Standard Operating Procedure			***51.035***
Design and Development of CRFs/eCRFs in CTIMPs and Clinical Investigations			
Version	***1.0***		
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1. SOP Category

NHS GGC Sponsor R&I

2. Staff Category

R&I Research Co-coordinators
Chief Investigators
Clinical Trial Monitors
Sponsor Pharmacovigilance
Sponsor Pharmacy
Project Management
Research Governance for University of Glasgow

3. Scope

This SOP applies to all research studies subject to MHRA regulation that are not carried out in partnership with a registered data management centre/CTU. Primarily the SOP is aimed at trials explicitly capturing data centrally for the purposes of the trial, and carrying out data management processes such as data cleaning, validation, and monitoring to maintain the integrity of the trial dataset.

The SOP is also applicable where a subset of data is collected for the purposes of the trial; for instance trials with consented patients that collect baseline data and demographics but all other data is collected via routine data sets e.g., safe haven data sets, NHS Digital etc. this SOP applies only to data collected via CRF/eCRF. It is not applicable to the routine data sets.

For trials with hybrid methods of data collection i.e. where data is collected via both a CRF/eCRF and via routine data it is important to fully document the data collection process and identify where this SOP is applicable.

4. Purpose

The purpose of the SOP is to describe the processes required to design and develop CRFs for the collection of data for research in accordance with regulatory requirements. The principles detailed within are applicable whether is collected via paper or electronically. The SOP takes into account the incorporation of central monitoring elements into the design process, piloting of CRFs to ensure fitness for purpose, and the Sponsor approval process.

5. Procedures

5.1. Design of CRFs/eCRFs

The choice to collect data via paper CRFs or an eCRF must be made at the time of trial setup and be costed within the grant, including any requirements for backup paper CRFs in the event of a system failure. There are many similarities involved in the design of the two types of CRF and in the case of paper CRFs the trial database should be set up to mimic the CRF as closely as possible. Therefore similar principles apply to both mediums.

It is important to take into account the type of data collected and the CRF/eCRF requirements. Where all data is explicitly collected for the purposes of the CTIMP/CIMD then this SOP must be followed in its entirety. The SOP is not applicable for data items collected via the use of routine data sets obtained via other means.

Trial CRF/eCRFs must be designed as per the trial protocol and reflect the content within. CRF/eCRFs must be unambiguous, easy to follow; and repetition should be avoided. Each form in a CRF/eCRF must be identified by a unique number and title responding to the relevant visit, each page within a form must be numbered.

Each page of a form must detail the patient trial number, centre code, patient initials, patient DOB, the date the form was completed, and the person completing the form. If the form is a repeating form visit number should be noted in the header. For paper forms, where a wet signature is collected, the signatory must also print their name.

For forms that collect information that requires clinical review, for example eligibility or forms collecting endpoint data, the signature of the PI, printed name, and date of completion must be collected.

CRF/eCRF Forms should contain guidance information if required; particularly where data being requested is important for the trial or where there could be ambiguity or a requirement of interpretation in what is collected e.g. CT scan results, etc.

The individual questions/data items on the form must be clear and unambiguous and where possible leading questions should be used to guide the user through the form.

Questions should be written in such a manner that a response is required and there is no option to leave a field blank. If "other" is to be used as a response then a free text box is required to allow the site to enter that data. The use of free text should be minimised wherever possible.

Where defined tests or visits are mandatory within the protocol, mechanisms should be in place to capture noncompliance with these tests or visits being entered, preferably including the reason for the noncompliance. It is acceptable that this is captured as part of the data management processes rather than within the trial CRF/eCRFs if this is the preference of the CI team and agreed by the Sponsor team.

Where laboratory tests are captured the required units should be clearly stated on the CRF/eCRF, it may be helpful to include alternative comparable units where there may be ambiguity (for example ng/ml and µg/l).

5.2. Central monitoring and trial CRF/eCRFs

Where central monitoring is to be used as a means of capturing deviations from the trial protocol then this should be considered when designing the trial CRF/eCRFs. Some examples of how this may be implemented are provided below:

- Where a visit date is captured and compliance with this visit date is important for the purposes of endpoints, safety, etc then it may be better to add fields to capture reasons for non-compliance etc. For example:
    - Did the patient attend this visit? Y/N
        - If N, reason for non-attendance
        - If Y, date of visit
        - Is this visit within the protocol defined window of X days/weeks/months? Y/N
        - If N, please state the reason as to why the visit was bought forward or delayed

- Where a scan is required within a certain time period as per the protocol then similar fields can be added. For example:
    - Did the patient receive the X week MRI scan at this visit? Y/N
        - If no, please state why the scan did not take place
        - If Y, was the scan within the protocol defined period of X days/weeks/months? Y/N
        - If Y, date of visit
        - If N, please state the reason as to why the visit was bought forward or delayed

- Where a laboratory result is captured then it is useful to include a "test not performed" option. Should the test be required to determine patient safety, eligibility etc, then should this option be ticked then the reason for not carrying out that test should be captured in a free text entry.

- For eCRFs only: For trials where the IMP dosage is dependent on body weight, surface area, a lab value, or where dose banding applies it is helpful to include the data needed to calculate the dose within the same visit the dose is calculated. Any permitted dose changes from baseline that have taken place can also be captured at this time. If possible fields should be included that automatically derive the dose from relevant data to allow for comparison with the data entered by site. If doses are not permitted to change from baseline then this should have a field to compare and check baseline with what is entered by site at subsequent visits. This may not be possible, or even necessary for all trials but should be taken into account for IMPs where dosing requires close monitoring.

In most cases the above examples are useful even where central monitoring is not in place as the data captured can be used by the trial monitors to assess potential protocol deviations.

5.3. Approval of the trial CRFs

Overall responsibility for the design of the CRF/eCRF lies with the designated data manager alongside the Chief Investigator; other parties within the trial management group should be consulted throughout the design process. In particular project managers, clinical trial monitors, Sponsor pharmacy staff, and the pharmacovigilance manager should be involved in the CRF/eCRF development process from an early stage

The final CRF/eCRF design should be reviewed and signed off by the designated data manager, the CI, the trial statistician, and where involved in the design clinical trial monitors, Sponsor pharmacy, pharmacovigilance, and project management where this differs from the

designated data manager. Where other parties have been involved in the CRF design their review may be required. Where safety data and SAE forms are required for a trial the PV manager will provide the required forms and should be included in the sign off process.

It is recommended that research staff at the Cis site, particularly those responsible for entering data, carry out a review of the CRF/eCRF prior to release to other sites.

5.4. Piloting trial CRFs

It is recommended that the trial CRF/eCRFs are reviewed by members of staff who will be responsible for entering data onto the forms. For example, research nurses, clinical trial coordinators, site data managers etc. Should the wider trial team review the CRF/eCRF set they should be included in the approval process described above.

5.5. Sponsor Approval

The process to approve the use of CRF/eCRFs will follow NHS GGC SOPs. SOP Risk Assessment (SOP 51.004) will be followed to document the type of CRF/eCRF being utilised including risks and action plans associated with developing, validating and undertaking user acceptance testing. The Sponsor oversight checklist (SOP51.018) will be followed to document the CRF/eCRF has been approved prior to RGL with any agreed staged development documented.

5.6. Amendments to the trial CRF/eCRFs

Where amendments to the trial CRF/eCRFs are required, it is important that the process above is followed as per the initial design.

It is preferable that the entire set of paper CRFs for a trial all be upversioned at the same time, even where only one form has changed, to ensure the CRF document set is consistent. This allows for ease of use by investigators, and simpler implementation of amendments.

For eCRFS it is preferable that updates to the database are released in line with the approval of the related amendment. It is possible for multiple versions of an eCRF to be live simultaneously but where this is required full documentation of how this will be controlled is essential.

The trial specific risk assessment captured on Form 51.004A will be revisited and the impact of the amendment to the CRF/eCRF readiness prior to the sponsor approval of the amendment will be documented and any risks addressed.

6. Referenced documents

SOP 51.004 Risk Assessment

SOP 51.018 Sponsor Oversight Checklist

7. Related documents

N/A

8. Document History

Version	Date	Description
1.0	11/02/2022	Initial release