Melbourne Children's observational studies protocol template: Notes to users

This Protocol Template is designed to be generic. Some subsections and suggestions will not be appropriate for your specific study. You must tailor the protocol contents to meet the needs of your study. Only include sections pertinent to the study, omit irrelevant sections, reorder and add sections as needed.

Once you have finished your template, highlight and right hand click on the contents page and select "update entire table" - this will automatically update the page and section numbers that have change. Ensure that you have deleted all of the annotations.

LEGEND

- *Guidance and instructions are given in purple font*
- *Some additional guidance is given in blue font (e.g. registration of your study – see section 1.1*
- *Example text is given in green font – you need to customise for your study*

We strongly recommend that researchers consult the freely-available article "Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration"* and complete the STROBE checklist early in the design process in consultation with MCRI's Clinical Epidemiology and Biostatistics Unit (CEBU). The checklists are available by individual study type** (cohort, case-control, and cross-sectional studies) or as a combination checklist (see Appendix 1 of this template).

** The article discusses each checklist item and gives methodological background and published examples of transparent reporting*
https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.0040296

*** The checklists are available at https://www.strobe-statement.org/index.php?id=available-checklists*

You are reminded that a protocol should be a standalone document. The HREA must be completed in addition to the protocol. The aim of the HREA is to ensure all ethical requirements in the National Statement are satisfied, whereas a protocol should be a detailed description of every aspect of your project. Therefore the two documents meet different requirements.

Protocol template version	Observational (non-intervention) protocol template Version dated 4 June 2019 This template has been developed by Murdoch Children's Research Institute's (MCRI) Clinical Research Development Office (CRDO) and the Clinical Epidemiology & Biostatistics Unit (CEBU) for the Melbourne Children's Trials Centre (MCTC).
Why do you need a protocol?	The protocol is essential for the conduct, review, reporting, and interpretation of any research study.

Why use this template?	This template is appropriate for observational studies. In an observational study researchers observe subjects and measure variables of interest without assigning an intervention to the subjects. In those studies where there is an intervention, the intervention that each subject receives is not determined by the researcher/investigator but is instead determined by the natural treatment process. For research that involves the researcher/investigator assigning participants to an intervention, please use one of the following templates available on the CRDO website: o Clinical trial protocol template – for drug/device interventions o Clinical trial protocol template – for non-drug/non-device interventions If you are not certain if this template is appropriate for your study, or you require guidance on developing a protocol, please contact CRDO
How to use this template?	There is a brief explanation in ***purple italics*** under each heading stating the information that should be contained in that section. A paragraph of suggested or example wording is included after this for standard sections in ***green italics***. You will need to input your study-specific information under each heading and remove explanatory information. It is not necessary to include text under a major numbered heading (e.g., 1, 2) that is immediately followed by numbered subheadings, (e.g., 2.1, 2.2). That is because certain numbered headings are used only for organisational purposes. Text should be entered under all numbered subheadings. As this is a template, users are reminded that not all sections or examples may be applicable to their study. Please delete any sections that are not relevant to your study.
Having completed the Human Research Ethics Application (HREA) do I still need a protocol?	Yes, in fact you should finalise your protocol prior to completing the HREA. The HREA form is used by ethics committees to conduct standard review of all projects. While you need to refer to your protocol to answer most questions in the HREA, it does not replace the need for a detailed protocol.
Resources	The guidance in this template has been derived from a number of sources including:

	• Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2), dated 9 November 2016 Annotated with TGA comments http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4.pdf • NHMRC Guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods (EH59, November 2016) https://nhmrc.gov.au/about-us/publications/safety-monitoring-and-reporting-clinical-trials-involving-therapeutic-goods#block-views-block-file-attachments-content-block-1 • Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.0040296 at http://www.plosmedicine.org/ • ClinicalTrials.gov Protocol Registration Data Element Definitions for Interventional and Observational Studies available from https://prsinfo.clinicaltrials.gov/definitions.html • ClinicalTrials.gov Observational Study Protocol Registration Template available from https://prsinfo.clinicaltrials.gov/Observational_Study_Protocol_Registration_Template.pdf • ANZCTR Data field definitions V20 (June 2018) available from http://www.anzctr.org.au/docs/ANZCTR%20Data%20field%20explanation.pdf Internal documents • RCH procedure " Epic: Appropriate Use for Research (RCH Procedure)", available on the RCH intranet • RCH procedure "Informed Consent in Research", available on the RCH Research Ethics Governance website. • CRDO – various standard operating procedures, guidance, forms and templates - refer to the CRDO internet site at https://www.mcri.edu.au/research/training-and-resources/clinical-research-development-office-crdo/resources-quantitative

PROTOCOL

<STUDY IDENTIFIER>

A short reference for the study, such as a protocol number or acronym, is optional. However it can be more practical than the full study title. The specified identifiers and titles must be consistent across all documents related to study.

[Insert full study title]

The full title should be kept brief but mention the study design and the population.

Protocol Number (if applicable): *[insert protocol number]*

Protocol Version # and date: *[insert version # and date here & in footer]*

Document history:

Table each change made to the protocol, with the most recent at the top of the table. The protocol may be updated due to queries raised by an ethics committee, or changes may be required during the life of the project.

A version date must always be present on every page (header or footer) of the draft and final protocols. The version date of an approved protocol should reflect the date of the last changes prior to an ethics submission.

Version Number and Date	Summary of changes
	Include here a simple reason for why the change was made, for example "updated post HREC review"

Statement of Compliance

This study will be conducted in compliance with all stipulation of this protocol, the conditions of the ethics committee approval, the NHMRC National Statement on Ethical Conduct in Human Research (2007 and all updates), applicable national and local regulations and in the spirit of the Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2), dated 9 November 2016 annotated with TGA comments.

Or for research to be conducted internationally (delete if not appropriate): <This study will be conducted in compliance with all stipulations of this protocol, the conditions of the ethics committee approval, ethical principles that have their origin in the Declaration of Helsinki, all applicable national and local regulations and in the spirit of the standards of Good Clinical Practice (as defined by the International Conference on Harmonisation),.>

TABLE OF CONTENTS

PROTOCOL SYNOPSIS

The protocol synopsis provides a brief outline of the key elements of the study. It allows a quick reference to the project details (as an abstract allows for a manuscript). The protocol synopsis should generally not exceed two pages in length) and is ideally presented as a table such as the following.

TITLE	*Insert full title*
STUDY DESCRIPTION	*A brief overview of the study design. This should be only a few sentences in length. A detailed schematic describing all visits and assessments should be included in the main protocol.*
OBJECTIVES	*Insert objectives copied from the body of the protocol. Include the primary objective and all secondary objectives.* • *<Insert primary objective>* • *<Insert secondary objectives>*
OUTCOMES AND OUTCOME MEASURES	*Specify specific outcomes and outcome measures (i.e. how the outcomes will be measured) for the objectives listed above* *N.B. Outcomes are also known by the term "Endpoint"* • *<Insert Outcome and outcome measure* *e.g. > IQ at 4 years of age as assessed by FSIQ*
EXPOSURES	*Specify specific exposures and exposure measures (i.e. how the exposures will be measured) for the objectives listed above* • *<Insert Exposure and exposure measure* *e.g. > Number of hours of screen time per day reported by the primary care giver*
POTENTIAL CONFOUNDING FACTORS	*Specify here any potential factors that may be confounders of any of the associations that will be investigated as specified in the objectives – this is critical to observational studies.* *Specify specific confounders and confounder measures (i.e. how the confounders will be measured) for the objectives listed above* • *<Insert Confounder and confounder measure* *e.g. > Highest level of education level achieved by the primary care giver (self-reported)*
STUDY POPULATION	*Population information, including any restrictions on gender, age, demographic group, general health status, geographic location. This should also include the planned sample size - total number of participants for the project and the approximate number per group if more than one group.*
DESCRIPTION OF SITES ENROLLING PARTICIPANTS	*Provide a brief description of participating sites (e.g. planned countries, planned number of sites).*
STUDY DURATION	*Estimated time (in months) from when the study opens to enrolment until completion of data analyses.*
PARTICIPANT DURATION	*Time (e.g., in days/months/years) it will take for each individual*

	participant to complete all participant visits.

GLOSSARY OF ABBREVIATIONS

All abbreviations used in the protocol, including appendices, should be listed with an explanation of each abbreviation. Accepted international medical abbreviations should be used. All abbreviations should be spelled out when first used in the text, followed by the abbreviation in parentheses. Common units of measure like mg or mL don't need to be defined in the text or this list.

*The following list is an **example only**. Add and delete abbreviations as appropriate for your protocol.*

ABBREVIATION	*TERM*
AE	*Adverse Event*
ANOVA	*Analysis of Variance*
BRF	*Biobank Registration Form (MCRI)*
CRF / eCRF	*Case Report Form / electronic Case Report Form*
GCP	*Good Clinical Practice*
GLP	*Good Laboratory Practices*
HREA	*Human Research Ethics Application*
HREC	*Human Research Ethics Committee*
ICH	*International Conference on Harmonisation*
MCBC	*Melbourne Children's Bioresource Centre*
MCRI	*Murdoch Children's Research Institute*
MedDRA	*Medical Dictionary for Regulatory Activities*
NHMRC	*National Health and Medical Research Council*
PI / CPI	*Principal Investigator / Coordinating Principal Investigator*
QA	*Quality Assurance*
QC	*Quality Control*
RGO	*Research Governance Office*
RCH	*Royal Children's Hospital (Melbourne)*
SAE	*Serious Adverse Event*
SAP	*Statistical Analysis Plan*
SoA	*Schedule of Assessments*
SOP	*Standard Operating Procedure*

This template uses the following terminology with regards to the term 'investigator':

- ***Single site studies***
  - ***Study Principal Investigator***
- ***Multi-site studies***
  - ***Coordinating Principal Investigator** – is used to describe the **overall study-level** Investigator*
  - ***Site Principal Investigator** (PI) – is used to describe the site-level Investigator*

INVESTIGATOR AGREEMENT

The investigator / institution should conduct the study in compliance with the protocol approved by the HREC/IRB/IEC. The Study Principal Investigator (single site study) OR Coordinating Principal Investigator (multi-site study) and Site Principal Investigator should sign the protocol (or an alternative contract) to confirm agreement.

I have read the protocol entitled "<***Enter study title***>".

By signing this protocol, I agree to conduct the study, after approval by a Human Research Ethics Committee or Institutional Review Board (as appropriate), in accordance with the protocol and:

- the principles of the Declaration of Helsinki
- the NHMRC National Statement on Ethical Conduct in Human Research (2007 and all updates)
- the Australian Codefor the Responsible Conduct of Research (NHMRC, 2007 and all updates)
- and in the spirit of the good clinical practice guidelines adopted by the TGA [Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2), dated 9 November 2016 annotated with TGA comments].

Changes to the protocol will only be implemented after written approval is received from the Human Research Ethics Committee or Institutional Review Board (as appropriate), with the exception of medical emergencies.

I will ensure that study staff fully understand and follow the protocol and evidence of their training is documented on the study training log.

Name	Role	Signature and date

1. ADMINISTRATIVE INFORMATION

1.1. Registration of observational research

In 2004 the International Committee of Medical Journals Editors (ICMJE), including editors of the Medical Journal of Australia, Lancet, New England Journal of Medicine and others) declared that they would not consider a trial for publication without evidence that it had been registered in a publicly accessible trials registry prior to enrolment of the first participant. ***Some journals, including the Lancet and BMJ, encourage prospective registration of observational studies in order to consider manuscripts of observational studies for publication. BMJ also supports the posting of results in publically accessible registries.*** *It is for this reason that MCTC recommends prospective registration of observational studies in a primary register of the WHO international clinical trials registry platform (ICTRP) or www.clinical.trials.gov Review CRDO's guidance on the requirements for and process of clinical trial registration ("Clinical Trial Registration of Investigator-Initiated Trials"), available on the CRDO website.*

On www.clinical.trials.gov you will find published protocols for different types of observational studies which you should find useful. Some examples of good observational study protocols are:

- *Mundy, L.K., Simmons, J.G., Allen, N.B., Viner, R.M., Bayer, J.K., Olds, T., Williams, J., Olsson, C., Romaniuk, H., Mensah, F. and Sawyer, S.M., 2013. Study protocol: the childhood to adolescence transition study (CATS). BMC pediatrics, 13(1), p.160.*
- *Zendarski N, Sciberras E, Mensah F, Hiscock H. A longitudinal study of risk and protective factors associated with successful transition to secondary school in youth with ADHD: prospective cohort study protocol. BMC pediatrics. 2016 Dec;16(1):20.*
- *Wake, M., Clifford, S., York, E., Mensah, F., Gold, L.C., Burgner, D. and Davies, S., 2014. Introducing growing up in Australia's child health checkpoint: a physical and biomarkers module for the longitudinal study of Australian children. Family matters, 95, pp.15-23.*
- *Lycett, K., Mensah, F.K., Hiscock, H. and Sciberras, E., 2014. A prospective study of sleep problems in children with ADHD. Sleep Medicine, 15(11), pp.1354-1361.*
- *Nardia Zendarski and Kate Lycett both included their published protocols in their PhD with publication which is highly recommended for PhD students who are conducting de-novo research studies.*

Enter the registry name and identifier – or enter name of intended registry e.g. ClinicalTrials.gov or http://www.anzctr.org.au/

Instructions for registering with ClinicalTrials.gov:

Specify the expected duration from first participant enrolled to final collection of data for the primary outcome(s). This information is required to generate the Anticipated Primary Completion Date.

Specify the expected duration from first participant enrolled to final collection of data for the primary and secondary outcomes. This information is required to generate the Anticipated Study Completion Date.

Instructions for registering with ANZCTR (applicable for patient registries):

Specify the anticipated time period over which each participant is to be followed. Provide a number and a unit of time (weeks, months, years).

1.2. Sponsor

Provide name and contact information for the study sponsor. The sponsor is the company or institution that takes responsibility for the initiation, management and financing (or arranging the financing) of the study. The factors which determine sponsorship include: the nature of the funding, the employer of the principal investigator and the duty of care to participants. Include, if applicable, the role of the sponsor in study design; collection, management, analysis, and interpretation of data; writing of the report and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities.

For MCRI investigator-initiated observational research, the Sponsor will generally be listed as MCRI. Taking on the role of Sponsor means taking on the liability for harm caused by the study design, the liability for not working to Australian regulation. In addition there is also the reputational risk associated with the potential discovery of poor quality or unsafe research audit or regulatory inspection. To mitigate these risks, the Sponsor must ensure that the study is conducted in accordance with the National Statement, the Australian Code, GCP and relevant regulatory requirements.

Where MCRI is the Sponsor, MCRI delegates some Sponsor responsibilities to the Investigator leading the study. In addition, in multi-site studies, the Coordinating Principal Investigator should ensure that required agreements (i.e. the Material Transfer Agreement at a minimum) are in place for participating sites and that each Site Principal Investigator understands their responsibilities in the conduct of the research.

***Example text where MCRI is the Sponsor**:*
"On behalf of the Sponsor, MCRI, the Coordinating Principal Investigator (Coordinating PI) (multi-site study) / Study Principal Investigator (Study PI) (single site study) will undertake and/or oversee those Sponsor responsibilities delegated by the Sponsor.
(include for multi-site studies) The Coordinating PI will also ensure that each Investigator at the participating sites conducts the study in compliance with the protocol, relevant approvals and regulatory requirements.

Study Sponsor	
Contact name	*If MCRI is the sponsor, insert Coordinating Principal Investigator name*
Address	
Sponsor *(where applicable)*	

1.3. Expected duration of study

Specify the expected duration of the recruitment period. For studies that are retrospective, provide the date ranges of the records. For example, "Cases will be included if the initial surgery was between 01 Jan 2007 and 31 Dec 2017. Follow-up information through to 01 Jun 2017 will be included, as well as history preceding the initial surgery."

Specify the length of time that an individual participant enrolled in the study will participate. Note that: enrolled" refers to those participants where the participant (or their legally authorised representative) has provided informed consent and has then been determined to be eligible for the study. It does not include participants who are pre-screened or screened* for the purpose of determining eligibility for a study, but are found to be ineligible.*

** Pre-screening refers to any assessment undertaken prior to informed consent (i.e. review of existing information - it does not involve any study-specific procedures). Screening refers to assessments undertaken, following consent, to determine final eligibility.*

1.4. Contributorship

Names, affiliations, and roles of other organisations (if any) providing support. Support may include funding, design, implementation, data analysis or reporting.

Name	Summary of contribution

1.5. Stakeholder involvement

A stakeholder can be understood as a person, group or organisation who has an interest (something to gain or lose) in the outcome of a planning process, program or project. Stakeholders can be internal or external and can include, for example, supporting departments on campus, other health organisations (primary, secondary, tertiary), government (local, state, federal), professional bodies, educational organisations, community organisations and, of course, children and adolescents, parents and families. Some may be consumers, in particular children and adolescents, parents and families.

The NHMRC increasingly expects that researchers will have involved stakeholders and consumers in the development of clinical study protocols. Explain here whether/how the protocol authors have consulted with stakeholders and how they have engaged consumers.

2. INTRODUCTION AND BACKGROUND

2.1. Background and rationale

The following section should give the reader a clear idea of the following:

- *What the research question is;*
- *An understanding that the research needed is original and relevant;*
- *How the proposed study will help fill the gap in the literature.*

Include the following:

- *Introduce the topic or medical/health indication*
- *Provide details of previous studies in children or adolescents(if available)*
- *Explain how the study will substantially add to science, change practice, save money, save lives and/or improve quality of life;*
- *Explain why the research needs to be conducted in the selected population.*
- *Provide a brief and focused review of findings of previous related studies, highlighting inadequacies in the body of evidence.*

2.2. Study aim (s)

This section states the overall aim of the study. In any study, you aim to do something. For example, you aim to verify, to investigate, to measure, to determine, to compare or to calculate.

- *Use the verb form starting with 'to' (e.g. 'to investigate').*
- *Avoid the noun form which often ends in '-ion' (e.g. 'investigation').*

Example text: *The aim of this study is to compare neurodevelopmental outcomes at age 2 years, between infants born very preterm and those born at term.*

3 STUDY OBJECTIVES AND OUTCOMES

*An **objective** is the purpose for performing the study (i.e. the scientific questions to be answered). Express each objective as a statement of purpose (e.g., to assess, to determine, to compare, to evaluate).*

*An **outcome** is a specific measurement or observation used to measure the objective. Outcomes should be prioritised and should correspond to the study objectives and hypotheses being tested. Give succinct, but precise definitions of the outcomes used to address the study's primary objective and secondary objectives (e.g., specific laboratory tests, clinical assessments of the condition, assessments of psychological characteristics, participant-reported outcomes, behaviours or health outcomes). Include the study visits or time points at which data will be recorded or samples will be obtained. Describe how outcomes(s) will be adjudicated, if applicable.*

*As well as the **outcome**, the **exposure** and any **potential confounding factors** should be specified if the objective is to investigate the association between an exposure and an outcome. While a number of observational studies may have the objective to describe the nature of an outcome alone, the majority will be intended to investigate exposure outcome associations. Exposures and potential confounding factors should be prioritised to correspond to the study objectives and hypotheses being tested and described succinctly but precisely (as for outcomes).*

Notes:

- *A table can be used to present the objectives along with their associated outcome (exposure and potential confounders) and outcome (exposure and potential confounders) measurement (see end of section for suggested format).*

3.1 Objectives

The objectives must be very precise statements about the overall aim that is to be achieved.

Types of objectives in observational studies can include:

- *Observation of progression/development of a condition where care is provided according to current care policy and practice.* On this Campus, observational studies will often have specific objectives to investigate health service use and other supports as well as health care costs.*
- *Screening (the study is designed to assess or examine persons/groups in a systematic way to identify specific markers or characteristics*
- *Psychosocial (the study is designed to observe the psychosocial impact of natural events).*

** Be careful using the terms natural history and natural conditions - many of the families in our observational studies will be following usual care practice, e.g. in cohorts of children with ADHD many will receive regular medication and/or other behavioural supports. Therefore it is preferable to word as given here.*

*It is common for a study to have between 2 and 4 specific objectives that are components of the overarching study aim. **There should only be one primary objective -** ensure that this supports the statistical outcomes, and that it is specific and objective.*

3.1.1 Primary objective

The primary objective is the main question to be addressed within the study. This objective generally drives the study's design and statistical planning (e.g., calculation of the sample size to provide the appropriate power for statistical testing). In observational studies, exposure is a major consideration in

determining objectives which seek to examine the association between the outcome and a risk/protective factor (exposure): clear specification and estimates of the distribution of the exposure for the population are required, as well as specification of which exposure levels will be compared.

Define the primary objective in terms of the population, exposure and outcome that will be measured in a single clear and concise statement.

Example text: *""The primary objective of this study is to measure the health status (with a particular focus on mental health measures) and the burden of sub-optimal health in a cohort of nationally-representative primary school aged children at the end of Grade 1; and investigate whether the burden of sub-optimal health is associated with the daily length of screen time experienced by the children."*

3.1.2 Secondary objectives

A study may or may not have secondary objectives. Secondary objectives consider outcomes of interest that may or may not be related to the primary objective. Secondary objectives may or may not be hypothesis-driven and may include more general non-experimental objectives (e.g. to develop a registry, to collect natural history data, to describe parents experiences).

It is often advised that the number of objectives should be kept low as too many objectives may make the study logistically difficult to perform – and also that the sample size calculation is based on the primary objective and it may not be possible to satisfy other objectives with this sample size. However, in observational studies, there are other considerations:

- *Study cohorts are sometimes used for studying a large number of objectives – if this is the case, build in scope for this. You may need to think about the cost effectiveness of large scale multi-purpose/omnibus cohorts compared with the ability to focus on very specific questions in specialist cohorts.*
- *A range of estimates of the power that the study would provide for different types of questions may be appropriate to support the power calculation for the primary objective. These calculations can help illustrate the scope of the study for future analyses (e.g. for large studies with multiple waves of follow up). Note that the sample size calculation should be discussed further in section 10.1.*

We strongly advise researchers to consult a biostatistician for advice on the design of the study – this should be done during the design stage to ensure that flexibility to address the types of analyses that may be envisioned can be built into the protocol.–

Example text*: "The secondary objectives of this study are:*

1. *To provide national data on the distribution of mental health, other health problems, and risk factors for future disease in Australian primary school children".*
2. *<insert>"*

3.1.3 Exploratory objectives

A study may or may not have exploratory objectives. Their purpose is to further explain or support findings of primary and secondary analyses and to suggest further hypotheses for later research.

Exploratory objectives may be hypothesis generating but equally often secondary analyses which are fully powered and will result in publication standard evidence – these may never have been imagined

at the design stage and are often opportunistic much later in the sequence e.g. the purpose of the LifeCourse repository is to enable this type of thinking.

3.2 Outcomes

*The **outcomes** (also known as endpoints) are the variables which are used to measure the objectives. This section of the protocol must clearly state which variables are to be measured are, at which study visits the outcomes will be obtained, the specific laboratory tests or other analytical measures to be used and the timeframe. Outcome measures should correspond to the study objectives and hypotheses being tested. A brief explanation (i.e. a justification) should be provided to explain why you have selected the outcomes listed in the protocol.*

For observational studies, we would also need analogous sections for exposures and for potential confounders – this is where the studies differ especially from intervention studies and are in many ways more difficult as you have to measure rather than administer the 'exposure' and don't have the benefit of random allocation so the potential for confounding is much more paramount.

*It is critical to be able to demonstrate both the validity and feasibility of administering these intended measures of **exposures** and **outcomes** and demonstrate that a comprehensive set of potential confounding factors can be identified and measured (supported by relevant literature).*

Primary outcome *There should be just one primary outcome that will provide a clinically relevant, valid, and reliable measure of the primary objective. The primary outcome is the basis for concluding whether or not the study has met its primary objective; the primary outcome measure should therefore be based on the primary objective of the study. It should reflect the specific key measurement or observation used to describe patterns of diseases or traits or associations with exposures, risk factors or treatment (e.g., systolic blood pressure, a specified validated questionnaire or clinical assessment scale).*

Secondary outcomes *The secondary outcomes are measurements that are related to the secondary objectives. Follow the same guidelines provided under primary outcomes to describe each of the secondary outcomes. It is recommended that the list of secondary outcomes be short, because the chance of demonstrating an association between and exposure and any secondary endpoint becomes increasingly large as the number of outcomes increases. When selecting outcomes, it is important to ensure that the outcomes are obtainable.*

Exploratory outcomes

<insert info here if applicable>

All outcomes should be clearly specified and include:

- *Their respective outcome measures (i.e. the method for measuring an outcome e.g., Likert scale from 0-10 measuring X, a specified validated questionnaire or systolic blood pressure level)*
- *A description of the metric used to characterise the measure (e.g., change from baseline, final value, time to event, maximum)*
- *The method of aggregation (e.g., medical, proportion) and the timeframe (i.e., total duration of the time period, specific time points) over which the measurement will be assessed.*

Examples of outcomes are (NB list not exhaustive):

- *Objective assessments (e.g. mortality rates);*
- *Subjective clinical assessments (e.g. validated rating scales);*

- *Measurements of various physiological functions (e.g. blood*
- *pressure);*

Additional notes:

- *A surrogate outcome can also be used. A surrogate outcome does not measure a clinical effect, but rather is something that can be measured that is thought to relate to the clinical effect (e.g. bone density is related to a reduced fracture rate). Provide justification for any surrogate endpoints.*
- *If a composite endpoint will be used explain its composite parts.*

The objectives and outcomes can be entered in either of the formats shown below (text versus tabulated):

Primary objective and outcome
<insert>

Second objectives and outcomes
<insert>

Table listing objectives, exposure, outcomes and outcome measures, and confounders

OBJECTIVE
Primary objective *Association between adhering to screen time guidelines and children's BMI*
Exposure: *Screen time*
Outcome & outcome measure *BMI - calculated according to directly measured height and weight*
Confounding factors: *Diet, exercise, mental health*
Secondary objective *Association between adhering to screen time guidelines and children's IQ*
Outcome & outcome measure IQ at 4 years of age as assessed by FSIQ

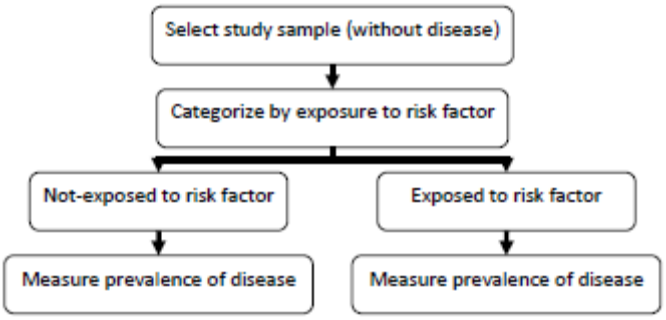
4 STUDY DESIGN

4.1Study design schema

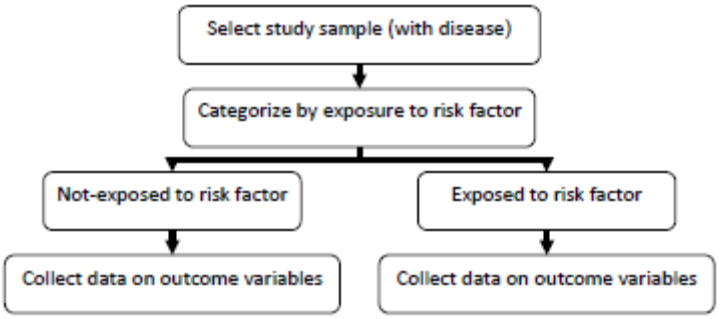
To increase readability of the protocol, include a flow chart showing the study design. Examples are shown below. The schema are quite simplified and reflect quite traditional design compared to extensive array of studies now undertaken so you should regard these examples only as illustrative - each proposed design should be considered on a case by case basis with advice from CEBU.

Regarding the prospective and retrospective cohort studies, note that use of the terms prospective and retrospective are not recommended as these terms are poorly defined. Where these terms are used, the protocol and flow chart should describe fully how and when the data is to be collected.

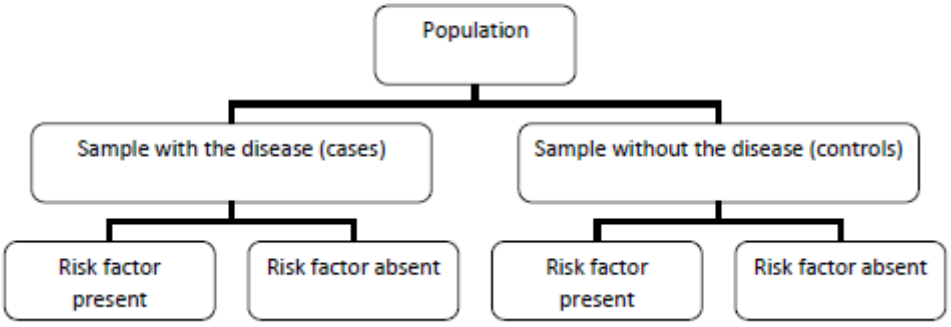
Prospective cohort Study:



Retrospective cohort Study:



Case-controlled Study:



Cross-sectional Study:

Population

Sample

Disease present and **Risk factor present**	**Disease absent and** **Risk factor present**
Disease present and **Risk factor absent**	**Disease present and** **Risk factor absent**

4.2Overall design

The scientific integrity of the study and the credibility of the data depend substantially on the study design. The study design should be capable of meeting the study objectives.

The description of the study design should be consistent with the Protocol Synopsis.

Provide a thorough description of ALL study procedures and assessments in a logical and sequential form.]

1. *Specify the type of study (e.g., cohort study, case-control study, cross-sectional study).*
2. *Specify the time perspective, that is the temporal relationship of observation period to time of participant enrolment, e.g. retrospective, prospective [includes cross-sectional (observations or measurements made at a single point in time, usually at subject enrolment) and longitudinal (observations or measurement are evaluated over a long period of time, typically months or years).*
3. *Specify the basic design elements including the total number of participants to be enrolled (target number) or the actual number of participants that are enrolled in the clinical study, the population to be studies (e.g. Adults aged 18-35) and any risk factors present.*
4. *Describe the setting (indicate if single site or multi-site, and list the participating countries if the study will be conducted in countries other than Australia).*
5. *Specify how the design will achieve the aims and objectives.*
6. *State what data will be collected (e.g. blood tests, MRIs, genetic testing, videos, photos, questionnaires etc.). For each item, specify how the data will be identified (previously known as identifiable, re-identifiable [code assigned] or non-identifiable [anonymised]).*
7. *Describe how you will collect, handle and store all types of data collected.*
8. *Specify the study duration (i.e. duration for each component of the study including study visits, how long recruitment is open for and how long analysis will take etc).*
9. *Specify the duration of participation for participants (mention any distinction between the intervention period and follow-up period, if applicable e.g. 'a 6 week intervention period with a two year follow up').*
10. *Specify whether the study requires any home visits, and what the home visit policy and procedures are.*
11. *Ensure that you have included within your study outline all information on all required contingency plans.*
12. *State whether the protocol will be used towards a student project, and if so, state what course and degree the student will undertake.*
13. *Provide a flowchart or table specifying visits and other relevant details.*
14. *List whether any sub-studies will be undertaken as part of the study.*

4.3Study population

The following sub-sections should include a description of the study population and methods of participant recruitment.

4.3.1 Eligibility criteria

Eligibility criteria define and limit the participants who can be enrolled in a study (e.g. those criteria that every potential participant must satisfy to qualify for study entry). They also define the population to which the study results can be extrapolated.

Even if the study is retrospective, there is a need to define the study population using including and exclusion criteria for each participant group. For example, the control population may have different selection criteria compared with the population with the disease of condition of interest.

Reasons for imposing eligibility criteria can include scientific rationales, safety concerns, regulatory issues and practical considerations.

Under the sub-headings in this section, list all the criteria that will be applied to determine a person's eligibility or ineligibility for the study. Use the following guidelines when developing a participant eligibility criteria (Inclusion Criteria and Exclusion Criteria):

- *The eligibility criteria should be clearly defined, straight-forward and unambiguous.*
- *The eligibility criteria should provide a definition of participant characteristics required for study enrolment.*
- *The same criterion should not be listed as both an inclusion and exclusion criterion (e.g. do not state age < 18 years old as an inclusion criterion and age ≥ 18 years old as an exclusion criterion).*
- *Identify any specific laboratory tests or clinical characteristics that will be used as criteria for enrolment or exclusion.*
- *If you have more than one study population, define the common inclusion and exclusion criteria followed by the specific inclusion and exclusion criteria for each sub-population.*

***Example text:** "Participants will be enrolled into the study only if they meet all of inclusion criteria and none of the exclusion criteria listed in the following sections."*

Under the sub-headings in this section, list all the criteria that will be applied to determine a person's eligibility or ineligibility for the study. Use the following guidelines when developing a participant eligibility criteria (Inclusion Criteria and Exclusion Criteria):

4.3.2 Inclusion Criteria

The inclusion criteria will be highly specific or each study and the following is general guidance only and not an exhaustive list. Consider criteria related to:

- *Demographic characteristics (e.g. sex, gender, age range).*
- *(where applicable) The condition under study the specific definition of the condition which will be used to assess patients for recruitment into the study and how it must be documented (e.g. diagnostic methods, criteria for classification etc).*
- *Clinical indicators of current status.*

***Example text:** "Each participant must meet all of the following criteria to be enrolled in this study:*

- *Is between the ages of <# and #> at enrolment*
- *Weighs between the ages of <# and #> at enrolment*
- *Has <condition> as determined by <insert detail of assessment necessary for definitive diagnosis of the study purpose>*
- *Provide a signed and dated informed consent form and (for paediatrics)/ or has a legally acceptable representative capable of understanding the informed consent document and providing consent on the participant's behalf."*

4.3.3 Exclusion Criteria

Exclusion criteria are characteristics than make an individual ineligible for study participation. Provide a statement that all individuals meeting any of the exclusion criteria at baseline will be excluded from study participation and then list each criterion. Consider criteria related to:

- *Specific clinical contraindications (where appropriate, specify grades of signs and symptoms).*
- *Specify any clinical (e.g. life expectancy, co-existing disease), demographic (e.g. age) or other characteristic that precludes appropriate follow-up in the study.*
- *Inability or unwillingness of participant or legally acceptable representative to give written informed consent.*

Example text: *"Participants meeting any of the following criteria will be excluded from this study:*

- *Has a recent (within # months of recruitment) history of <insert (e.g. anxiety, depression etc)>*
- *Has clinically significant (list any abnormalities that are not allowed)*
- *Has a prior diagnosis of <insert condition>*
- *Is unable to attend for assessments"*

Justification for exclusion of a specific population: *If a specific population is excluded (e.g. elderly or paediatric populations, women or minorities), provide a clear and compelling rationale and justification to establish that inclusion is inappropriate with respect to the health of the participants or the purpose of the research. Limited English proficiency should not be an exclusion criterion, but feasibility does need to be considered. Inclusive methods such as translation of questionnaires of the use of interpreters should be considered. Extra care is necessary to ensure validity of information is maintained when participants have limited English proficiency or other aspects of literacy, and ability to provide valid information in the format requested.*

4.4Recruitment of potential participants

4.4.1 Recruitment planning

Full details regarding participant identification and recruitment should be given in this section of the protocol unless a separate, more detailed plan is referenced (e.g. a Study Manual). Include the information below:

- *The target study population – describe the population (gender, race and ethnicity, age) and identify anticipated estimated number to be enrolled in order to reach the target of <insert>' participants (keeping in mind that some participants who provide consent may be found to be ineligible during the screening procedures).*
- *Anticipated accrual (recruitment) rate and timeline*
- *Anticipated number of sites, countries (if applicable) and participants to be enrolled*
- *Recruitment settings (e.g. inpatient hospital setting, outpatient clinics, community services, or general public)*
- *Describe the group from which the study population will be selected. For example:*
    - *Cohort Studies: clinics (hospital and community), referring doctors, electoral rolls, schools etc.*
    - *Cross-sectional Studies: (a) prospective participants - clinics, referring doctors, and (b) retrospective data - medical records, registries, databases etc.*
    - *Case-Control studies: (a) controls - advertisements, letters from GP's, family members etc.), and describe how they will be matched; (b) study population – clinics, referring doctors. In general controls should reflect the population from which the cases arose. Provide a justification for how potential selection or participation bias has been avoided.*
- *Types of recruitment strategies planned. For example, for clinical research, this could include the Royal Children's Hospital (RCH) electronic medical record (Epic)*, clinic lists, clinical referrals, patient advocacy groups or social media. For public health research, it could include school-based recruitment, electoral role sampling, school-based recruitment or social media*

** For information on the process for accessing Epic for HREC-approved research, refer to the RCH procedure "Epic: Appropriate Use for Research (RCH Procedure)", available on the RCH intranet.*

- *If the study requires long-term participation, describe procedures that will be used to enhance participant retention (e.g., multiple methods for contacting participants, visit reminders, incentives for visit attendance) and whether those methods are the same for all participants.*
- *The sampling method used, e.g. probability sample or non-probability sample.*
    - *Probability sample: Exclusively random process to guarantee that each participant or population has specified chance of selection, such as simple random sampling, systematic sampling, stratified random sampling, cluster sampling, and consecutive participant sampling.*
    - *Non-probability sample: Any of a variety of other sampling processes, such as convenience sampling or invitation to volunteer.*

The sampling method is a critical aspect to get right so should be a part of the design consultation with CEBU. A key aspect of the quality of an observational study is how well it represents the population it is intended to with regards to the sample frame or denominator chosen, the participation rates and ensuring that participation is not selective according to particular characteristics such age or socio-economic position. It is critical to ensure that the study findings are applicable to the intended population.

If participants will be compensated or provided any incentives (e.g. vouchers, gift cards,) for study participation, describe this here or alternatively in Section 12.

***Example text:** "In a two-stage clustered sampling design, 10% of all Australian postcodes will be randomly selected, stratified by state and urban/rural locale; 10 year old children within the selected postcodes will then be randomly selected from the Medicare database."*

4.4.2 Stages of recruitment

Determining eligibility of a potential participant can only commence once the study has received ethical approval and site-specific authorisation (governance). Studies vary in the complexity of how eligibility is assessed. While for some studies, it is possible to determine full eligibility prior to informed consent, other studies will require a multi-step assessment process (i.e., the person meets initial criteria but additional procedures or study specific testing are required to finalise eligibility - this cannot be undertaken until informed consent has been provided).

For the purposes of studies at the Melbourne Children's campus, the following definitions apply to recruitment stages:

- ***Pre-screening** refers to the evaluation of generalised characteristics prior to consent and screening to initially determine eligibility (following ethical and governance approval of the study). The characteristics may be determined from the medical record, a referring clinician or other sources as appropriate to the study (including self-referrals by potential participants), but not via any procedures undertaken specifically for the study.*
- ***Screening** refers to the collection of information that is in addition to clinical care, it is collected for the reason of assessing eligibility for the study. Some examples of this are: testing cognition, assessing level of physical function, taking blood samples, and requesting medication history. As such this information is always collected after consent has been obtained.*

- ***Screen failure*** *refers to participants who consent to participate in the study but who are found, during the screening procedures, to be ineligible for enrolment (because the inclusion criteria was not met or an exclusion criterion was met).*

- ***Enrolment*** *refers to participants who have provided informed consent, have been screened for study eligibility and have been deemed eligible. (N.B. for clinical trials, enrolled refers to participants who have been assigned to the trial intervention).*

4.5Consent

Overview

The National Statement on Ethical Conduct in Human Research states that if you want people to take part in your research project, you need to get their informed consent. This means that they:

- *Voluntarily agree to take part in the study and*
- *Understand what the study involves.*

Methods of consent vary according to the nature, complexity and level of risk of the study and also the personal and cultural circumstances of the potential participant. Common methods for recording consent are:

- *Written – for example, the potential participant signs a Participant Information and Consent Form.*
- *Verbal – for example, you ask the person whether they agree to take part in your study and record their response in writing or on an audio device.*
- *Implied – for example, the person gives consent by filling out and returning a survey.*

An Opt out approach is another option; this is where the person is included in the research unless they give their express decision to be excluded. Note that their decision must be informed. Use of an Opt out approach requires justification to (and approval from) the Human Research Ethics Committee (HREC).

It may be appropriate to use different types of consent for different elements of a study. For example, you might seek explicit written consent for participation in clinical research. You might then use an Opt out approach if you are seeking to use participants' information as part of a registry.

In the protocol, describe the consent procedures to be used in the study. State whether the following fundamental conditions for a valid informed consent will be met for each participant:

- *Disclosure of relevant information to prospective research participants and/or their legally acceptable representatives*
- *Comprehension of the information provided*
- *Voluntary agreement of the participant, free from coercion*

Research involving minors

Research involving children and young people raises specific ethical concerns in that the capability of minors to provide fully informed consent will vary with their maturity and intelligence as well as the complexity of the research. Researchers should bear in mind that, even without full competence, minors may have some understanding of the research as well as the benefits and burdens of participation. They should therefore be involved in the discussion and decision making even where not asked to provide consent themselves. Researchers should refer to the RCH procedure "Informed Consent in Research", available on the RCH Research Ethics Governance website.

In the protocol, state whether consent from mature minors will be sought as well as from the parent/legal guardian. State who will obtain consent and outline the roles and responsibilities of those involved in the consent process, including the responsibility for determining the capability of the minor to provide consent. Also identify different information statements and consent forms that are needed for the study (e.g., study participation, future use of specimens, and information statements for minors).

***Example text** (for the use of written consent):*
"Prior to performing any study-specific procedure (including screening procedures to determine eligibility), a signed consent form will be obtained for each participant.

The process will be that the investigator or delegated member of the study team will discuss the study with relevant family members: parent/legal guardian and the child/adolescent participant (where appropriate). Age appropriate (clarify <written, oral or other>) information should be provided to the child/adolescent in accordance with their level of maturity (where appropriate).

The investigator will provide the Parent/Guardian Information and Consent Form to the parent/legal guardian and, where appropriate, the Participant Information and Consent Form to the child/adolescent. This document will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation.

The investigator will conduct the informed consent discussion and will check that the parent/guardian and, where appropriate, the participant comprehend the information provided. The investigator will answer any questions about the study.

The parent/legal guardian will be invited to provide written consent. Where deemed competent and mature to provide consent, the child/adolescent will also be invited to provide written consent. The level of maturity will be determined by the Investigator in accordance with local process. Consent will be voluntary and free from coercion.

The investigator who conducted the consent discussion will also sign the informed consent form. A copy of the consent form will be given to the parent/legal guardian and to the participant where the participant has signed a consent form...

It will be documented in the participant's record (state whether this is the hospital medical record or the participant's study ("shadow" file) that consent has been provided. When the all the inclusion/exclusion criteria have been addressed and the eligibility of the participant confirmed, the participant is considered enrolled."

Describe the procedures for the documentation of ineligibility for participants, and for reasons for the non-participation of eligible participants (i.e. maintaining a record of all participants screened but not entered into the study). Specify what data will be recorded on these participants.

5 STUDY VISITS AND PROCEDURES

5.1 Study timeline

To help the reader understand complex protocols it is very useful to include a flow chart of study. .

5.2 Schedule of assessments

The Schedule of Assessments (SoA) details the specific timing of procedures/evaluations.

Describe procedures for collection of all study data including clinical observations, laboratory results, biospecimens, images, questionnaire responses, etc. In the following sub-sections:

- *Include notation as to what the test is expected to measure*
- *Describe how the assessment will be done, what measurements will be obtained, where and by whom (reference to a separate manual may be necessary if tests are complicated).*
- *Specify units (if applicable)*
- *Procedures and tests that are performed exclusively for research purposes must be identified and differentiated from those that would occur regardless of the research (i.e. standard of care)*
- *Point out any procedures, situations or materials that may be hazardous and the precautions to be exercised to minimise the risks*
- *Specify if any particular member of the research team must conduct certain assessments (e.g., physician, psychologist).*

Where applicable, permissible time windows for evaluations should be presented (i.e. ± x days/weeks).

Example Schedule of assessments

	Assessment/Procedure	Visit 1 Baseline / Screening	Visit 2 (3 months)	Visit 3 (6 months)	Visit 4 (12 months)
Example procedures	Informed Consent	x			
	Demographic Information	x			
	Parent questionnaire reporting key exposure measures	x	x	x	x
	Consent for data linkage e.g. to geographic information systems providing environmental exposures	x			
	Weight Measurement	x			
	MRI		x	x	
	QOL50- questionnaire		x	x	x
	Blood Collection	x	x	x	
	Biopsy	x			

Example Schedule of assessments

Event	Screening*[1]	Entry*	Study Week	
			48 weeks*	96 weeks*
History	x	X		
Interim History			X	X
Physical exam		X	X	X
MENTAL HEALTH MEASURES				
PARENT/PRIMARY CAREGIVER COMPLETED				
Primary Caregiver Questionnaire (PQ)*** (Assesses the participant and parent/primary caregiver/family demographics)		X	X	X
Symptom Inventories-4 (SI-4) Primary Caregiver Checklist (Assesses the participant)		X	X	X
Adult Inventories-4 (ASRI-4, AI-4) (Assesses the parent/primary caregiver)		X	X	X
Family Environment Scale (FES) (Assesses the parent/primary caregiver and family environment)		X		
Child Behaviour Checklist (CBCL) (Assesses the participant)		X		
Child Cognitive Impulsivity Scale (Assesses the participant)		X		
PARTICIPANT COMPLETED				
Youth's Inventory-4 (YI-4)***** (Assesses the participant)		X	X	X
Caregiver-Child Interaction (Assesses parent/primary caregiver communication style/family environment - participant ≥ 12 years of age-completed)		X		
Wechsler Intelligence Scale for Children - WISC-IV IQ (Letter-Number and Coding Subscales) (Assesses the participant)		X		
Child Cognitive Impulsivity Scale (Assesses the participant)		X		
PAIN MEASURES				
Pain Level Assessment (Assesses the participant - participant and parent/primary caregiver completed)		X	X	X

1. The Informed Consent will be signed at the screening visit. Screening and entry can occur at the *same visit or up to six weeks apart.*
2. History – includes source documentation for clinical diagnoses; neuropsychiatric diagnoses; and lifetime exposure to neurotropic medications.

**Insert allowable windows for each visit (i.e. the amount of time before and after the due visit)*

Recommended content can be displayed using various schematic formats.

5.2.1 Standard Care and Additional to Standard Care Procedures (where applicable)

Standard of care costs are usually covered by health service funding (e.g. Medicare) but determining standard of care can be complex given acknowledged variation in health care. Standard of care is defined as how clinicians actually practice clinical care, that is, any procedures that a participant would receive in their usual course of treatment, regardless of whether they were participating in the research project. Procedures that are standard of care are not usually paid for by the research project; instead they are funded by the health services funder (e.g. Medicare, the Pharmaceutical Benefits Scheme, or a patient's private health insurance).

In table format LIST all procedures, assessments, and tests (e.g., CT-scans, MRI, blood tests etc) that form part of standard care and that are additional to standard care. Include testing times, dosages and volumes (where applicable).

Standard Care Procedures		
Procedure	**Time/Visit**	**Dosage/Volume**

Additional To Standard Care		
Procedure	**Time/Visit**	**Dosage/Volume**

6 STUDY VISITS AND PROCEDURES

6.1Description of procedures

List and describe all procedures and evaluations to be done as part of the study to:

- *determine participant eligibility and enrol participants*
- *support the determination of the primary, secondary and exploratory objectives outlined in the protocol*

The protocol should provide a high-level discussion of all procedures. More detailed information can be provided in a Study Manual or SOP.

Note that the specific timing of procedures/evaluations to be done at each study visit should already have been captured in the Schedule of Assessments (SoA) - the time points for these procedures do not need to be included again here.

For each assessment:

- *Specify how the test (e.g. diagnostics, physical or mental performance assessments) will be conducted, who will conduct it, how measurements will be obtained (specify units where applicable) and what information will be collected and documented. Reference to a separate manual/SOP may be necessary if tests are complicated.*
- *Specify if any particular member of the research team must conduct certain assessments and whether they will be required to undertake study-specific training or certification*
- *Specify whether the tests need to be timed in relation to other activities*
- *Detail efforts to standardise procedures and assessments (where applicable) such as the required equipment specifications for a radiology assessment, a consistent laboratory method throughout the study; use of single, central laboratory for multi-site studies).*

- *Specify whether there are any samples being collected and stored for future research (where samples will be stored for future research, provide the information required in Section 9 and Appendix 17.2)*
- *Other*
    - *Provide justification for any sensitive procedures (e.g., provocative testing, deception).*
    - *Point out any procedures, situations or materials that may be hazardous and the precautions to be exercised to minimise the risks*
    - *Procedures, tests and interventions that are considered experimental and/or procedures performed exclusively for research purposes must be identified and differentiated from those that would occur regardless of the research (i.e. standard of care)*

The procedures could include:

- *Medical Record Review: Include a listing of the variables that will be collected from the medical record, e.g. date of birth, weight*
- ***Physical examination** (e.g., height and weight, organ systems, motor or vision assessment, or other functional abilities). If appropriate, discuss what constitutes a targeted physical examination.*
- ***Vital signs** (e.g., temperature, pulse, respirations, blood pressure). Carefully consider which vital signs (if any) should be measured to ensure that only essential data are collected. Include any specific instructions with respect to the collection and interpretation of vital signs. For example will blood pressure measurement be made sitting or lying down? Will more than one measurement be made and averaged?*
- ***Electrocardiograms (ECGs)**: specify if the ECG is for screening purposes only. Include any specific instructions for the collection and interpretation of the ECG (e.g., time points relative to other evaluations). If ECGs will be analysed at a central laboratory, instructions for the collection (e.g., equipment), transmission and archiving of the ECG data should be summarized in this protocol, and further outlined in the Study Manual. If the ECG will be read locally, indicate how these will be handled and in what format (e.g., digital or paper), as well as instructions with respect to local review.*
- ***Administration of questionnaires or other instruments by researchers** (such as gait assessment tools). Non-standard and non-validated instruments should be included in an Appendix.*
- ***Completion of participant-reported outcomes by parents/participants** (such as a daily diary, periodic quality of life questionnaires).*
- ***Radiographic or other imaging assessments**. State the specific imaging required and, as appropriate, provide description of what is needed to perform the specialized imaging. Details describing how to perform the imaging in a standard fashion and equipment specifications may be described in the Study Manual or a separate SOP.*
- ***Biological specimen collection and laboratory evaluations**. Include specific test components and estimated volume and type of specimens needed for each test. Specify laboratory methods to provide for appropriate longitudinal and cross-sectional comparison (e.g., use of consistent laboratory method throughout the study, use of single, central laboratory for multi-site studies). If more than one laboratory will be used, specify which evaluations will be done by each laboratory. In addition, discussion should include whether any laboratory tests (e.g., diagnostics) that will be used are being developed concurrently or are commercially available. Special instructions for the preparation, handling, storage, and shipment of specimens should be briefly explained in this section with detailed discussion in the Study Manual.*

- ***Special assays or procedures required*** *(e.g., immunology assays, pharmacokinetic studies, flow cytometry assays, microarray, DNA sequencing). For research laboratory assays, include specific assays, estimated volume and type of specimen needed for each test. If more than one laboratory will be used, specify which assays will be done by each laboratory. Special instructions for the preparation, handling, storage, and shipment of specimens should be briefly explained in this section with detailed discussion in the Study Manual.*
- ***Counselling procedures, including any dietary or activity considerations*** *that need to be adhered to during study participation.*

Include in this section a discussion of the results of any study specific procedures that will be provided to participant (e.g., radiographic or other imaging or laboratory evaluations).

6.2 Notes on study visits

In this section, list the procedures, observations, measures etc to be conducted at the study visits. Section 8 will describe how the data should be documented.

6.2.1 Screening / Baseline

Discuss the sequence of events that should occur during screening and the decision points regarding eligibility. List the maximum time following consent for finalising eligibility (i.e. screening tests and evaluations to be completed within, for example, 28 days of consent).

Example text*: "Enrolment (Visit 1, Day 0)*

- *Obtain and document consent from potential participant.*
- *Review medical history to determine eligibility based on inclusion/exclusion criteria.*
- *Obtain demographic information, medical history, medication history, and alcohol and tobacco use history.*
- *Record results of physical examinations."*

6.2.2 Standard study visits

List each study visit, including visit number and the allowable time window for the visit or, alternatively, list key visits. For the visits listed, detail the evaluations/procedures/specimen collections to be completed (in chronological order, if applicable).

Example text: *Visit 2, Day X ± Y {Repeat for each visit, providing a study-appropriate window for the visit}*

- *Record results of physical examinations.*

6.2.3 Final study visit

Define when the final study visit should occur and any special procedures/evaluations or instructions to the participant. If study results will be shared with participants, discuss when and how they will receive this information. Think about whether you will want to contact the participants in the future, and whether consent needs to be obtained now to do so.

(Where applicable) Note that all safety events (study conduct-related adverse events etc) will be followed until resolution or alternatively to stabilisation; ensure referrals are in place where applicable.

Example text: *Final Study Visit (Final Visit, Day X ± Y)*

- *Record results of physical examinations.*
- *Provide final instructions to participant (e.g., follow-up of ongoing study conduct-related adverse events, oral hygiene instructions)".*

6.2.4 Unscheduled visit

Specify how unscheduled visits will be handled and documented.

6.3 Participant withdrawals and losses to follow up

6.3.1 Withdrawal of consent

Participant withdrawal from the study may occur if the participant or their legal guardian withdraws their consent to continue any study involvement. In contrast to interventional studies (clinical trials), participants in observational studies are not usually required to attend a visit to enable safety evaluations to be conducted. If, however, there is a particular concern in your study regarding participant safety, add information in this section regarding the plan for participant assessments.

Example text *"Participants are free to withdraw from the study at any time upon their request or the request of their legally acceptable representative. Withdrawing from the study will not affect their relationship with, or care by, the hospital and affiliated health care professionals.*

A dedicated Case Report Form (CRF) page will be used to capture the date of participant withdrawal of consent and (if provided) the reason."

6.3.2 Losses to follow-up

Describe the nature and duration of study participation. Validity of the study is a potential issue when participants are lost to the study, as information that is important to the outcome evaluation is then lost. Participants are considered lost to follow-up when they do not attend scheduled study visits and cannot be reached to complete all protocol-required study procedures. Note what attempts will be made to obtain follow-up data and the point at which a participant will be declared lost to follow-up (e.g. number of phone calls to participant, phone calls to next-of-kin if possible, certified letters, medical record review, phone calls to other hospitals.).*

> ** Note that where a participant was not able to be contacted for a given wave of follow up (e.g. for a long-term survey), the participant may still be willing to participate in a subsequent wave of follow up and could be re-contacted if this is built in to the protocol design.*

Describe the plans to minimise loss to follow-up and missing data.

Example text: *"A participant will be considered lost to follow-up if he or she fails to return for <specify number of visits> scheduled visits and is unable to be contacted by the study site staff. The following actions must be taken if a participant fails to return to the clinic for a required study visit:*

- *The site will attempt to contact the participant and reschedule the missed visit <specify time frame> and counsel the participant on the importance of maintaining the study visit schedule and ascertain if the participant wishes to and/or should continue in the study.*
- *Before a participant is deemed lost to follow-up, the Site Principal Investigator (Site PI) or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.*
- *Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up."*

6.3.3 Replacements

Provide information on whether or not participants who withdraw from the study will be replaced by further recruitment to maintain the required sample size.

6.3.4 Study Closure

The end of the study for a given participant is defined as completion of all study visits/procedures as shown in the Schedule of Assessments.

The end of the study is considered completed when the last participant's last study visit has occurred. At the end of the study, the Study PI (single-site study) or Coordinating PI and Site PI (multi-site study) should ensure that Human Research Ethics Committees (HRECs) and Research Governance Offices (RGOs) are informed along with funding bodies (where applicable).*

** In cohort studies, the study is often left open at the end of a given stage (depending on what participants initially consented to). For example, a stage may be completed, but when later follow up is resourced the study staff would re-contact participants (except where consent had been withdrawn). This all needs to be carefully considered at the initial consent stage to future proof the research.*

Example text:

A participant is considered to have completed the study if he or she has completed all study visits as shown in the Schedule of Assessments,

The end of the study is defined as completion of the last visit or procedure shown in the Schedule of Assessments in the study at all study sites. At this stage, the Study PI will ensure that the HREC, RGOs and regulatory and funding bodies have been notified (single-site study) OR the Coordinating PI will ensure that all HRECs and RGOs as well as all regulatory and funding bodies have been notified.

7 POTENTIAL RISKS RELATED TO STUDY CONDUCT

Major risks in undertaking research can be broadly categorised into:

1 *Risks to the safety and rights of the study participants*

Although observational studies are generally expected to involve lower risk for study participants than studies involving an intervention, observational studies still involve a level of risk.

Consideration needs to be given to psychological events such as anxiety or depression that may result from participation. Even a survey that asks questions about a participant's mood or feelings can evoke psychological stress or embarrassment. Safety events may also result from resulting from a procedure in the study such as blood sampling.

Safety concerns for participants in observational studies may also relate to disclosure of risk of harm to self or another including, for example, mental health concerns, concerns regarding family violence and so on. Where observational studies are studying sensitive areas (e.g. childhood trauma or maltreatment) there can be risk of triggering safety concerns.

2 *Risks to the successful conduct of the study (e.g. inadequate funding, poor recruitment, poor quality data/samples, risks to the staff when undertaking home visits etc).*

Researchers should conduct a risk assessment and detail in the protocol their plan for managing the risks identified - refer to the CRDO Risk Assessment and Risk Management Tool available on the CRDO website (this has been developed for clinical trials but can be used for observational studies – just delete sections that are not relevant). Any unexpected, significant issues arising during the study should be reported to the approving Human Research Ethics Committee(s) and to the authorising Research Governance Offices. The Coordinating PI is also responsible for providing any updated safety information to all Site PIs.

8 DATA AND INFORMATION MANAGEMENT

*As noted in the National Statement (NS 2007, updated 2018 chapter 3.1 Element 4), the **term 'data'** is intended to refer to bits of information in their raw form, whereas the **term 'information'** is intended to refer to data that have been interpreted, analysed or contextualised.*

All research results in data to be analysed which supports or refutes the study hypothesis. Poor data and information results in a waste of effort and resources and puts participants at risk of harm. It is for this reason that institutions, sponsors, and regulators should invest effort into ensuring that research data and information is of high quality and validity as well as protecting the confidentiality of research participants.

*The following sub-sections should include a brief description of the data handling (generation, collection, access, use, analysis, disclosure, storage, retention, disposal, sharing and re-use) and record keeping for the conduct of the study. As outlined in the National Statement [NS 3.1.45], each study should develop a separate **Data Management Plan** to provide full detail. **Standard Operating Procedures** should also be developed to detail study operations, including participant recruitment, data collection and data management (including change management).*

*Note that a description of the analysis activities should be provided in section 10 of the protocol and a separate **Statistical Data Management Plan** should also be developed.*

8.1Overview

National guidelines (National Statement on Ethical Conduct in Human Research [NHMRC, 2007 updated 2018; The Australian Code for the Responsible Conduct of Research 2007, updated 2018) require that the Principal Investigator maintains (during the study and archives retains for the minimum, mandatory archive period) appropriate research records along with a record of their location. For data and information management, this includes:

- *Essential Documents for the study related to data management **(e.g. Data Management Plan, Data Dictionary)** (refer to the CRDO website for the relevant SOP). Essential documents are those documents which, when taken together, support the validity, quality and integrity of the data produced and demonstrate compliance by the investigators with regulatory and good clinical practice requirements as applicable.*
- *The Principal Investigator should also maintain a site-specific record of the location(s) of source documents, bearing in mind all locations for these (e.g. pathology, radiology, Investigator's office). Source documents contain all original data and information, records of clinical findings, observations, and other activities necessary for the reconstruction and evaluation of the study. They can be hard copy or electronic. A **template Source Document Plan** is available on the CRDO website.*

Example text

The Principal Investigator is responsible for storing essential study documents relevant to data management and maintaining a site-specific record of the location(s) of the site's data management-related Essential Documents.

*The Principal Investigator is responsible for maintaining adequate and accurate source documents that include all key observations on all participants at their site. Source data will be attributable, legible (including any changes or corrections), contemporaneous, original, accurate, complete, consistent, enduring and available. Changes to source data (hardcopy and electronic) must be traceable, must not obscure the original entry, and must be explained where this is necessary. A site-specific **Source Document Plan** will be maintained to indicate the location(s) of source documents.*

The Principal Investigator will also maintain accurate data collection forms (also known as case report forms - CRFs) and be responsible for ensuring that the collected and reported data is accurate, legible, complete, entered in a timely manner and enduring. To maintain the integrity of the data, any changes to data (hardcopy and electronic) must be traceable, must not obscure the original entry, and must be explained where this is necessary.

Any person delegated to collect data, perform data entry or sign for data completeness will be recorded on the delegation log and will be trained to perform these study-related duties and functions.

*Full details of all processes are provided in a separate study-level **Data Management Plan**.*

8.2Data management

*Describe the plan to ensure that the data collected are attributable, legible, contemporaneous, original, accurate, enduring, available, and complete. Full details covering the following should be provided in a separate **Data Management Plan** but a summary (at minimum) must be provided in the protocol. The data management plan should be supplemented by **Standard Operating Procedures** to address operations such as data collection, data management, data analysis, safety reporting and management of changes to data.*

For reference only: National Statement requirements	*Suggested wording*
Generation and collection – how and data be generated and collected	**8.2.1 Data generation (source data)** *What is the source of the data you will capture? Will you collect existing data, will you generate new data or will you use both?* *Source data are all information, original records of clinical findings, observations, or other activities in a study necessary for the reconstruction and evaluation of the study. Electronic source data are data initially recorded in electronic form.* *Source data are contained in source documents (paper or electronic). Examples of paper or electronic source documents are: medical records [at RCH the Electronic Medical Record (EMR) is Epic]; participant diaries; researcher diaries; memos; recorded data from automated instruments (e.g. blood pressure measurement); participant- or researcher-completed questionnaires or rating scales; videos; photographs; laboratory results; ECGs and reports; and imaging scans and reports.* ***Source document plan*** *For each discrete item of source data (e.g. blood pressure, standard lab test results, demographics), the location of the source should be clearly defined prior to participant recruitment; this can be defined in:* • *a study-specific Source Document Plan (refer to template on the CRDO website)* • *and/or the Data Management Plan.* *Note The following regarding the collection of source data directly onto the data collection form* • *When data is entered directly into your electronic data collection forms, the data collection form /database becomes your source document for that information. For source data being captured directly into an instrument (the data collection form, a diary or other site-designed worksheet), whether it be*

	paper or electronic, and the following factors should be considered when designing the instrument: ○ *The data to be collected directly should be specified in the protocol.* ○ *The investigator or participant response should not be biased by pre-set values present within the instrument. An optional comment field may be appropriate to record additional information, in an event where the pre-set values available do not match the type of data collected.* ○ *Note that the data collection form should not be the only record of a participant's inclusion in the study. Study eligibility and participation should, ideally, be captured in a participant's medical record or in a study participant folder (the folder for an individual participant labelled with the name of the study and containing identified documents such as the signed informed consent form [photocopy or original], test results to confirm eligibility [if applicable]).* ***Example text*** *In this study, the following types of data will be collected (examples only given below):* • *personal identifying information (names, dates of birth, contact details, Epic ID)* • *sensitive information including health data (genetic information, disease/diagnosis, medical history)* ***Source Document Plan*** *The source documents for this study include the RCH electronic medical record, questionnaires completed by the participant and/or researcher (paper); recorded data from automated instruments, laboratory reports and the signed parent/guardian (and, where applicable participant) information and consent forms. Each site participating in the study will maintain a site-specific* ***Source Document Plan*** *that will document the source, i.e. original recording, for each data discrete item/ category of items collected for the study. This Source Document Plan, signed and dated by the Principal Investigator, will be prepared prior to recruitment of the first participant and will be filed in the site's Investigator Site File.*
Generation and collection – how and by whom will data be generated and collected Use – how and by whom Storage and access during the study. Access – how and by whom, conditions under which access may be granted to others Disclosure – the purpose for which it	8.2.2 Data capture methods and data use, storage, access and disclosure during the study *Your* ***Data Management Plan*** *will cover in detail the management of the captured data but your protocol should cover the points listed below.* ***Data collection*** *In this section of the protocol, provide a brief outline of the following:* • *Whether data capture and entry will be paper and/or electronic.* • *Whether any relevant data standards (e.g. ICD10 for disease coding, CTCAE for coding adverse events, CDASH for standardising data collection formats and structures across studies and sponsors) that are being utilised as a part of the study.* • *Data capture processes - who will process the collected data, how, when and where*

will be disclosed, to whom?	*Note: You should develop a Data Dictionary to provide a detailed description for each data variable (i.e. the source of the variable, coding information if used [for example, MedDRA, SNOMED CT], and expected ranges [if relevant]) or can be exported from the project's database(s) – for example, REDCap).* ***Data storage and access*** *State how and where hardcopy data will be stored and how access will be restricted. State how and where electronic data will be stored, how it will be backed up and how access will be restricted (e.g. setting user permissions).* ***Use of the data*** *Specify how the data will be used (e.g. for the analyses specified in the protocol and Statistical Analysis Plan).* *Complete also the section overleaf on data sharing.* ***Access to data*** *Describe in this section who will have access to the data and study documents, noting that for the purposes of quality assurance reviews, audits, and evaluation of study safety, progress, and data validity, each site must permit authorised representatives of the sponsor, HREC, Research Governance Office and regulatory agencies to examine source records for participants.* ***Disclosure of data*** *Describe whether there are any situations in which personally identifiable information or data will be released to third parties.* ***Example text – customise for your study*** *Data collection methods* *Data for this study will be collected and entered using hardcopy and electronic data collection forms which will be completed by the parent/guardian (and/or participant where applicable) and researchers.* *The following publicly available research data collection tools will be used:* *<insert>* • *<insert>* *The following licensed research data collection tools will be used:* • *<insert>* • *<insert>* *The following data standards will be used for coding the data:* • *<insert e.g. ICD10 for disease coding>* *Full information on the data variables is located in the Study Data Management Plan.* *Use of the data* *The data will be used for the analyses specified in the protocol and Statistical Analysis Plan.* *Following the completion and analysis of the study, the data will be retained long-term*

	following the mandatory archive period for use in future research projects. *Storage and access* *Hard copy data will be stored by the Site in a locked cabinet in a secure location, accessible to the research team only.* *Electronic data will be securely stored in MCRI's REDCap database system and in files stored in MCRI's network file servers, which are backed up nightly.* ***Files containing private or confidential data will be stored only in locations accessible only by appropriate designated members of the research team.*** *REDCap is hosted on MCRI infrastructure and is subject to the same security and backup regimen as other systems (e.g. the network file servers). Data is backed up nightly to a local backup server, with a monthly backup taken to tape and stored offsite. REDCap maintains an audit trail of data create/update/delete events that is accessible to project users who are granted permission to view it. Access to REDCap will be provided via an MCRI user account or (for external collaborators) via a REDCap user account created by the MCRI system administrator. The permissions granted to each user within each REDCap project will be controlled by, and will be the responsibility of, the study team delegated this task by the Principal Investigator. REDCap has functionality that makes adding and removing users and managing user permissions straightforward. All data transmissions between users and the REDCap server are encrypted. The instructions for data entry to REDCap must be read and the training log signed prior to personnel commencing data entry on REDCap.* *Authorised representatives of the sponsoring institution as well as representatives from the HREC, Research Governance Office and regulatory agencies may inspect all documents and records required to be maintained by the Investigator for the participants in this study. The study site will permit access to such records.* *Disclosure* *The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorised third party, without prior written approval of the sponsoring institution. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the HREC, Research Governance Office or regulatory agencies.*
Methods to reduce identification of participants	8.2.3 Data confidentiality *Detail how personal information and data about potential and enrolled participants will be collected and maintained in order to protect confidentiality before, during, and after the study. Include procedures for maintaining participant confidentiality, privacy protections, and any special data security requirements. (Refer to section 3.1.40 of the National Statement for discussion about research where removal or separation of identifiers may not be required).* ***Note that the 2018 update of the National Statement no longer uses the terms 'identifiable', 'potentially identifiable', 're-identifiable', 'non-identifiable' or 'de-identified' as descriptive categories for data or information due to ambiguities in their meanings. Rather, the identifiability of information is a characteristic that exists on a continuum.*** ***The risks related to identifiability of data and information in research are greatest***

where the identity of a specific individual can reasonably be ascertained by reference to an identifier or a combination of identifiers (examples of identifiers include the individual's name, image, date of birth or address, attribute or group affiliation). Risk may also arise where identifiers have been removed from the data or information and replaced by a code, but where it remains possible to re-identify a specific individual (by, for example, unlocking the code or linking to other data sets that contain identifiers). Due to technological advances, risks may arise in relation to data and/or information that has never been labelled with individual identifiers or from which identifiers have been permanently removed.

As outlined in the updated National Statement (2018):

- *Researchers and reviewers must consider the identifiability of data and information in order to assess the risk of harm or discomfort to research participants or others who may be at risk.*
- *Researchers should adopt methods to reduce the risk of identification during collection, analysis and storage of data and information. Methods to reduce identifiability and the consequent risks may include:*
  (a) minimising the number of variables collected for each individual;
  (b) separation and separate storage of identifiers and content information; and
  (c) separating the roles of those responsible for management of identifiers and those responsible for analysing content." (NS 3.1.41)
- *Where research involves linkage of data sets with the consent of participants, researchers should advise participants that use of data or information that could be used to identify them may be required to ensure that the linkage is accurate. They should also be given information about the security measures that will be adopted, for example the removal of identifiers once linkage is completed.*

Additional comments:

- *If data are to be generated in one location and transferred to another group, describe the responsibilities of each party, including the expectations regarding time to transfer.*
- *Discuss any additional features to protect confidentiality and privacy.*

The security arrangements should be proportional to the risks of the research project and the sensitivity of the information (NS 3.1.46).

Example text

Data confidentiality

"Participant confidentiality is strictly held in trust by the Principal Investigator, participating investigators, research staff, and the sponsoring institution and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participating participants.

	To preserve confidentiality and reduce the risk of identification during collection, analysis and storage of data and information, the following will be undertaken: *(1) The number of private/confidential variables collected for each individual has been minimised. The data collected will be limited to that required to address the primary and secondary objectives (include exploratory where applicable).* *(2) Participant identifiers will be stored separately to the data collected; documents with identifiers will be stored separately to participant data. (This is the ideal situation – if any data and identifiers are not stored separately, ensure there is restricted access e.g. use REDCap's permission control functionality. Amend wording in this section to reflect your planned practice). Participant data and samples will be identified through use of a unique participant study number/code assigned to the study participant ("re-identifiable"). The Site Principal Investigator is responsible for the storage of a master-file of names and other identifiable data with the participant ID; access to this document will be restricted to the site study team and authorised persons as listed previously. The master file should be stored securely, and separately, from study data in locked/ password-protected databases with passwords kept separately. If additional information such as age, ethnicity, sex or diagnosis especially where rare) is included in the data, discuss whether this might make specific individuals or families identifiable and outline strategies to address.* ***Consult with the CEBU team to discuss strategies*** *(e.g. "top and bottom coding" of data to limit identification of outliers).* *(3) Separation of the roles responsible for management of identifiers and those responsible for analysing content. The data will be analysed by the statistician, who will be provided with anonymised data identified only by the unique participant study ID. As above, if any included data items might make specific individuals or families identifiable discuss and outline strategies to address -* ***consult with CEBU to discuss strategies.***
Quality assurance	8.2.4 Quality assurance *Provide a brief description of:* • *Plans for data cleaning (e.g. checks for invalid characters, out-of-range values, invalid dates, data that is not consistent with data in other data fields, repeated participant IDs etc).* • *Plans for source data verification (where applicable) to assess the accuracy, completeness, or representativeness of data by comparing the data in the database to the original source of the data (not applicable for data items where data is entered directly into the database and therefore the database is also the source).* • *Plans for site monitoring and auditing (where applicable)*
Analysis – how and by whom	*Ensure that this is covered in the STATISTICS section*
Storage post-study ARCHIVE (after study finished and during archive period) • how will the data be stored post-	8.2.5 Archiving - Data and document retention ***Archiving*** *How will the data be stored post-study? What is the minimum, mandatory retention period for the data for this study?*

study • what is the retention period Disposal –process for safe and secure disposal	*The time period for which study data, information and documents must be retained (the archive period) is determined by the type of research and relevant legislation, code and guidelines. Where more than one legislation/code/guideline is relevant, the one with the longest retention period applies.* ***However, also keep in mind the importance placed in the updated (2018) National Statement on collecting and retaining data and information for use by future research projects so that the benefits of research can be shared [NS 3.1.50).*** *Below is some guidance on current minimum retention requirements for research in Australia - contact the RCH Research Ethics Governance group to further discuss the requirements for your particular study. You must also comply with MCRI data management policies.* • *All research – in general at least 5 years from publication (The Australian Code for the Responsible Conduct of Research 2007)** • *All research – retention of any new health data for at least 7 years for adults or until age 25 for children [VIC HRA]* • *Clinical trials - must archive for at least 15 year post-trial completion (TGA) or until child aged 25 years (whichever is the later) (VIC HRA)* • *Gene therapy research data - must retain permanently (The Australian Code for the Responsible Conduct of Research 2007)** • *Research that has community or heritage value - must retain permanently, preferably within a national collection (The Australian Code for the Responsible Conduct of Research 2007)** ** The revamped Code (2018) does not include guidance on required data retention periods - we are awaiting the release of the supporting guide "Management of Data and Information in Research".* *Describe how long and where all research data, information and documents will be kept following the end of the study. During the archive period, data should be stored in a way that allows re-identification in case this is needed (e.g. for regulatory audits). Outline how the data will be secured and how confidentiality of stored data will be ensured.* *State who (i.e. person's position) will be the custodian during the archive period, who will have access to the stored data and outline any procedures that may be followed to dispose of the data at the end of the archival period.* *Specify that records should not be destroyed without the written consent of the Coordinating Principal Investigator / Site Principal Investigator. In multi-site studies, the Coordinating Principal Investigator should inform Site Principal Investigators when these documents no longer need to be retained.* ***Destruction*** *If the plan is to destroy data and documents after the required archive period, state this here and describe the planned method of destruction. Secure destruction of research data involves using irreversible methods to ensure that the data is no longer usable. It is particularly critical that confidential or sensitive data is made unreadable.* *Hardcopies should be disposed of via a confidential shredding process.*

	For electronic data, note that deleting files does not destroy the information completely; it may be necessary to utilise software which permanently erases data (Seek guidance from MCRI IT). Consider also other data devices.* ** It may not actually be possible to completely expunge data from institutional backups [i.e. those back-up tapes held off-site].*
Data sharing – plans for permitting re-use of data both internal and external?	8.2.6 Data sharing *Except where there are justifiable ethical reasons, the National Statement requires research data be made available for future research projects (see extract below). Indicate the plan for whether data will be shared following completion, analysis and publication of this study; justify if the plan is not to share the data.* • *"In the absence of justifiable ethical reasons (such as respect for cultural ownership or unmanageable risks to the privacy of research participants) and to promote access to the benefits of research, researchers should collect and store data or information generated by research projects in such a way that they can be used in future research projects. Where a researcher believes there are valid reasons for not making data or information accessible, this must be justified." (NS 3.1.50).* • *Data sharing statements should indicate the following: whether individual de-identified participant data (including data dictionaries) will be shared; what data in particular will be shared; whether additional, related documents will be available (e.g. study protocol, statistical analysis plan, etc.); when the data will become available and for how long; by what access criteria data will be shared (including with whom, for what types of analysis).* ○ *MCRI is currently (as of May 2019) developing a policy/procedure for the process involved in sharing data for future ethically-approved research.* *Ensure you seek appropriate consent (i.e. extended or unspecified consent) for this.* *Data sharing (review and customise for your study)* *Beginning 'x' months following analysis and article publication, the following will be made available long-term for use by future researchers from a recognised research institution whose proposed use of the data has been ethically reviewed and approved by an independent committee and who accept MCRI's conditions for access:* • *Individual participant data that underlie the results reported in this article after de-identification (text, tables, figures and appendices)* • *Study protocol, Statistical Analysis Plan, PICF*
Long-term custodianship (after archive period finished)	***Long-term custodianship (after archive period finished)*** *As noted previously, the National Statement specifies that research data should be retained and made available for future research projects, except where there are justifiable ethical reasons. Indicate the plan for long-term data retention for this research project.* *After the archive period, the data may be anonymised for preservation to reduce the risk of re-identification. As outlined previously, technological advances mean that identification can occur even where data and/or information has never been labelled with individual identifiers or from which identifiers have been permanently removed*

	(e.g. linking to other data sets that contain identifiers). The risk of re-identification is related to the data context as well as what it will be used with and for. *State who (i.e. person's position) will be the long-term custodian following the archive period.*
Sample management	***Sample management: Specimen & Biobanking*** *A biobank is defined as "…collections of human biological materials (biospecimens) linked to relevant personal and health information (which may include health records, family history, lifestyle and genetic information) and held specifically for use in health and medical research" (NHMRC Biobanks Information Paper, 2010).* ***In this section of the protocol, outline whether a biobank will be established.*** ***Registration of a Biobank*** *If your research includes the collection of samples and associated data to be stored for use in future research with extended* or unspecified consent**, you will need to register your biobank.* *For biobanking with the Melbourne Children's Bioresource Centre (MCBC) [note that the* ***MCRI Biobanking*** *Facility forms part of the MCBC] - complete a Biobank Registration Form (BRF). The BRF is available on request (biobanking@mcri.edu.au) or via the RCH Research Ethics Governance website (click on the link on the Application Coversheet).* ** Extended consent is defined as that given for the use of data or samples in future research projects that are (i) an extension of, or closely related to, the original project; or (ii) in the same general area or research (e.g. genealogical, ethnographical, epidemiological, or chronic illness research).* **Unspecified consent is defined as that given for the use of data or samples in any future research.* ***Sample storage and management*** *MCBC encourages standardised processing of biospecimens through the use of common processing protocols. These protocols are located on the MCBC website (MCRI intranet) at https://intranet.mcri.edu.au/rso/scientific-services/biobanking* *This link provides details of general laboratory protocols for sample types commonly processed by the Facility. In devising these protocols, the MCRI Biospecimen Advisory Committee and MCBC have drawn upon local, national, and international expertise, and published evidence that compares and contrasts various methodological approaches.* *Some studies will have specific downstream requirements that may not be fully met by these general protocols, so that flexibility will be required. MCBC staff are available to discuss such study-specific processing requirements.* ***If an investigator seeks an alternative facility to store and manage samples, provide full detail on the items listed below and describe all sample processes relevant to your study, including how samples are tracked (using the approved institutional database), stored and retrieved for use. In this section of the protocol, outline the following (N.B. if not using MCBC to manage and store the biobank***

provide full detail here):

- *Biobank name, location and custodian (position with overall responsibility for the biobank)*
- *Purpose of the biobank (purpose and timeframe i.e. fixed date or indefinite)*
- *Types of samples and type of associated data*
- *Consent type and process*
    - *Sample/record identification and confidentiality (e.g. how will samples/records be identified, who will have access to the identification codes?)*
- *Access to samples/data – who may access and what are the requirements for access (e.g. prior independent ethical approval).*
- *Security and back up – what systems will be in place to ensure integrity of the tissue samples (e.g. temperature alarms on storage units)*
- *Destruction – in what circumstances will this be done (e.g. participant request, consent expiry, biobank expiry or other discontinuation of data bank).*

9 STUDY OVERSIGHT

9.1Governance structure

Appropriate oversight of study conduct, protocol compliance and safety should be established for each study. Describe the role and composition of any committees set up for the study (define membership, function and frequency of review); it is advisable to establish terms of reference for committees. Create subheadings for separate committees.

Delete those sections not relevant for your study.

9.1.1 Study Steering Committee (SSC)

An SSC may be established for studies that are large, complex or potentially controversial or where there is a need to include key stakeholders in oversight of the study. An SSC should include some member(s), who are independent of the PI and Institution, who can provide expert advice. The SSC provides overall supervision and ensures that the study is conducted to the required standards but it should be noted that the day-to-day management of the study at a site remains the responsibility of the Site PI and Study Management Group. The SSC, through the Committee Chairperson, provides advice to the Coordinating PI (multi-site studies) or Study PI (single site studies).

Example text: *"A SSC will be established to provide expert advice and overall supervision, and ensure that the study is conducted to the required standards. The SSC will meet at least annually, with more frequent meetings as needed, and will work to a Terms of Reference.*

9.1.2 Coordinating Committee / Centre

Multi-site studies may establish a group to coordinate study operations across all participating sites and provide operational support. This could involve ongoing review of participant recruitment (including enrolment, withdrawals and completions), the development and oversight of study operating procedures, data management and protocol adherence.

Example text: *"A Coordinating Centre will be established to provide central coordination of study operations across all participating sites as well as operational support and oversight in areas such as: participant recruitment, study operating procedure development, data management and protocol adherence.*

9.1.3 Lead Sites for other countries

Where a multi-site study is being conducted in other countries, the study should identify a Lead Site and a Lead Principal Investigator for each country.

9.1.4 Site Study Management Group (SMG)

All studies should establish a small group at each site to oversee the day-to-day conduct of the study. This group should include the key individuals responsible for the day-to-day management of the study, such as the Study PI (single-site study) OR Site PI (multi-site study), study coordinator, research assistant, data manager, statistician etc. The group should closely review all aspects of the conduct and progress of the study and should meet regularly (informally or formally) to ensure that there is a forum for identifying and addressing issues. Particular attention should be paid to: progress towards study milestones (recruitment accrual, timelines etc); adherence to the protocol; and adherence to good research practices. Evidence of this oversight should be documented in meeting minutes, emails and documented phone calls.

Example text: *The Site PI is responsible for supervising any individual or party to whom they have delegated tasks at the study site. They must provide continuous supervision and documentation of their oversight. To meet this GCP requirement, a small group will be responsible for the day-to-day management of the study and will include at a minimum the Site PI and project manager/research nurse/study coordinator. The group will closely review all aspects of the conduct and progress of the study, ensuring that there is a forum for identifying and addressing issues. Meetings must be minuted with attendees listed, pertinent emails retained and phone calls documented.*

9.2Quality management, assurance and control

Quality Management is the overall process of establishing and ensuring the quality of processes, data, and documentation associated with clinical research activities. It encompasses both quality control (QC), and quality assurance (QA) activities. QA can be described as the process of building quality systems (i.e. implementing policies and procedures and adhering to guidelines) to prevent errors – so QA aims to be preventative. QC activities are undertaken to check for quality – their aim is detection of errors.

The Study PI (single-site study has / The Coordinating PI and Site PI have responsibilities in relation to quality management.

The <Study PI> / <Coordinating PI> should develop SOPs that identify, evaluate and control risk for all aspects of the study, e.g. study design, source data management, training, eligibility, informed consent and adverse event reporting.

In addition to study-specific SOPs and/or a Study Manual provided by the <Study PI> / <Coordinating PI>, each site (both clinical and laboratory) should implement a quality management plan using SOPs that describe:

- *Staff training methods and how such training will be tracked.*
- *How data will be evaluated for compliance with the protocol and for accuracy in relation to source documents.*
- *Who will be responsible for addressing quality assurance issues (correcting procedures that are not in compliance with protocol) and quality control issues (correcting errors in, for example, data entry).*
    - *If applicable, calibration exercises conducted prior to and during the study to train examiners and maintain acceptable intra- and inter-examiner agreement.*
- *How data and biological specimens (when applicable) will be evaluated for compliance with the protocol and for accuracy in relation to source documents, which documents are to be*

reviewed (e.g., CRFs, clinic notes, specimen tracking logs, questionnaires, audio or video recordings), who is responsible, and the frequency for reviews.

Example text (customise as needed):

"The <Study PI> / <Coordinating PI and Site PI> has/have responsibilities for quality management.

The <Study PI> / <Coordinating PI> will build quality assurance (QA) into the study by developing procedures that identify, evaluate and control risk for all aspects of the study, e.g. study design, source data management, study team training, participant eligibility, and informed consent.

The <Study PI> / <Coordinating PI> will also implement quality control (QC) procedures, which will include the checks within the data entry system; any missing data or data anomalies will be communicated to the site(s) for clarification/resolution. QC activities will also be undertaken by study monitors, who will check that the study is conducted and that data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, good clinical practice and applicable regulatory requirements.

In addition, the site/each site will perform internal QC activities to check that study conduct, data and biological specimen collection, and essential documentation is in compliance with the protocol, good clinical practice and applicable regulatory requirements. An individualised quality management plan will be developed to describe a site's quality management. "

In the event of non-compliance that significantly affects human participant protection or reliability of results, the <Study PI> / <Coordinating PI> will perform a root cause analysis and corrective and preventative action plan (CAPA).

10 STATISTICAL METHODS

*This section should be prepared in close collaboration with the study statistician. Please note that the study design should be considered in context with the planned statistical analyses to address the primary objectives. If the **design i**s not robust to begin with, it is often impossible to rescue robust findings at the **analysis** stage. The analyses can be so varied for observational studies, especially once you begin working with longitudinal data across multiple waves, and all the different types of modelling approaches. Please seek advice from your study statistician or CEBU.*

10.1 Sample Size Estimation

Specify and justify the sample size in terms of the primary objective for the study. The methods or computer program used for the determination of sample size should be documented or referenced, as should the estimates of any quantities used in the calculation. The justification normally states the following:

- *The relevant outcome measure used for calculations (almost always the primary outcome) – or the range of outcomes that the study will plan to investigate*
- *The relevant primary exposure measure used for calculations (almost always the focal exposure of interest) – or the range of exposures that the study will plan to investigate*
- *Statistical method used to calculate the sample size*
- *Assumptions used in calculations:*
    - *Assumed event rate for dichotomous outcome (or mean and standard deviation of continuous outcome), justified and referenced by historical data as much as possible*
    - *Assumed distribution of the exposure (prevalence, proportions within categories or mean and standard deviation), also justified*
    - *Assumed dropout rates, withdrawal, missing data, etc., also justified*

- *For time-to-event outcomes, the number of expected events within the planned follow-up period*

- *The values of Type I and Type II error rates and (if applicable) related considerations how to address multiplicity*
- *In diagnostic studies: expected values of measures of diagnostic accuracy (sensitivity, specificity, predictive values) as well as prevalence of the indication to be diagnosed.*

10.2 Statistical Analysis Plan

A separate statistical analysis plan (SAP) should be developed but this section of the protocol should contain the key elements of the analysis plan, describing the general methodology for dealing with the data and addressing each of the objectives. However, it does not need to be detailed by variable. The full details for each variable will be included in the SAP, which can undergo edits and versioning outside of the protocol and therefore not trigger an HREC re-review with every version or edit, as long as the key elements of the plan do not change. If there is a separate SAP, refer to the SAP in this section of the protocol.

Describe the analytical principles and statistical techniques to be employed in order to address the primary and secondary objectives, as specified in the study protocol or plan.

Detail the statistical methods planned for analysing primary and secondary outcomes.

List each outcome variable, beginning with the primary outcome, and provide for each:

- *A description of the how the data will be presented (e.g. mean, median, IQR)*
- *A description of the statistical method used for analysis*
- *Details of adjustment for covariates (if applicable)*
- *Data transformations to be used (if applicable)*
- *Methods to account for missing, unused or spurious data*

10.3 Population to be analysed

This section should be very specific in defining the participant populations whose data will be subjected to the study analyses (e.g. all enrolled participants, all participants with available data…).

10.3.1 Handling of missing data

If there is likely to be missing data it is important to outline the statistical methods planned to handle missing data (e.g., complete case analysis, multiple imputation).

10.3.2 Methods of analysis

Description of the statistical methods for the analyses of primary and secondary objectives. Be clear on the primary as well as any secondary analyses that are planned and ensure that the text is consistent with the stated objectives and the sample size section. Major features of the analysis should be outlined.

Include methods for any additional analyses that are planned of the study data (e.g. subgroup and adjusted analyses). If results of these additional analyses will be considered to be supportive/exploratory in nature or if they are an integral part of the primary analysis they need to be included here. Outline sensitivity analyses that will be performed to assess robustness of the results with respect to potential violations of assumptions for valid statistical inference.

11 ETHICS AND DISSEMINATION

All research must be approved by a Human Research Ethics Committee (HREC) and receive institutional governance authorisation via the local Research Governance Office (RGO) before it can commence. In this section, you should detail how you will seek HREC approval and RGO authorisation and how any changes to the study will be communicated to the HREC, RGO and others.

11.1 Research Ethics Approval & Local Governance Authorisation

Example text: *"This protocol and the informed consent document and any subsequent amendments will be reviewed and approved by the human research ethics committee (HREC) prior to commencing the research. A letter of protocol approval by HREC will be obtained prior to the commencement of the study, as well as approval for other study documents requiring HREC review.*

Each participating institution will also obtain institutional governance authorisation for the research and associated HREC-approved documents. A letter of authorisation will be obtained from the RGO prior to the commencement of the research at that institution. Institutional governance authorisation for any subsequent HREC-approved amendments will be obtained prior to implementation at each site.

11.2 Amendments to the protocol

Plans for communicating important protocol modifications (e.g., changes to eligibility criteria, outcomes analyses) to relevant parties (e.g., investigators, HRECs, study participants, registries, journals, regulators).

Example text: *"This study will be conducted in compliance with the current version of the protocol. Any change to the protocol document or Informed Consent Form that affects the scientific intent, study design, participant safety, or may affect a participants willingness to continue participation in the study is considered an amendment, and therefore will be written and filed as an amendment to this protocol and/or informed consent form. All such amendments will be submitted to the HREC, for approval prior to being implemented."*

11.3 Protocol deviations and serious breaches

A protocol deviation is "Any breach, divergence or departure from the requirements of Good Clinical Practice (or the clinical protocol)" (Reporting of serious breaches of good clinical practice or the protocol for trials involving therapeutic goods, NHMRC, 2018). All protocol deviations must be documented and reported to the Study PI (single site study) or Coordinating PI (multi-site study)>.

Those deviations that are deemed "likely to affect to a significant degree the rights of a participant or the reliability and robustness of the data generated…" are classed as ***Serious Breaches****. See below for the reporting requirements for serious breaches*.*

In this section, outline the process that will be followed to detect, document, report and follow-up on protocol deviations and serious breaches.

** Potential serious breaches must reported within 72 hours to the Sponsor (which in the case of campus-led investigator-initiated studies will be the Coordinating Principal Investigator at MCRI) and within 7 days to the site's Research Governance Office and approving HREC.*

- *For single-site studies, the event must be reported to, and assessed, by the Study PI (single site study) within 72 hours and reported to the Site RGO and approving HREC within 7 days>.*
- *For multi-site studies, the Sit PI must report the event to the Coordinating PI within 72 hours and to the Site RGO within 7 days. The Coordinating PI must report to the approving HREC within 7 days.*

Example text: "All protocol deviations will be recorded in the participant record (source document) and on the CRF and must be reported to the <Study PI> / <Site PI>I, who will assess for significance. Those deviations deemed to affect to a significant degree rights of a study participant or the reliability and robustness of the data generated in the clinical study will be reported as serious breaches. Reporting will be done in a timely manner:

- *<The Study PI will assess the event within 72 hours and report to the Site RGO and approving HREC within 7 days>.*

OR

- *<The Site PI will report to the Coordinating PI within 72 hours and to the Site RGO within 7 days; the Coordinating PI will review and submit to the approving HREC within 7 days>.*

Where non-compliance significantly affects human participant protection or reliability of results, a root cause analysis will be undertaken and a corrective and preventative action plan prepared.

Where protocol deviations or serious breaches identify protocol-related issues, the protocol will be reviewed and, where indicated, amended.

12 PARTICIPANT REIMBURSEMENT

If participants will be compensated or provided any incentives (e.g. vouchers, gift cards,) for study participation, describe the amount, form and timing of such compensation in relation to study activities (include financial and non-financial incentives). Describe who will receive incentives (if not the participant). For example, if minors, state whether the minor or the parent/guardian will receive the incentive. If incapacitated adults, state if payment will be provided to the participant or to a legally authorized representative or guardian.

13 FINANCIAL DISCLOSURE AND CONFLICTS OF INTEREST

Detail any financial or other competing interests for investigators for the overall study and each study site.

14 DISSEMINATION AND TRANSLATION PLAN

Plans for investigators and sponsor to communicate study results to participants, healthcare professionals, the public, and other relevant groups (e.g., via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions.
Identify who holds the primary responsibility for publication of the results of the study.

15 ADDITIONAL CONSIDERATIONS

This section should include a description of any additional considerations not currently covered in this protocol template.

16 REFERENCES

List references here

17 APPENDICES

17.1 APPENDIX 1: STROBE STATEMENT—CHECKLIST OF ITEMS THAT SHOULD BE INCLUDED IN REPORTS OF OBSERVATIONAL STUDIES

The combination STROBE checklist is provided below. For individual checklists for cohort studies, case-control studies and cross-sectional studies go to the STROBE website https://www.strobe-statement.org/index.php?id=available-checklists

The checklist should be completed in conjunction with the freely-available article "Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration" and with CEBU staff. The article discusses each checklist item and gives methodological background and published examples of transparent reporting - see https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.0040296

STROBE checklist for cohort, case-control, and cross-sectional studies (combined)

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any pre-specified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the

		number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (e.g., average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

17.2 APPENDIX 2: Specimens for biobanking - completed biobank registration form

If samples are being collected and stored for future research, include a scanned copy of the completed and signed BioBank Registration Form" in this section.*

** available on request (biobanking@mcri.edu.au) or via the RCH Research Ethics Governance website (click on the link on the Application Coversheet)*