GUIDANCE

Title: **Guide to CRF Design & Development**

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Document History

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CONTENTS

1. PURPOSE

This guide outlines best practice for the development of electronic case report forms (eCRFs) in clinical trials.

This guideline should be used in conjunction with MCTC231 SOP | CRF Design and Development.

2. BACKGROUND

The design of the electronic CRF (eCRF) and its completion has a direct impact on the quality of the data collected during a clinical trial. A well designed eCRF:

- ensures that no essential data are missed,
- ensures that data queries are kept to a minimum,
- aids good data management practice, and
- assists with statistical analysis and reporting.

In addition, the eCRF allows the Sponsor-Investigator to verify that the protocol is being followed.

3. SCOPE

This guidance applies to all clinical trials sponsored by the Murdoch Children's Research Institute (MCRI) and is applicable to all MCRI researchers involved in clinical trials, including Sponsor-Investigators, Statisticians, Database Programmers/Developers, Data Managers, Clinical Trial Managers, Trial Coordinators, and those holding Honorary positions within MCRI.

This guide covers electronic CRFs only as used in EDC (electronic data capture) systems such as REDCap and OpenClinica.

4. GUIDANCE

4.1. Regulations and Standards

The pertinent sections from ICH E6(R3) Guideline for Good Clinical Practice include:

Section 3.1 Trial Design:

> *"The sponsor should ensure that all aspects of the trial are operationally feasible and should avoid unnecessary complexity, procedures and data collection. Protocols, data acquisition tools and other operational documents should be fit for purpose, clear, concise and consistent".*

Section 3.10 Quality Management:

> *"Quality management includes the design and implementation of efficient clinical trial protocols, including tools and procedures for trial conduct (including for data collection and management), in order to ensure the protection of participants' rights, safety and well-being and the reliability of trial results".*

Section 3.16.1 Data Handling:

> *"The sponsor should pre-specify data to be collected and the method of its collection in the protocol…The sponsor should ensure that data acquisition tools are fit for purpose and designed to capture the information required by the protocol".*

Section 4.2.1 Data Capture:

> *"At the point of data capture, automated data validation checks to raise data queries should be considered as required based on risk, and their implementation should be controlled and documented."*

In addition to E6(R3), the following standards may also inform eCRF design:

- Medicines and Healthcare products Regulatory Agency (MHRA) 'GXP' Data Integrity Guidance and Definitions
- General Principles of Software Validation; Final Guidance for Industry and FDA Staff (2002)
- The World Health Organization Technical Report Series No. 996 Annex 5 Guidance on good data and record management practices (2016)
- FDA Guidance for Industry Providing Regulatory Submissions in Electronic Format – Standardized Study Data
  European Medicines Agency (EMA) Guideline on computerised systems and electronic data in clinical trials

4.2. Data Identification and Data Definition

4.2.1. Protocol review

The protocol will dictate the data points required for the study's objectives and corresponding primary, secondary, and exploratory endpoints (although the CRF development process may identify data collection gaps in the protocol). The schedule of assessments will determine what data is expected to be collected at each sequential visit or study timepoint and will in turn guide the grouping of data fields and how they are assigned to particular CRFs.

Statistical input around features such as randomisation, blinding, and specific variables (e.g., collection of composite, surrogate, or categorical variables) may also affect the CRF design.

4.2.2. Quality checks based on Protocol

Once CRF design is complete, the following quality checks should be performed:

- All protocol-specific procedures/events pertaining to study endpoints have corresponding forms and data collection fields in the CRF
- All the procedures/events are collected in the appropriate visits/time points.
- The time points or window periods of all procedures/events are as per the protocol.
- The format of the data fields is in line with the protocol if specified. The data fields are free text only if specified in the protocol; otherwise, data fields should have protocol-specified options to select and enter the data in the CRF
- The drop-down lists/codelists/data dictionaries associated with the data fields have all the options specified in the protocol

- The names/terminologies of the laboratory/test parameters are as per the protocol specifications and applicable standards, such as MedDRA (Medical Dictionary for Regulatory Activities)), CDISC, etc. The applicable standards and/or libraries are used
- The instructions on the CRF match the protocol
- There is no duplication of data collection, i.e., there is no overlap of the same data fields between CRFs

4.3. eCRF design

4.3.1. Collect necessary data only

The protocol should clearly state which data will be collected in the study. This will include:

1. Demographic and subgroup data requirements
2. Primary/secondary/exploratory outcome data for statistical analysis
3. Relevant intercurrent event data
4. Specific safety data collection requirements and protocol deviation reporting

In addition, eCRFs may contain fields collecting data to support:

1. Administration data, particularly recording that protocol described events and procedures occurred. This data may allow for reconciliation with data that will form part of the final study dataset but is not recorded directly in the EDC system such as the recording of blood samples collected and sent to central labs for analysis.
2. Other fields to support data review and study management.

A statistician-led review of draft eCRFs to confirm they collect all data necessary for analysis is recommended.

4.3.2. Construct eCRFs with reference to existing templates

Always use institutional or globally published templates as a starting point for eCRFs where possible to guide:

1. Variable names
2. Question text
3. Prompts
4. Data type
5. Allowable values/code lists where relevant

Using standard templates, particularly those based on CDISC CDASH templates (e.g., https://www.cdisc.org/standards/foundational/cdash/library-cdash-crf-examples), will:

- Reduce eCRF development time
- Reduce site retraining and queries, and improve compliance and data quality
- Facilitate efficient monitoring, reducing queries
- Enhance traceability from eCRF to trial dataset, and contribute to eventual interoperability of data

4.3.3. Use a logical order of elements on each CRF from perspective of data entry

Group related fields for a single clinical encounter together, especially if multiple time points or visits may appear together on one form. For example, if heart rate and temperature are taken every hour for 4 hours on study day 1, the form can collect the data for hour 1 (e.g., heart rate result and unit, temperature result and unit), followed by the data for hour 2, hour 3, and hour 4. In this scenario, the CRF should clearly identify (e.g., with use of subheadings or field labels) which time point within study day 1 each data field belongs to.

4.3.4. Ensure questions and instructions are unambiguous and unbiased

CRF questions and completion instructions should be unambiguous and should not "lead" the site to answer the question in a particular way. This includes providing options for "Other" and "None" when applicable.

Order of responses (e.g., Yes/No/Unknown) should be consistent from question to question and CRF to CRF to minimise errors. Exceptions to this would be cases where a validated instrument is used (e.g., a standardized assessment questionnaire), where the instrument's format should be copied exactly.

4.3.5. Questions should be self-explanatory

CRF questions should be as self-explanatory as possible, thereby reducing the need for separate instructions.

If required, short instructions may be placed on the CRF page, especially if the prompt or question is not specific enough. More detailed instructions may be presented in a separate CRF completion guideline if necessary. All instructions should be concise.

4.3.6. Do not collect duplicate data

Collecting the same data more than once creates the opportunity for discrepancies between the entered values and requires extra reconciliation. It is better practice, for instance, to have an instruction on treatment CRFs to enter adverse reactions on AE CRFs than collect such data both in the treatment CRF and as an AE. Likewise, all end of study data (date of death/last date known alive) should be recorded in the appropriate CRFs and not in Follow-up CRFs.

4.3.7. Utilise data type and validation and range checks

Ensure that the field type selected is appropriate for the type of data being captured, and that values entered are appropriately validated (e.g. not allowing decimal values where integer values are expected). Furthermore, where feasible, apply minimum/maximum range checks to values to detect where unexpected values have been entered.

4.3.8. Avoid checkboxes if possible

"Yes/No/Unknown" responses are preferred over "Check all that apply" checkboxes, because a non-response to the former can be presumed to be missing data, whereas a checkbox where no option was selected could either mean that none of the options applied, or that the response is missing. This ambiguity could lead to a misinterpretation of critical data and can be difficult to monitor.
Exceptions to this recommendation include assessments where the majority of the options would be answered “no” (such as ECG abnormality data) or validated instruments that use checkboxes.

In cases where the sponsor chooses to use "Check all that apply" checkboxes, additional quality checks should be considered (e.g., source data verification) to ensure the data collected in the CRF are correct and complete.

4.3.9. Add “Not performed” fields

CRFs should contain an indication that a planned exam/assessment was not performed. For example, the data collection instrument/CRF could contain a field that allows the site to record an indication that a vital signs assessment was not performed (e.g., VSPERF="N").

This provides a definitive indicator that an assessment has been missed as opposed to having been overlooked and will thus reduce queries. It also, through additional fields that can be made visible on indication that an assessment did not take place, seek reasons why this occurred which may assist in monitoring protocol compliance and study management.

4.3.10.“Ongoing” fields

For events or interventions that may have start and end dates (such as Adverse Events, Concomitant Medications etc), consider adding a “Check if ongoing" field in conjunction with end date fields.

Monitoring processes should be put in place to ensure sites regularly review all ongoing events and update those that have ended.

4.3.11.Unambiguous dates

Collection of dates should use an unambiguous format, such as DD-MON-YYYY, where each part of the date is a unique format: "DD" is the day as a 2-digit numeric value; "MON" is the month as a 3-character letter abbreviation in English, or similar character abbreviation or representation in the local language; and "YYYY" is the year as a 4-digit numeric value, e.g. 29-FEB-2025. This is to prevent the possibility of errors due to different date-element ordering practices. For example, the date "06-08-02" is ambiguous because it can be interpreted as June 8, 2002, or August 6, 2002, or August 2, 2006.

If the EDC has the facility, allowing the selection of the date from a calendar is recommended.

4.3.12.24-hour clock for time

To eliminate ambiguity, times should be collected with the use of a 24-hour clock, using the hh:mm:ss format for recording times.

Use only as many of the hh:mm:ss elements as are needed for a particular field. Sites should be cautioned not to "zero-fill" time components if these are not known (for example 21:00:00 means "exactly 9 pm", but if the site does not know how many seconds after 9 PM, they should not record the seconds).

4.3.13.Manually calculated fields

Manually calculated fields should not typically be recorded within the CRF when the raw data on which the calculation is based are recorded in the CRF.

The following exceptions apply:

- When a treatment and/or study conduct decision should be made based on those calculations. In such cases, it may be useful for the calculated field to be recorded within the eCRF as this may be important to show how an investigator determined a protocol-defined endpoint from collected raw data

4.3.14.Limit free-text fields

Questions with free-text responses (i.e., with no validation checks/restrictions on the entered data) should be limited to cases of specific safety or therapeutic need in reporting or analysis, such as adverse events, concomitant medications, or medical history - generally in cases where the data will be subsequently coded. This is because processing of free text requires clinical data management (CDM) resources to review the text for safety information and for inconsistencies with other recorded data and may eventually be of limited use in analysis.

Limiting free-text also reduces time required to review data for potentially personally-identifying information (PII).

4.3.15.Standardised coding

Adverse events, medical history, and prior and concomitant medications are often coded to standard dictionaries. The Medical Dictionary for Regulatory Activities (MedDRA) and the World Health Organization Drug Dictionary (WHO-DD) are both common examples.

To facilitate coding, guidance should be given for detailed verbatim reporting of adverse events to ensure coding can be performed without further querying, e.g. “Congestion” as a verbatim term would require querying to determine if it were lung, nose, ear or other type.

Collection route, anatomical location and indication for medications, in addition to dose and frequency, may assist in coding.

4.3.16. Units

Data should be transcribed into eCRFs in the units they were reported in source documents rather than require conversion prior to data entry. CRFs should therefore be designed to allow for the selection of different units (e.g. Centigrade or Fahrenheit, mmol/L or µmol/L), with allowable ranges for entered values adjusted accordingly.

4.3.17. Translations

Translations of CRFs into other languages should be done under a controlled process by experts who understand both the study questions and the language and culture for which the CRF is being translated.

Translations may require author approval and a separate validation of the translated instrument.

4.4. Review

The CRF design process should include adequate review and approval steps, and each reviewer should be informed on the scope of the review they are expected to provide.

The review team should ideally include most of the following:

- Medical and scientific experts
    - These should provide sufficient information to ensure clinical data standards staff, subject matter experts, and clinical data management staff understand the background, context, and medical relevance of the efficacy and/or safety data.
- Clinical data management, standards subject matter experts and CRF designers
    - These should review the protocol to ensure that proposed data can be collected and should ensure that appropriate standards are used to develop the CRF.
- Statisticians
    - These should review the CRF against their planned analyses to make sure all required data will be collected in an appropriate form for those analyses.
- Clinical operations staff
    - These should review the CRF to make sure the questions are unambiguous and that requested data can be collected.
- Programmers
    - These should review the CRF to ensure that the manner in which the data are collected on the CRF is consistent with relevant metadata standards.
- Regulatory experts
    - These should review the CRF for compliance with all applicable regulations.
- Data entry staff

    - These should review the CRF to ensure that the data are collected in a form that can be entered accurately.
- Pharmacovigilance personnel
    - These should review the CRF to ensure appropriate data capture, and processes to support expedited reporting.

It is preferable that eCRFs and other data-collection instruments should be developed in conjunction with the protocol (and the first draft of the Statistical Analysis Plan, if available) so that eCRFs fully reflect the requirements of the protocol and the protocol aligns with what is operationally feasible to accurately collect via eCRFs.

5. SUPPORT

Researchers are encouraged to contact MCRI system administrators with questions or queries regarding best practice eCRF design and development:

REDCap related eCRF enquiries	REDCap CRF design assistance can be requested via the MCRI REDCap Helpdesk: https://redcap.mcri.edu.au/community/post.php?type=question&space=9
OpenClinica related eCRF enquiries	Research Teams should contact OpenClinica@mcri.edu.au for assistance with designing CRFs in OpenClinica.

6. COLLABORATORS

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7. RELATED DOCUMENTS

- MCTC195 Template | Data Management Plan
- MCTC231 SOP | Case Report Form (CRF) Design and Development
- MCTC233 SOP | OpenClinica Change Management
- SOP | REDCap Project Change Control (Clinical Trials)
- MCTC234 Template | CRF Change Version Log
- MCTC235 SOP | User Acceptance Testing (UAT)
- MCTC236 Template | User Acceptance Testing (UAT) Log
- MCTC076 Guidance | Electronic File Naming Conventions

DOCUMENT END