MELBOURNE CHILDREN'S TRIAL CENTRE (MCTC)

Guidance document title: # Data collection for research: source documents and the Case Report Form (CRF)

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Contents

1. PURPOSE

To provide guidance in the procedure for data collection and data recording for all human research studies carried out at the Melbourne Children's. This includes the definition and use of source documents and the design and development of study-specific Case Report Forms (CRFs).

2. RESPONSIBILITY AND SCOPE

This guidance applies to all Melbourne Children's employees (including visiting medical officers, visiting health professionals, contractors, consultants and volunteers of The Royal Children's Hospital, Murdoch Childrens Research Institute and Department of Paediatrics University of Melbourne) who propose to undertake, administrate, review and/or govern human research involving Melbourne Children's patients and staff.

The standard applies to:

- Any human research study requiring the collection of data, in particular to studies where it is necessary to develop data collection tools.
- All research projects whether the data are collected specifically for the study or where the study uses data collected routinely as part of a hospital visit.
- All research studies including and observational and intervention studies (e.g. randomised controlled trials).

3. APPLICABILITY

The designated writer of research guidance documents and all relevant research staff.

4. PROCEDURE

4.1. Case Report Form

According to the definition provided in ICH-GCP, a Case Report Form (CRF) is:

- "a paper or electronic document designed to record all of the protocol-required information to be recorded on each participant as part of a medical study. The design of the CRF should meet the specific data requirements set out in the study protocol. In addition, basic form design concepts should be adopted regardless of the protocol. Such concepts relate to consistency in the use of reference codes, terminology and format. Standardisation will save time and errors in the design of forms and computer programs used in the data processing and statistical analysis."

A CRF should be used to document each participant's study data for all human research studies at Melbourne Children's (. This may be a paper or an electronic document and should cover all of the data required for the study as described in the protocol. The CRF should be prepared according to the criteria set out in this document.

4.2. Source Documents

Before designing a CRF it is important to know how each item of data will be collected and where it will be first recorded. Any place where the data item was recorded for the first time is known as the source document for that item of data.

The main ways for recording collected study data are:

- **Data is entered directly into the CRF and therefore the CRF acts as the source document.** As the CRF is the first place that the data are recorded, the CRF is also considered source data. Note that data items collected directly for the purpose of the study (e.g. diary cards, participant-completed questionnaires) are also considered part of the CRF. The protocol should identify the data items that are to be recorded directly into the CRF pages (i.e. where the data is not first entered to the participant's record).

- **The participant's medical or other record is the source document.** In this case, the data required for the study are recorded first in the participant's medical or other original records (e.g. hospital medical record, participant study progress notes, laboratory results, x-ray reports, ECG tracings) and then entered onto a paper or electronic CRF. The data on the CRF or in the database must be consistent with the original record. Note that medical or other records are independent of the study and may therefore lack precision, detail, documental consistency and completeness as required by the study CRF.

In practice, most studies use a combination of these two approaches, with some data recorded first into the participant's records and some data recorded directly into the CRF. It is important to specify any data items that will be recorded directly into the CRF and to list what the source document is for each item of data collected; this can be documented in, for example, a study manual or a document providing instructions on how to complete the CRF pages (often referred to as a 'CRF Completion Guide').

All source documents must be retained in a durable and retrievable form and measures must be taken to prevent accidental or premature destruction of these documents (see section 4.7).

4.3. Case Report Form creation

Individual CRF pages can be either paper (where blank forms are printed out and completed by hand) or electronic (where data is entered directly into an electronic system by either the participant or research team).

Electronic CRFs can save time as data does not need to be entered from the paper CRF to the database. They can also aid quality, as data entry errors such as out-of-range or incomplete data can be highlighted immediately and corrected. Where the CRF is web-based, this means that different sites in a multisite study can enter their own data on to a single combined database. It is useful to have a back-up system (e.g. paper CRF pages) in case of system failure during the participant's visit.

When correcting data on paper or electronic CRF pages, it is essential that there is an audit trail detailing any changes, including who made the changes and when. For electronic CRF entry, this requires a unique electronic signature or password. For more detailed guidance, contact CEBU.

For sponsored studies (i.e. commercial industry or investigator collaborations), the paper or electronic CRF will be provided by the sponsor in most cases.

When to start preparing

CRF creation can begin as soon as the final study protocol is available. The final protocol should specify all required data items. The CRF should be finalised prior to enrolling participants. It is advisable to develop the CRF in conjunction with the database, which will be used for data analysis.

How to develop the CRF

The CRF, which includes study-related scales and/or questionnaires, should be designed with input from the Principal Investigator (PI) and other members of the Study Management Group (SMG) (including the person responsible for the statistical aspects of the study) and wider study team. It is useful to seek input from the members of the team who will be collecting the study data.

It is generally useful to separate the CRF into sub-sections for each study visit so that it is clear what data collection is required for each visit. Brief instructions or suggested responses can be added to the CRF in order to guide the person filling in the CRF. For a study with more complex data collection, it is preferable to provide a separate document with detailed instructions on how to complete the CRF; this is known as a CRF manual.

Once the draft CRF document has been completed, it is recommended that the CRF designer circulate the draft to the SMG for their review (ensure the timeline for responses is clear). Once feedback has been received, the designer should finalise the CRF by integrating/modifying the CRF accordingly. The final CRF, which should include document version details (number, date), should be approved by the PI and ideally the statistician before being sent to the rest of the SMG and study team. A file copy should be filed with the study documentation.

Updating the CRF

CRF pages may need updating during the study, for example reformatting to improve data collection or the addition or modification of data items to reflect protocol amendments. CRF pages should be revised by following the process steps described for creating the initial document. The updated CRF should be reviewed by the SMG and be approved by the PI prior to being implemented. It is important to version-control the CRFs and to ensure that all study staff are using the current version of the document.

CRDO and CEBU can provide assistance with the development of CRFs.

4.4. Format of a Case Report Form

Title page (not always necessary)

This should contain the following:

- The study acronym or a shortened version of the study title and any other study information, e.g. protocol version number and date
- If not pre-printed, a space to insert the participant's unique study number assigned to them for this study.
- CRF version number and date

Instruction page for completing Case Report Form pages

Provide a list of instructions for completing CRF pages and include the items listed below. Note that these instructions refer to paper CRF pages. The instructions should be modified accordingly for completing electronic CRF pages.

- Pen: Always use a dark colour pen (e.g. black or blue ink) when writing on paper CRF pages (photocopies and scans better).
- Text: Write clearly and legibly (capital letters are often preferable).
- Identification of participant: Ensure the participant unique study identifier is clearly stated on the designated portion of each page.
- Missing/unavailable data: Do not leave any data boxes empty. If data are missing, put a single line through the blank section and add a comment stating why the item was "not available" (NA) or "not done" (ND). Any strike-throughs should be initialled and dated.
- Corrections: All entries must remain readable (this is called the "audit trail"); corrections must not obscure the original data and it must be clear who made the corrections and when. Any errors on the CRF should be corrected by drawing a single line through the incorrect value/text so that it is still legible. Write the correct value/text clearly as near

as possible to the original value. Initial and date the change. Remember - never make changes with correction fluid (e.g. “white out”).

- Dates: It is recommended that dates be recorded in the form DD/MMM/YYYY, writing the month as 3 letters (so as not to confuse the day and month with the American date format).
- Times: should be recorded using 24-hour notation (e.g.0800 for 8am).

Main body of the CRF

Each CRF page should be labelled with the CRF version details (number, date) as well as the following:

- The study acronym or a short title to identify the study (including the protocol number, and drug name where applicable).*
- If not automatically inserted, a designated space in the header of the page to document the participant‘s unique study number.*
- The visit number labelled at the top of the page*
- Space at the bottom of each page for the person entering date into the CRF to sign and date.

* Recording these details on each CRF page helps track CRF pages (e.g. in the case of separated pages).

The order of the data items in the CRF should follow the order in which the data is to be collected, except for data that is collected on ongoing logs (e.g. record of adverse events, record of concomitant medications). A standard CRF may contain the following sections:

- **Flow chart (optional)** This is useful for longer studies with a number of visits. a flow chart shows the timing of each study visit and can also list the assessments performed at each visit (per the protocol). Note that where a flow chart of events is included in the protocol, this can be included here.
- **Inclusion / exclusion criteria, including details of informed consent** This section should list the protocol-specified inclusion and exclusion criteria. This is where the researcher checks that the participant fits each inclusion criterion but does not fit any exclusion criteria. This section should also include a check that the participant and/or parent/guardian has provided consent for enrolment into the study (where applicable). Note that informed consent should be obtained before any study data are collected.
- **Screening Procedures** The data items included in this section will reflect the specific screening requirements of the protocol. They may include procedures such as the collection of blood pressure data, ECG, urine and blood samples. The CRF needs to provide adequate space for the documentation of screening results, and normal ranges for blood values where applicable.
- **Medical history / physical examination** Again, the extent of detail in these sections will reflect the type of study and the study population. For example, an observational study involving healthy participants may require little medical history or physical examination. A detailed history and examination would be needed for the study of a specific condition in a population with that condition (e.g. asthma).
- **Baseline Characteristics** Participant demographics such as, gender, height, weight (where required) and month/year of birth (note that exact birth dates may allow identification of individuals which is in conflict with the important premise of storing and processing individual study data in an anonymised way).

- **Visit pages** The pages for each visit should allow all protocol-specified procedures and assessments to be documented. The data collected at the study visits will vary greatly depending upon the type of study. Each visit should also provide opportunity to question the participant regarding any adverse events, concurrent illnesses, the use of concomitant medications, and the compliance with prescribed use of the study medication (where appropriate).

Other pages that may be required (depending on the type of study) are:

- **Randomisation details** For randomised trials there should be a page to record the details of randomisation including: the date of randomisation; the randomisation number assigned, and the details of the assigned intervention in the case of open label studies (where the assigned intervention is not concealed or 'blinded').
- **Adverse Events pages** Adverse Events (AE) may be recorded on the CRF pages for the specific study visit but are more usually collected on an AE 'log', which is a running tabulation of adverse events occurring during the study (see Appendix B for an example of an AE log).
- **Serious Adverse Events pages** Serious Adverse Events (SAEs) are usually captured in more detail on one or more detailed pages for each event, designed specifically for this purpose. Data should be collected regarding, for example, event onset, description, duration, treatment and resolution. For clinical trials, there should also be an assessment of whether the event is possibly related to the intervention (i.e. causality). Refer to the SAE form provided on the RCH Research Ethics and Governance website.
- **Concomitant medications** Where details of concomitant medications are collected throughout the study, this is generally done using a "ConMed Log" (see Appendix D for an example of a ConMed log), which is a running tabulation of drug changes during the study. Alternatively, this information can be collected as part of the form for each study visit. Whether this information is collected – and how – will again depend on the type of study.
- **End of study page** The final section of the CRF should provide an area to document details regarding the end of the individual's study follow up e.g. withdrawal prior to the participant's planned final study visit or study completion (the final participant visit for the study is often referred to as the termination visit). In case of withdrawal, a withdrawal CRF page should include space to capture the reason for withdrawal. If occurrence of adverse events led to termination of an individual's study participation, additional concluding documentation on the respective adverse events CRF forms is required. The end of the study page should refer to the CRF forms which have to be completed in conjunction with a specific type of study end. Which form(s) is/are required will depend on the study and should be determined from the protocol.

Refer to the appendices to this document for some examples of common CRF pages and also refer to sites such as the National Cancer Institute, which is part of the US National Institutes of Health. Advice on developing forms can also be obtained from CRDO or CEBU. CEBU can also provide advice on programs for CRF page generation and storage of data.

4.5. General principles for designing CRF pages

- Keep adequate amounts of free space on each page of the CRF – don't make the form too crowded.
- Ensure alignment, margins, spacing and fonts are consistent throughout the CRF.
- Include tick boxes and boxes to enter numbers where applicable. For example:

Height: ☐☐☐ cms

Have you been admitted to hospital during your current pregnancy?

Yes ☐

No ☐

- Ensure boxes for text are large enough
- Align text and boxes as much as possible.
- Include units where applicable(e.g. mm Hg, ml/L etc)
- Collect raw data rather than calculated data e.g. for age collect month and year of birth and visit date rather than age in years.
- Do not collect the same data twice e.g. month/year of birth and age at visit.
- Remember to note whether the person completing the page should "Tick all that apply" or "Select one". For example:

  Since the start of your current pregnancy have you felt depressed for two weeks or longer? (Please tick only ONE response)

  Yes, and I still feel depressed ☐
  Yes, I felt depressed a while ago but I feel better now ☐
  No, I haven't been depressed since becoming pregnant ☐

- When capturing dates, include a note of what format the date should be recorded in. For example:

  Date of birth: ☐☐ / ☐☐☐ / ☐☐☐☐ DD/MMM/YYYY (e.g. 01/JAN/2013)

- Limit the use of free text to as little as possible. For example provide a list of options where possible. If necessary you can always include an "Other" option with space to provide additional details.
- Tables can be a much clearer and more concise way of collecting data where you have repeated data in the same form. For example:

If you have been admitted to hospital during your current pregnancy, please fill in the following table:

	How many nights did you spend in hospital?	**What was the reason for your admission?** *(e.g. high blood pressure)*
First admission to hospital	☐☐ nights	
Second admission to hospital	☐☐ nights	
Third admission to hospital	☐☐ nights	
Fourth admission to hospital	☐☐ nights	

4.6. Data collection

CRF pages should be identified only by the participant's unique study identifier to maintain the participant's confidentiality. The participant's name (or other personal identifiers) must not appear on the same document. The PI should retain a confidential master list linking the participants' unique study numbers with participant names; this should be accessible only those working on study data retrieval.

Source documents should be identified by the participant's name or other personal identifiers (e.g. hospital record number) allowing the participant to be identified. Again, to maintain the participant's confidentiality the unique study identifier (assigned to the participant at study entry) should not be recorded on the source document. The exception to this is when the data is directly entered onto the CRF so that the CRF becomes the source document – in these cases the CRF should be identified by the unique study identifier.

Source data should be entered onto the paper/electronic CRF pages as soon as possible following the participant visit. The data is usually entered by a study team member to whom the PI has delegated this responsibility. Delegation of this, and any other study responsibilities, should be documented on a "Signature Log and Delegation of Duties" template (refer to CRDO research resources site).

Efficient data collection and management are essential elements of conducting a research study. Data is entered into a database in readiness for statistical analysis. However, prior to statistical analysis, the data must be validated to ensure that it accurately represents the data collected. There are various methods for ensuring data is correct. Contact CRDO or CEBU for guidance.

4.7. Data retention period

As per the RCH procedure "Investigators' Responsibilities in Research", collected health information must be retained for at least 7 years following the 18th birthday of the participant. Note that for clinical trials, data and documents should be retained for a period of 15 years following study completion (or for at least 7 years following the 18th birthday of the participant – whichever is the greater).

4.8. Documenting clinical research study participation in the medical record

Per the RCH procedure "Investigators' Responsibilities in Research", documentation of study participation should be recorded in the participant's medical record (medical progress notes) in cases where the research impacts the ongoing clinical care of the patient. See the referenced document for full details.

5. GLOSSARY

Case Report Form (CRF): A paper or electronic data collection document used in human research. It is a tool used to collect data on each study participant. The CRF consists of CRF pages.

CEBU: Clinical Epidemiology and Biostatistics Unit, Melbourne Children's

Clinical trial: Any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome.

Clinical Research Coordinator: A research worker who works at a clinical research site under the immediate direction of a Principal Investigator, whose research activities are conducted under Good

Clinical Practice guidelines. May also be called a research coordinator, study coordinator or (for clinical trials research) a clinical trial coordinator.

Concomitant medication: A concomitant medication (con-med) is a drug or biological product, other than a study drug, taken by a participant during a clinical trial.

CRDO: Clinical Research Development Office, Melbourne Children's

Good Clinical Practice (GCP): A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

International Conference on Harmonisation (ICH): International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use is a joint initiative involving both regulators and research-based industry focusing on the technical requirements for medicinal products containing new drugs.

Investigator - Principal Investigator (PI): One person is responsible for the conduct of a human research study and ensures that the study complies with GCP guidelines. If a study is conducted by a team of individuals at a study site, the Principal Investigator is the responsible leader of the team. In this instance, the PI may delegate tasks to other team members including associate investigators / sub-investigators. Delegation of any tasks by the PI must be fully documented.

Investigator - Sub or Associate Investigator: Any individual member of the human research study designated and supervised by the investigator at a study site to perform study-related procedures and/or to make important study-related decisions (e.g., associates, residents, research fellows, clinical research coordinators). The PI will designate the Associate Investigators for their study site.

Melbourne Children's: This term is used to encompass all staff from The Royal Children's Hospital, Murdoch Childrens Research Institute and Department of Paediatrics University of Melbourne who initiate or carry out research based at the RCH site under one or more of these institutional affiliations.

Source Data: Source data is the original recording of an item of data. "All information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial." (S*ection 1.51, Notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95) Annotated with TGA Comments).*

Source Document: A source document is a document in which an item of data is first recorded for the study participant. Common source documents include (but are not limited to): the patient's medical record; laboratory results and notes; radiology x-rays, scans and reports; ECGs; data recorded by automated instruments; images or photographs; pharmacy dispensing and other records; participant-completed diaries and questionnaires; and researcher-completed diaries, completed questionnaires or rating scales; and other participant-related communications.

Study protocol: A document that describes the objective(s), design, methodology, statistical considerations, and organisation of a research study.

Study Team: Refers to the extended group of people involved in a research study. This includes the investigator team and any additional members of staff who are involved in the set-up or conduct of the study e.g. research nurse, research assistants, data entry personnel, pharmacists.

Standard Operating Procedure (SOP): Detailed, written instructions to achieve uniformity of the performance of a specific function.

Study or Trial Management Group (SMG or TMG): All human research studies should establish a small group 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 PI, trial coordinator, research nurse, 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; adherence to good research practices.

Trial Steering Committee (TSC):
A TSC is an advisory committee, providing advice to the PI (and through the PI to the TMG). A TSC may be established for clinical trials that are large, complex or potentially controversial or where there is a need to include key stakeholders in oversight of the study. A TSC, which should include some member(s) who are independent of the PI and Institution, can provide expert advice. The TSC, through the TSC Chairperson, provides advice to the PI who has ultimate responsibility for the day-to-day management of the study.

6. REFERENCES

CEBU website http://www.mcri.edu.au/research/core-facilities/cebu/http://www.rch.org.au/cebu

CRDO website http://www.mcri.edu.au/research/core-facilities/clinical-research-development-office/

RCH Research Ethics and Governance website http://www.rch.org.au/ethics/

RCH SOP "Investigators' Responsibilities in Research (RCH 0498)

NHMRC National Statement on Ethical Conduct in Human Research (NHMRC, 2007 updated March 2014). http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/e72.pdf

Notes for Guidance on Good Clinical Practice (TGA, 2000) website (this is the TGA-annotated version of the international guidelines adopted for use in Australia) http://www.tga.gov.au/industry/clinical-trials-note-ich13595.htm#.VCDjK62_l9B

7. APPENDICES

7.1. Appendix A: An example of an eligibility form

7.2. Appendix B: An example of an Adverse Event log

7.3. Appendix C: An example of a Concomitant Medications log

APPENDIX A: AN EXAMPLE OF AN ELIGIBILITY FORM TO ALLOW RANDOMISATION OF AN ENROLLED PARTICIPANT

XXX Study: Eligibility Form

Please complete this form for every person who is consented /enrolled in the XXXX study to determine eligibility for randomisation.

Date assessed ☐☐/ ☐☐ / ☐☐☐☐ DD/MM/YYYY

Participant Details

ID ☐☐☐

Gender (tick): ☐ male ☐ female

Has signed informed consent been given by the patient and/or parent/legal guardian?

☐ Yes

☐ No Record reason (if provided) _____

_____

NB: Must be 'yes' for patient to be eligible

Has verbal consent been given by the patient's treating clinician?

☐ Yes

☐ No Record reason (if provided) _____

_____

NB: Must be 'yes' for patient to be eligible

Inclusion Criteria (Answer all items)

All items must be marked 'Yes' for the participant to be eligible.

	No	**Yes**
Inclusion Criteria 1	☐	☐
Inclusion Criteria 2	☐	☐

Exclusion Criteria (Answer all items)

All items must be marked 'No' for the participant to be eligible.

	No	**Yes**
Exclusion Criteria 1	☐	☐
Exclusion Criteria 2	☐	☐
Exclusion Criteria 3	☐	☐
Exclusion Criteria 4	☐	☐
Exclusion Criteria 5	☐	☐
Exclusion Criteria 6	☐	☐
Exclusion Criteria 7	☐	☐
Exclusion Criteria 8	☐	☐

Outcome

The participant is:

☐ **not eligible** for the study

☐ eligible for the study but will **not be randomised** due to other reasons. Please specify:

_____

_____

} ***Stop here.*** *Sign and submit this form.*

☐ **eligible for the Study and will be randomised**

Signature of Principal Investigator (or delegate): _____

Name: _____ Date: _____

APPENDIX B: AN EXAMPLE OF AN ADVERSE EVENT (AE) LOG

Did any Adverse Events occur during the study? ☐ **Yes** ☐ **No**

Adverse Event	Date/Time of Onset	Date/Time of Resolution	Frequency	Severity	Serious	Relation-ship	Study Agent Action	Treatment	Outcome
Diagnosis only (if known) or Signs/symptoms (list one per line)			1= Single Episode 2= Intermittent 3= Continuous	1 = Mild 2 = Moderate 3 = Severe	Yes No	1 =Not Related 2 =Possibly Related 3 =Related	1 = None 2 = Dosage decrease 3 = Interrupted 4 =Patient withdrawn 5= Drug discontinued 6 = Not applicable	Yes No *For any drug treatment (record drug on Con Med page)*	1 = Resolved 2 = Resolved with sequelae 3 = Ongoing 4 = Death 5= Unknown
					☐ Yes ☐ No			☐ Yes ☐ No	
					☐ Yes ☐ No			☐ Yes ☐ No	
					☐ Yes ☐ No			☐ Yes ☐ No	

Principal Investigator Signature: _____ Date: _____

APPENDIX C: AN EXAMPLE OF A CONCOMITANT MEDICATIONS (CONMED) LOG

Medication Therapy	Indication	For AE?	Dose				Start date	> 30 Days?	Stop date	Ongoing?	Study Team sign/date
			Amount	Unit	Route*	Frequency**					
		☐ Yes ☐ No						☐		☐	
		☐ Yes ☐ No						☐		☐	
		☐ Yes ☐ No						☐		☐	
		☐ Yes ☐ No						☐		☐	

*Route Codes:			**Frequency Codes:	
GT – Gastric	IV - Intravenous	SQ - subcutaneous	QD = 1 time daily	PRN = as needed
NG = Nasogastric	NAS = Nasal	RE - Rectal	BID = 2 times daily	BID/QOM = Twice a day every other
TO = Topical	PO - Oral	IH = Inhaled	month	
IM = Intramuscular	IN - Intranasal		TID = 3 times daily	w/meal = with meals
			QID = 4 times daily	w/snack = with snack