical research
  - data analysis process for clinical research by authorised researchers from the SAN
  - data re-identifying process whenever is needed e.g. study a result to match with a specific participant so that the confirmed information (including the final research result) could be sent to the participant (on request), to recruit a participant who may be eligible for a study etc. (if they have consented to be on the Research Register). This process will be carefully conducted by authorised personnel to ensure the linkage is absolutely accurate and patient safety is not compromised. The person may be e.g. site study personnel who are directly involved with participant contact and recruitment for SAWD and/or the Research Register, or the data custodian
  - accessing by the custodian under the normal purpose (refer to the responsibilities of the custodian below)

- in the cases of any secondary use of re-identifiable data we, the research personnel from the SAN will always endeavour to protect participants' information, the demographic data in particular, this information should not be used UNLESS it is absolutely necessary. This is to ensure there is no risk of exposing patient information (to third party) and no threat to patients' wellbeing. Seeking participants' further consent and keeping participants well informed when the re-identifiable data is used for any secondary usage which could be beyond the original consent.
- any unnecessary data usage will be prohibited. All authorised users will be responsible for preventing such action especially the data custodian who will work closely with the Governance body from the SAN in ensuring the protection of participants' information and their privacy.

➤ *Patient privacy and information security*

It is clear that patient privacy and information security are essential to this database and the Research Register. Without our assurance and proper measures in place, participants' information (privacy) could be at risk and the database could not be seen as compliant with the relevant privacy Acts and the GCP principles.

The following are the key measures that relate to privacy, patient rights and information security, as the owner of the database and Research Register, the SAN management endeavour to ensure patients' rights, privacy and their information are properly handled and protected:

- Seeking consent from individual participant for collecting and accessing their information (data) within the database
- Consent will also be sought from participants for data linking with other approved research projects within the SAN database however, only subject ID will be used in the linkage data so that patients' other identifiable data will be removed to protect patients' privacy
- Strong governance arrangements will be established such as:
  - A management committee and data custodian that are responsible for overseeing and managing day-to-day operations of the database/Research Register, approve data usage requests, ensure operations comply with ethical conducts also, handling complaints
  - Ensure every user (within the SAN) complies with the guidelines/ethical standards and the security measures and have signed the *User Agreement* before being permitted to use the database/Research Register (refer to the section of "security"). The required training is compulsory for every authorised user.
  - Quality assurance and monitoring (process) is well implemented (refer to "quality assurance process and monitoring")
  - The safety for both patient and their data will not be compromised, e.g. the data can only be used once it has been reviewed
  - Protection of participants' rights and privacy will be well fulfilled, e.g. participants are well informed (providing necessary patient information and proper explanation) before taking part in SAWD, consent is required for data to be collected and stored in the database and Research Register and for data linkage. A complaint process is well established and participants will be well informed
  - Providing a point/solution at which patient complaints could be directed in the first instance, but should not be the final arbiter of such complaints

- The SAN management will seek ethical approval for the following cases:
  - collecting patient information in the database and Research Register and the collection method
  - the way of data storage, security, access and potential usages (primary and secondary)
  - information using for clinical research and patient clinical management (primary usage)
  - participant information, any advertising materials and consent form
  - the method and handling process for complaints
- Data security measures are in place (refer to the section “data storage and security” in above)
- Patient rights:
  - It is absolutely voluntary for every participant to participate in SAWD and join the Research Register
  - Participation in SAWD and/or joining the Research Register is not a condition for patients to receive treatment through the Clinic.
  - Consent needs to be given for information to be collected and for its use for an agreed/approved purpose. Additional consent plus information, and/or ethical approval is also needed for further uses if that is not covered by the original consent
  - Every participant is free to withdraw from SAWD/the Research Register at any time without any reason that needs to be approved;
  - Patient’s current or future management of asthma will not be affected as the result of withdrawal.
  - Patient privacy is well protected under the Privacy Act 1988
  - Need to be well informed and fully understand of the purpose, method, demand, risk and potential benefits of SAWD and/or the Research Register
- Patient privacy: The SAN management will ensure that all personnel from the SAN understand and respect patient privacy and fully comply with relevant laws and principles such as:
  - current commonwealth and state privacy Acts;
  - information privacy principles (Re. *the eleven Information Privacy Principles extracted from Section 14 of the Privacy Act 1988 (Cth)*)<sup>1</sup>
- Infrastructure/facility requirements:

This database and Research Register is built using REDCap through HMRI IT. An off-site back up system is also provided, along with ongoing IT support so that no further requirements are needed other than a few desk top computers which are capable of web browsing for staff personnel to carry on tasks at the SAN headquarters.

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<sup>1</sup> The Federal Privacy Act 1988 is Australia's national law for the protection of personal information when handled by Federal and ACT Government Agencies and many private sector organisations. Within the Act, eleven Information Privacy Principles have been developed to govern things such as the collection, storage, use and disclosure of personal information. The Principles also provide individuals with certain rights to access their personal information and correct any errors.

## Appendix 5: The data collection process:

- The database is accessible from any remote location by entering a username and confidential password into the highly secured webpage
- Obtain participant’ written informed consent, assign unique ID code, then collect relevant information, demographics, clinical details, medical assessments and questionnaires. (Data fields existing in the database are also reflected in the paper CRF). Enter data in relevant forms in SAWD REDCap. **Refer to the SAWD REDCap Data Entry Guide.** Complete ‘Enrolment Details and Demographics Form’ as soon as possible following enrolment of participant. (6-monthly follow-up data collection is collected and entered for participants confirmed eligible).
- An **error/warning message** from some data fields may be displayed when an error or incorrect entry occurs during data entry. This is to ensure data is entered correctly.
- Some data fields may contain sub-fields to allow additional information to be added e.g. Respiratory medication, Spirometry, Skin Allergy test etc.
- Some forms allow for **uploading of documents** (eg. Spirometry or blood test reports, evidence of VAO). Documents should be DE-IDENTIFIED prior to upload.
- At the end of each form, select the **Form status** as ‘Complete’ or ‘Incomplete’ then select ‘Save Record’ or ‘Save and Continue’. The ‘Unverified’ status may be selected by data entry personnel who require that the data be reviewed by an additional staff member.
- The data will then be instantly saved and stored in the central repository with the Form status indicated i.e. ‘Complete’ will indicate ready for monitoring/review. Once data is reviewed and queries addressed, it will be Locked (and is ready for use).
- *Editing:* each individual completed form can be amended at anytime by the author UNLESS the data is locked. Again, the “old” data will be superseded every time when the new entry is saved and a subsequent review process is required to ensure the new entry is checked. NB, the system (audit history) will record every amendment activity (four “Ws” such as: what (activity), by who, when and where).
- *Reviewing:* it is expected that each site will fulfil the responsibility of reviewing process/data quality control processes (a dual review is preferred) to ensure the data quality. A built-in auto check is also in place within the system as part of quality control process i.e. every time before a form is saved and closed down, the auto check (function) will also be activated to ensure the data entry is handled appropriately (e.g. all mandatory fields have been completed, all error messages have been resolved).
- Please note, at the end of review process, the system will display a status for review accordingly (i.e. Incomplete, Complete or Complete+locked) for each individual form so that an incoming authorised user will be able to know if this specific data is ready for review and/or use (Incomplete, Complete or Complete+locked).
- *Query resolution:* queries will be opened and closed by data monitors through the ‘Resolve Issues’ tool in REDCap. Queries will be addressed to the coordinator at the relevant site. Queries are to be answered through the system.

- *Eligibility and severity confirmation:* Data monitors will review data entered to confirm participant eligibility and severity according to the data entered.
- Data reports can be produced by those authorised, e.g.
  - how many eligible patients, how many patients were entered in a given period, how many patients are severe etc;
  - different types of summary reports: patient baseline summary, outcome trend summary, outcome trend summary for individual site and/ or all participants
  - data queries: missing data/CRFs from one specific site or entire SAWD;
  - periodic audit report

Furthermore, the SAN management committee holds the rights to carry on a random check onto the Database or the data from an individual site (e.g. during a monitoring process at a specific site) to ensure every site fully complies with the QA requirements.

**14 Protocol Version Control**

<b>Version</b>	<b>Date</b>	<b>Prepared by</b>	<b>Change Description</b>
1.0	29/10/2012	Michael Guo/ Erin Harvey	N/A
2.0	04/12/2012	Erin Harvey	Improvements to protocol under discussion and confirmation of participating centres.
3.0	10/12/2013	Michael Guo/ Erin Harvey	Table 1, appendix 1, 2, 5, 7, 8, 9 and 10 - Improvements to protocol under discussion
4.0	01/12/2015	Erin Harvey	<i>Administrative changes and clarifications</i> - update of Coordinating investigators, inclusion of steering committee members & update of contacts, removal of participating site list, clarification of timing around tests and schedule of assessments, details, use and location of new online database

**END OF PROTOCOL**