A Study Team's Guide to the Design and Maintenance of a Case Report Form (CRF) when setting up a Clinical Trial of an Investigational Medicinal Product

A Case Report Form (CRF), according to the ICH GCP guidelines, is 'a printed, optical, or electronic document designed to record all the protocol required information to be reported to the sponsor on each trial subject.' *ICH GCP section 1.11*

It is the tool for the collection of all clinical research data on each individual subject in a clinical trial.

When designing case report forms, do take into consideration the Data Protection Act – 1998.

http://www.bartsandthelondon.nhs.uk/research/data_protection.asp

Please take into consideration the following points below when designing the CRF for your trial. Any breach of data protection or confidentiality needs to be reported to the Research Governance and GCP Manager at the JRO who will discuss the case with the Information Governance Manager:

Patient identifiable data vs anonymised data

The definitions given below are taken from the DOH Confidentiality NHS Code of Practice November 2003, which can be downloaded from the DOH web site www.doh.gov.uk.

Patient identifiable information:	Key identifiable information includes: • patient's name, address, full post code, date of birth; • pictures, photographs, videos, audio-tapes or other images of patients; • NHS number and local patient identifiable codes; • anything else that may be used to identify a patient directly or indirectly. For example, rare diseases, drug treatments or statistical analyses which have very small numbers within a small population may allow individuals to be identified.
Anonymised Information	This is information which does not identify an individual directly, and which cannot reasonably be used to determine identity. Anonymisation requires the removal of name, address, full postcode and any other detail or combination of details that might support identification.
Pseudonymised Information	This is like anonymised information in that in the possession of the holder it cannot reasonably be used by the holder to identify an individual. However it differs in that the original provider of the information may retain a means of identifying individuals. This will often be achieved by attaching codes or other unique references to information so that the data will only be identifiable to those who have access to the key or index. Pseudonymisation allows information about the same individual to be linked in a way that true anonymisation does not.

Protocol and CRF Development

It is of the utmost importance that the information captured in the CRF matches that listed in the final version of the protocol. All the data elements/points within the CRF must support the identifiable objectives of the protocol, in the form of the primary and secondary endpoints. It should also serve to ensure the eligibility as well as the safety of the patient.

If during the study life cycle, amendments are made to the protocol that are pertinent to the data collection endpoints, there should be changes made to the CRFs to reflect this and these documents should mirror each other. Any changes that are made should be documented and version controlled and filed in the Trial Master File (TMF) and the Investigator Site File (ISF) - if the study is multi-site.

The Chief Investigator (CI) or delegate is responsible for the design and development of CRFs. The CI is also responsible for ensuring there are adequate CRFs for use in the study at all participating sites. Instructions should be given to all participating sites on how to complete the CRF to ensure data is collected in a standardised fashion and meets the data protection act. A CRF completion guide may be useful in a multi-centre study and a system to show training has been completed, for example a CRF training signature sheet. If an electronic CRF is to be used, ensure that any delegated person (s) to enter CRF data has signed a signature form/sheet to declare that their signature is the equivalent to a handwritten signature. After this signature has been obtained, the CI/study team must ensure that access rights and logins are kept securely. Please see below for example wording for signature sheets:

'By signing this agreement I confirm that the electronic signature associated with my <name of database and location ie if web hosted etc> login is the legal equivalent of my handwritten signature and should be treated as such in accordance with 21CFR Part 11(j). I shall keep my login in a safe and secure location and will not permit any other user to access the system with my user details/ login.

Name (Print) : _____

Signature : _____

Date : _____'

It is important that the CRFs **SHOULD NOT** collect any additional data that is not to be analysed or outside the requirements of the study aims.

The intention of the CRF is to collect complete and pertinent data and to ensure consistency and standardisation with regards to data collection. Therefore, it is necessary that these forms are clear, easy to use and collect the relevant information.

Source Documents and CRF Development

Source data is the information within the original records and certified copies of original records of clinical findings, observations or any other activities that have been conducted within the clinical trial that are required for the reconstruction and evaluation of the Clinical Study. The source data is located within the source documents.

Source documents are original documents, data and records. This encompasses hospital records, laboratory notes and results, pharmacy dispensing records, prescription forms, X-Rays, ECGs, subject diaries or evaluation checklists, microfilm and magnetic media, records at the laboratories.

It is important to establish which documents are to be used to provide source data for the study. This data is obviously study specific, and types of source documentation to be utilised should be detailed in at the start of the trial.

Elements to be considered in CRF Design

- CRFs **SHOULD NOT** contain any patient identifiable material – When Patients are entered/randomised onto a study, they should be allocated a code number known as the patient identifier which can include their initials alongside an allocated number generally pertaining to their entry onto the study.

- CRFs should be appropriately versioned and dated – if there are changes to be made to these documents, the version number and date should be updated accordingly, especially in the case of a protocol amendment that may lead to changes in the design of the CRFs.

- CRFs should be consistent with the protocol, as previously detailed.

- It is vital that it is documented within the site delegation log in which members of the study team have been appropriately trained with regards to their study role, including the protocol and their role requirements, including the correct completion of the CRFs.

- Avoid duplication of data collection – for example collecting the patient's age and their date of birth. Only ask for DoB if you feel this is needed.

- Avoid free text, where possible tick box options should be given. This particular option should be exhaustive – in that there should be a N/A or Other box option, when applicable. Where the 'Other' box is an appropriate option, there should allocated space for further information to be collected.

- For data points where actual values are to be captured, the number of boxes given should be adequate and if appropriate, reflect the number of decimal places desired.

- The measurement unit should be specified.

- Lab values should be detailed/referenced (with regards to units), if there are any conversions that are necessary (e.g. in multi-site studies - local lab unit of measurement variation), there should be space in which this can be completed and documented, with the original figure alongside the conversion factor.

- A study schedule/flow chart showing timelines, active treatment periods etc as per protocol should be in the CRF. There should also be included a table that details the members of the study team and their roles with regards to this element of the study. This should also encompass any back up staff with regards to illness/holidays/unavailability of staff.

- CRFs should be well aligned, and the arrangement of data fields should be clear, logical and user friendly. Consistency with regards to formatting

should also be adhered to with regards alignment, margins, spacing and fonts.

- Particular attention to the header and footer of these documents should be taken, with the study code as well as the patient number pertaining to the study to be highly visible and be considered to be a standard.

- There should be space for the person making the clinical assessment as to the patient's viability to participate within the study or/and the person who is completing the CRF to sign and date the page. This acts as verification and confirmation that the data collected is accurate.

Considerations for CRF Layout

The following guidance should be taken into consideration with regards to the appearance of the document.

- A Table of Contents is to be inserted and used as a reference for the sequential order of the CRFs with regards to ease of use.

- CRF pages should be sequentially arranged in order of patient visits.

- The data fields should be arranged to ensure that they are easy to use, clear and logical.

- Maintain consistency with the formatting. Ensure that the alignments, margins, spacing and fonts are consistent throughout the CRF.

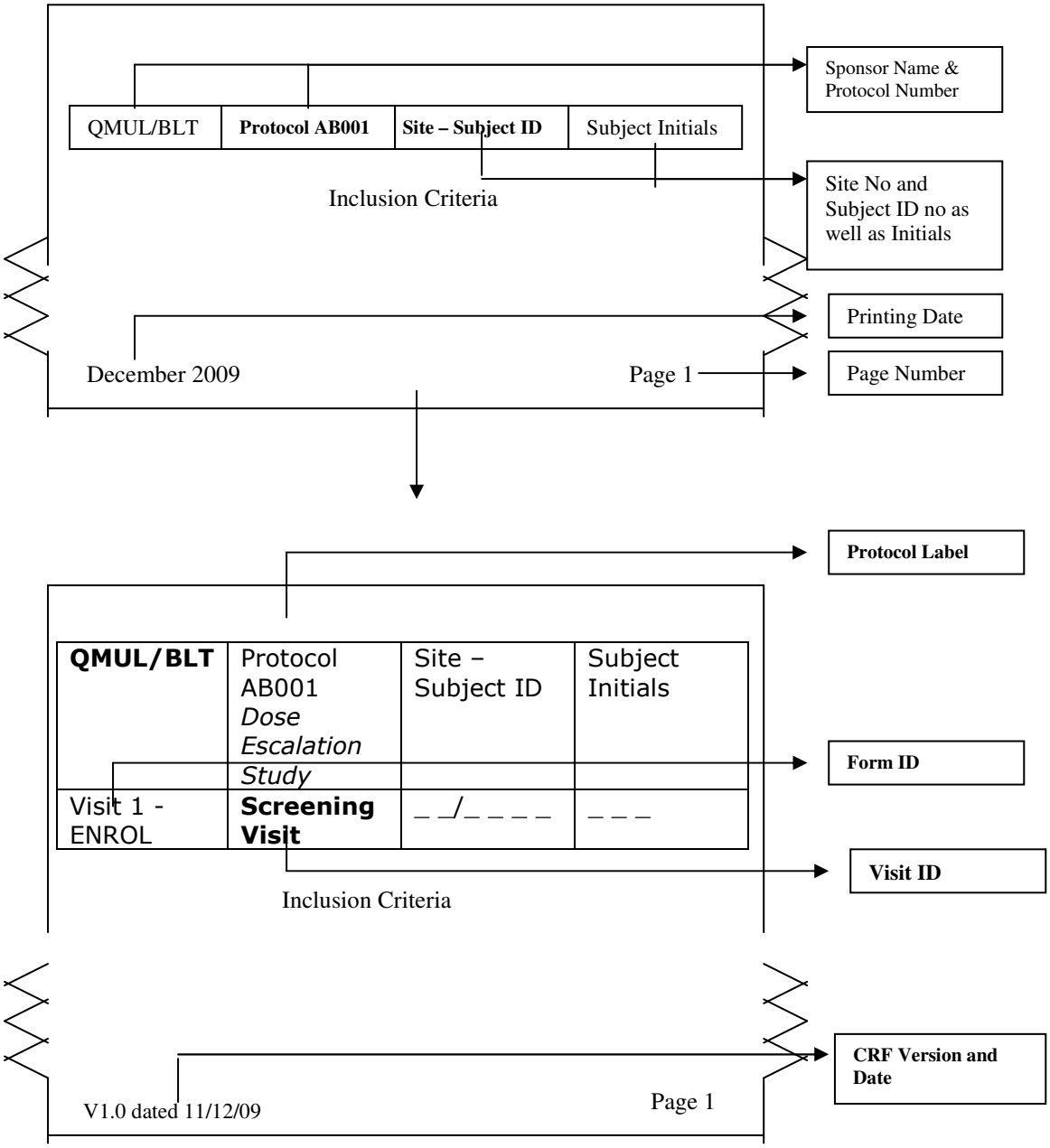
- If the pages are to be stored within a file or are to be bound into a booklet, ensure that the margins should allow enough room for this reason.

- The separation of sections using section dividers should be used to ensure clarity and be user friendly. (For example, Visit 1 section, Visit 2 section, IMP record, concomitant medications, adverse events).

- It would be beneficial to utilise No Carbon Required (NCR) paper for the CRFs as means for the original to be kept by the site whilst the additional copy could be used as a means of generating data queries during source data verification. Please see the appendix for contact details for NCR/CRF printing at BLT

- All CRF pages should be paginated, with headers and footers with the study code and participant code to be highly visible to ensure if any pages get misplaced, they can be easily reunited and all the data is recovered.

Please see the diagram below to demonstrate what would be considered to be a poorly and an improved design for header and footer design for the CRF:



It may be advisable in the case of multi-centre studies to incorporate other site specific identifiers to ensure it is known where the CRF pages have originated from, as demonstrated in the diagram above.

Data Recording on the CRFs

The CRFs should collect all the information reflected in the trial, relating to patient eligibility, treatments, outcomes, and endpoints, all of which are detailed in the protocol. It is likely that the following information is to be collected.

- Patients Initials (the first letter of the patient's forename, middle and surname constitute their initials e.g. John Edward Smith, the initials JES should be utilised. If the patient does not have a middle name, simply use a dash e.g. William Knight, the initials W-K should be utilised.)
- Date of birth or Age (age is preferable)
- Staff Initials
- Date of Informed Consent
- Inclusion/Exclusion Criteria – utilising tick boxes would be preferable.
- Patient Demographics
- Relevant Medical History
- Results of physical examination
- Baseline data as stipulated by the protocol
- Primary and Secondary Endpoints
- Dosing and Compliance data
- Date of visit
- Lab data, ECGs, etc.
- Adverse Events

Supplementary Forms to support CRFs (please see appendix for template documents for some of these forms)

These forms are required in order to support the information which is to be collected within the CRF:

- AE Reporting form
- Concomitant medication
- Medical History
- Physical Examination checklist
- Treatment Form (Doses, Toxicity)
- Withdrawal/Completed study form
- Randomisation/registration form
- End of Treatment form (end result of study)
- Death
- Relapse/recurrence
- Follow-ups

CRF Signing Off and Training

- The CRF design should be reviewed by CI, data manager (if applicable) and the statistician (if possible), before it is completely signed off.

- There should be a clear, consistent procedure for the completion of the CRF pages, this should include procedures for any amendments that need to be made to the CRFs as well as instruction for corrections. This can be provided within a training session or/and instruction to be included on the CRF pages.

- Each study is individual with its own specifications, with the responsibilities that are to be allocated to trained study members documented in the site delegation log.

CRF Completion

- There should be fixed timelines with regards to CRF completion after each subject's assessment/visit, ensuring data entry is completed on a regular basis. These timelines should be adhered to, to ensure consistent data collection, maximising completeness and accuracy throughout the life cycle of the trial. In the case of multi centre studies, copies of the CRFs should be sent to the lead site on a **regular basis** to ensure that a lack of data entry does not occur.

- Permanent ink should be used in the completion of the CRFs. It is advisable that blue or black ink is utilised so that photocopying can be carried out if necessary.

- Ensure that there are no blank spaces left. If the data at the time of completion cannot be entered, please use phrases that explain why, such as '*unknown*', '*missing*' and '*test not done'*. Please do not utilise ambiguous phrases as *'not available'.*

- Ensure that the data entered corresponds with what has been documented in the source data (e.g. Medical Records, ECG, Lab Results), and that it is accurate and legible.

- If there are notable discrepancies with the source data, there should be an explanation given in the CRF and the significance noted.

- If there are Lab values outside the laboratory's reference ranges or other range pre-identified within the study protocol, or if a value shows significant variation from one assessment to the next, the significance should be documented within the CRF along with the course of action taken.

- If a correction needs to be done, it is imperative that there is no over-write nor should correction fluid be used under any circumstances.

- Corrections if required are to be made in the following fashion:

    - Cross out the incorrect entry with a single line so that the incorrect entry is still legible
    - Enter the correct data values
    - Initial and date the correction
    - If not obvious, please give an explanation of the correction and why it was made.

- The CRFs should be kept separately from the trial master file and site files – however, there should be a file note in place within the file to document the location of storage.

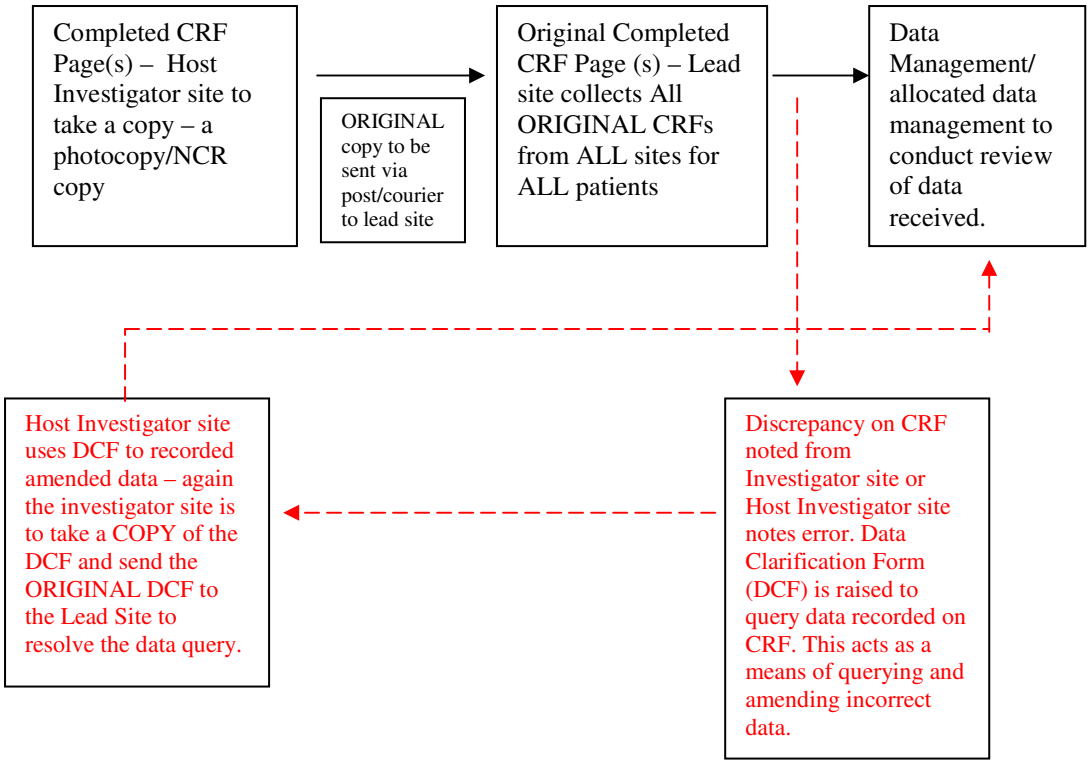
- Each set of entries made on the CRF should be signed off and dated by the trained and authorised individual completing the CRF. The Chief Investigator or the Principal Investigator (if multi-site) should then review the data entered into the CRF, validating their review with a signature and date of review on each CRF page (or at the end of each visit, but page signature is suggested) for every trial subject in their care.

- In the case of multi-centre studies, please ensure that **ALL ORIGINAL** CRFS are to be sent to the lead centre to their data management personnel for review, whilst copies are to be kept at the local sites that are

participating within the study, whether it be a photocopy or an NCR copy (non carbon copy paper).

- If the lead site becomes aware of a data discrepancy documented on the CRF the lead site can raise a query raising a **data clarification form/email/query (data query)**. This form/email/process acts as a means to request amended data to rectify the incorrect data in the CRF whilst maintaining an auditable data trail for the clinical study.

- In the case of multi centre studies, please ensure that **ALL ORIGINAL** data queries to be sent to the lead site, again to the relevant data management personnel for review, whilst copies are to be kept at the local sites that are participating within the study, whether it be a photocopy or a NCR copy. Please see the diagram below to visually demonstrate the process with regards to data collection, as previously described.



APPENDIX

- **Contact for NCR Paper**
- **CRF Templates and Supplementary Form Templates**
- **Source Data Verification Assistance**