

The Clinical Research Center Research Practice Manual



Guideline for Developing Case Report Forms (CRFs) – RPG-02

Guideline

Purpose

The purpose of this Guideline is to document CRC recommendations for the development of study Case Report Forms (CRFs). When properly designed and constructed, the CRF will minimize data collection and data entry errors, simplify database development and maximize the overall quality of data collected.

Definitions

Case Report Forms are the research instruments or tools designed to collect the data that are necessary to answer the research questions of a specific protocol.

The Good Clinical Practice (GCP) standard developed by the International Conference on Harmonization, defines Case Report Form (CRF) as ‘the printed, optical or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.’

Traditionally, CRFs are hard copy paper documents completed by trained research study staff. The data recorded on the CRFs are subsequently data entered into a study database. In the circumstances of electronic CRFs (eCRF), data may be directly entered into a study database through electronic CRF screens that mimic the hard copy CRF method. This approach is referred to as electronic data capture (EDC). Even in an EDC environment, hard copy CRFs, are required to be developed in order to serve as the blue print for database development.

Generally, data recorded on a CRF include basic subject-specific sociodemographic information such as birth date, ethnicity, race, education level; data from study specific examinations, measurements or specialty tests; data abstracted from the subject’s medical record or other source documents such as ambulatory and in-patient records, laboratory results, other tests and special procedures. Design of research surveys and questionnaires require special considerations that are addressed in the “CRC Research Practice Guideline for Developing Surveys”.

Procedure

Planning

Prior to designing the CRF, the investigator and study team should carefully review the study protocol and do the following:

1. Develop the list of variables that need to be collected. Use the research questions specified in the IRB-approved protocol to guide development of the variable list. For each research question, make a list of the specific, measurable variables that are needed to answer that question. Limit the variables included on the CRFs to those required to answer the research questions posed in the IRB-approved protocol.
2. Identify the best source for the data to be collected. For each variable listed, identify where the data will come from, i.e. the data source. It is important to assess the strengths and limitations of all data source options to determine the best data (most accurate and reliable) source for each variable. For calculated or derived study variables, document the original measurements or values on the forms and in the database, whenever they exist, and conduct the calculations during the analyses. For example, record the original measurements of height and weight and calculate BMI during the analyses.
3. Determine the timing and availability of the data to be collected. Data points that will be collected at the same time (e.g. same study visit) or from the same location (e.g. lab results from Power Chart), or available at the same time (e.g. lab results from batched runs from central labs) should be grouped together (e.g. one CRF for local lab data available within 24 hours of the visits and another CRF for central lab data available twice per year).
4. Determine the data management system. Early in the planning stage, the Principal Investigator should determine the data management system that will be employed for the study. CRF design may be significantly affected by the functionality of the data management application used. In choosing the data management system, the PI should consider the size and complexity of the study, e.g. a simple Excel spreadsheet is not a good choice for a large, complex study.
5. Determine the regulatory requirements for the study. There are CRF content and formatting conventions that will support compliance with FDA regulations if the research study is FDA regulated. Regulatory requirements should be evaluated by the PI and his or her study team to meet the FDA requirements for the specific study under consideration.

Development

Well-designed CRFs will support the goal of accuracy and completeness in data collection and compliance with human subject's protection regulations. Whenever possible, Investigators should use already existing CRFs as templates and modify as needed to create study specific CRFs. Note: CRF design standards may change depending on the data management application used.

1. Content standards

- Include a data field for the unique, confidential subject identification (ID) number on each page of every form. The CRC standard is to include a data field for the subject ID number in Section A of page 1 (as item A1) and at the top of every page thereafter. (see Attachment 1)
- NEVER use the subject's name, medical record number, or social security number as a study identifier, and never include such identifiers on the same CRF that includes other research data.
- Include a standard section at the beginning of each form and include key variables that identify the subject and the research event. The CRC routinely labels this as, "Section A. General Information," and includes the subject's unique study ID number, date of study visit or event, an event or visit code, and ID / initials of person completing the form.
- Dated signatures by a PI or their IRB approved designee on the study are necessary on some CRFs according to FDA regulations and to support best practices. These include but are not limited to CRFs that serve as source documents, CRFs that document study eligibility criteria, and any printouts of test results that also serve as CRFs.
- Include a header on the first page and include the name of the study, the form name, the assigned form number and version date of every approved CRF that was used to collect data.
- Include a standard footer on every page and include the form name, form number and page number in the footer.
- Database technology will perform best all around when the number of variables on the CRF is reasonable. The CRC recommends 100 variables or less per CRF and never more than 200. Application specific restrictions vary; refer to the database applications manual or consult with CRC staff.
- Provide variable definitions and abbreviated instructions on the CRF for proper form completion wherever applicable. Provide complete instruction in a complementary Question-by-Question CRF Completion Guide in the Study Manual of Operations (see the CRC Research Practice Guideline for Developing a Manual of Operations).

- Avoid use of unconventional abbreviations.
- Phrase questions in the positive.
- When possible, use closed-ended questions and assign numeric codes to each of the response categories. Avoid open-ended open text questions.
- Provide clear skip pattern instructions when subordinate questions are not applicable.
- List all parts of a question series on the same page, i.e., don't allow the page to break in the middle of a question leaving some response options on one page and others on a subsequent page.
- Use standard coding conventions and formats for close-ended questions across all forms in a protocol. The CRC recommends the following standards:

Standard coding conventions

Code descriptor	Numeric Code
Yes	1
No	0
Not applicable	-3*
Missing	-9*
Refusal / don't know / not recorded	-8*

* these are negative numbers

2. Formatting standards

To minimize data recording and data entry errors, consider who the end users will be when deciding about design issues such as formatting and font size.

- For paper CRFs, use adequate font size for readability. The CRC routinely uses 11 point font as a default font size; larger or smaller fonts may be appropriate in some instances to accommodate end users.

- Use adequate line spacing for easy readability to minimize data recording and data entry errors. The CRC commonly uses 1.5-line spacing.
- When possible, format the questions and responses vertically on the form so the reader's eyes will automatically "find" the next item, thus minimizing missed questions.
- Assign a number to each question and sub-question to provide a clear reference to every item on paper. Note that some data management systems may assign system question numbers in the electronic database.
- Specify the unit of measurement wherever applicable. Use metric measure wherever applicable.
- Format data fields for continuous measures so that the required level of precision (e.g. to the 2nd place to the right of the decimal) is obvious to data collectors.
- Use subsections to divide the form and organize it by topic. For example, Section A: General Information; Section B: Demographic Data; Section C: Physical Examination, etc.
- Document "dates" consistently following a standard format: MM/DD/YYYY.
- Use a table format when there is a series of questions that have the same response categories, and organize the questions in rows and responses in columns.

3. CRF Version Control

When drafting CRFs, always save the most recent version of the document with a unique version date added as an extension to the MS Word document name. Then update the version in the header and standard footer on each page of the CRF.

For example, to revise a CRF in development, open the document named, "Form1_version 10-01-09.doc" and save it as "Form1_version 10-20-09.doc". Then update the version in the header and footer to 10-20-09.

Please note: Do not use the auto-date feature in MS Word; as this feature will change the date every time the document is opened, regardless of whether a change was made to the document or not.

Ensure that all approved versions of Case Report Forms used during the study are archived with correct dates of approval.

4. QC Review for programmability

A CRC Project Manager/Research Coordinator should complete a critical review of the CRFs prior to pre-testing to evaluate the form for programmability. The Project Manager/Research Coordinator will evaluate variables and coding schemes for compatibility with the selected database application. Changes recommended by the Project Manager/Research Coordinator should be approved by the PI and the CRF should be revised prior to pre-testing.

5. Pre-Testing

CRFs should be pre-tested prior to study start-up to evaluate the logic, wording and general construction of the CRFs as well as the overall feasibility of the data collection plan and procedures. A pre-test should be completed by experienced study staff with a small number of subjects or volunteers. Ideally, those responsible for data collection will assist with pre-testing data forms. The lessons learned from such a pre-test may trigger changes to CRFs prior to database programming and study start-up when changes are more costly and cumbersome. Moreover, the overall quality of the data suffers and data analysis is more complicated when data differ across subjects or across time. A thorough pre-test will minimize costly changes required subsequent to study start up.

6. Review and Approval of Final CRFs

The last step in the CRF development process is to incorporate all the changes that resulted from the pre-test and obtain official 'sign-off' from the Principal Investigator and the study Biostatistician prior to sending CRF for database programming.

The study Principal Investigator and Biostatistician should provide an official 'sign-off' of each CRF to certify each is final and includes all variables required to answer the protocol research questions. This sign off should be provided in writing via a hard copy or electronic method. The official 'sign-off' should be maintained in the study research files. Frequently, the PI will ask all Co-Investigators, Biostatistician, the Study Project Director and/or Study Coordinator to review and 'sign-off' on all or a sub-set of the CRFs prior to providing his/her own final 'sign-off'.

While other key study staff should be included in the 'sign-off' procedures, the PI is ultimately accountable to ensure the CRFs are complete prior to forms programming and study start-up. While changes to CRFs are inevitable, compliance with 'sign-off' procedures will keep form changes to a bare minimum.

The CRC requires PI 'sign-off' of all CRFs when the CRC develops the database or will perform statistical analyses.

7. Convert CRFs to a PDF document for use in the field

If the study uses hard copy CRFs, always convert the study CRF documents to PDF documents prior to distribution to data collectors. Do not distribute the final approved CRFs as Word documents to data collectors to avoid inadvertent or intentional alterations to the approved master CRFs. Changes to CRFs should be made only by authorized persons with PI approval.

Examples of CRFs (attachment I, II, and III)

Review the Related Content below for some examples of CRFs developed by CRC staff. The CRC can provide these and many other examples of commonly used CRFs in MS Word format on request.

Acknowledgement: The following CHB staff made substantive contributions to the development of this Guideline: Qiaoli Chen, Tracy A. Antonelli, Sarah Krathwohl.

CRP SOP R02: ATTACHMENT I: EXAMPLE CRF

Form 1	Beverages And Student Health (BASH) Study Provisional Eligibility	Version 1: 09/06/2006
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SECTION A: GENERAL INFORMATION

- A1. Subject ID number: _____ - _____ - _____
- A2. Subject initials: _____
- A3. Date form completed: (MM / DD / YYYY): _____ / _____ / _____
- A4. Initials of person completing form: _____

Instructions: Information on this form is to be collected from the subject's primary care giver during the telephone screen.

SECTION B: SCREENING QUESTIONS

B1. Is your child enrolled in Grade 9 or 10 during this school year?

- Yes 1
- No..... 0 (NOT ELIGIBLE)

B2. Does your child have brothers or sisters who also received invitation letters to participate in this study?

- Yes 1
- No..... 0 (GO TO B3)

B2a. Only one child from a family can be enrolled in the study. If more than one child is interested and eligible, we must randomly choose who can participate. Are you still interested in continuing with the screening for this child?

- Yes 1
- No..... 0 (NOT ELIGIBLE)

B3. Does your child drink one or more servings a day of any sugary drink? By one serving we mean 12 ounces or about the size of a can of soda. Soda, fruit punch, lemonade, iced tea, coffee drinks, sports drinks, and energy drinks are a few examples of sugary drinks.

- Yes 1
- No..... 0

B4. Does your child live in more than one household during the school year?

- Yes 1
- No..... 0 (GO TO B5)

B4a. How often does your child reside in the second household?

B4b. *Interviewer:* Does the number of times the child resides in the second household exceed one weekend every two weeks?

- Yes 1 (NOT ELIGIBLE)
- No..... 0

Subject ID: _____ - _____ - _____

B5. How many people live in the house with your child? ____

B6. Does your child have access to a working telephone in the home where he/she lives?

Yes 1

No..... 0 (NOT ELIGIBLE)

B7. Does your child have any past or current medical problems or illnesses?

Yes 1

No..... 0 (GO TO B8)

B7a. Please describe these problems or tell us the diagnosis of his/her medical condition:

B7b. *Interviewer:* Is the condition a physical, mental, or cognitive handicap that prevents participation?

Yes 1 (NOT ELIGIBLE)

No..... 0

B8. Does your child have a medical condition known as phenylketonuria or PKU?

Yes 1 (NOT ELIGIBLE)

No..... 0

B9. Has your child ever been diagnosed with an eating disorder such as Anorexia, Bulimia, or Binge Eating Disorder?

Yes 1 (NOT ELIGIBLE)

No..... 0

B10. Is your child currently taking any medications for any reason?

Yes 1

No..... 0 (GO TO B11)

B10a. What are the names of the medications he or she takes?

B10b. *Interviewer:* Does the child take any medications that affect body weight?

Yes 1 (NOT ELIGIBLE)

No..... 0

B11. Do you plan to move out of your current school district in the next two years?

Yes 1 (NOT ELIGIBLE)

No..... 0

Subject ID: _____ - _____ - _____

SECTION C: SELF-REPORTED HEIGHT AND WEIGHT

C1. What is your child's current height?

_____ . _____ in

C2. What is your child's current weight?

_____ . _____ lbs

Interviewer: Calculate BMI and percentile: <http://apps.nccd.cdc.gov/dnpabmi/Calculator.aspx>

C3. Subject's BMI _____ . _____ kg/m²

C4. Is the subject's BMI \geq 75th percentile for age and gender?

Yes 1

No 0 (NOT ELIGIBLE)

CRP SOP R02: ATTACHMENT II: EXAMPLE CRF

Form 2	Pretend Study Baseline Infusion Record	Version 1: 10/10/2006
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SECTION D: INFUSION INFORMATION

D1. Did the patient have a change in gamma globulin product from the previous infusion?

Yes..... 1

No 0

D2. Which product did the patient receive for this infusion?

IVIG..... 1

SCIG 2

D3. Select the brand name of the drug administered at this infusion:

Carimune NF..... 1	Iveegam EN11
Flebogamma 5%..... 2	Octagam 5%12
Gamimune N 5%..... 3	Panglobulin NF13
Gamimune N 10%..... 4	Polygam S/D 5%.....14
Gamimune N S/D 5%..... 5	Polygam S/D 10%.....15
Gamimune N S/D 10%..... 6	Sandoglobulin16
Gammagard Liquid..... 7	Venoglobulin-I17
Gammagard S/D 5%..... 8	Venoglobulin-S.....18
Gammagard S/D 10%..... 9	Venoglobulin-S 5%19
Gammar-P I.V. 10	Venoglobulin-S 10%20

D4. Record the Lot Number of the product given: _____

D5. Record the concentration of the product given: ____ % weight/volume

D6. Record the maximum infusion rate: ____ mg/kg/min

D7. Record the total dose infused: ____ mg/kg

D8. Record the total infusion time: ____ : ____ (HH:MM)

SECTION E: ADVERSE EVENTS

E1. Did the patient have any significant infusion-related reactions during this infusion?

Yes..... 1

No 0 (END OF FORM)

E2. Reaction severity grade:

Mild 1

Moderate..... 2

Severe..... 3

CRP SOP R02: ATTACHMENT III: EXAMPLE CRF

Association of Anti-IgA Antibodies with Adverse Reactions to Gamma Globulin Infusion		
Form 3	Infusion Record	Version 08/15/2006

SECTION A: GENERAL INFORMATION

- A1. Subject ID number: _____
- A2. Date of Infusion (MM/DD/YYYY): ____/____/____
- A3. Initials of person completing form: _____

SECTION B: INTERCURRENT INFECTIONS

- B1. Did the patient exhibit symptoms of an intercurrent infectious illness at this infusion?
- Yes..... 1
- No..... 0

SECTION C: PRE-INFUSION MEDICATIONS

- C1. Did the patient have a change in any pre-infusion medications?
- Yes..... 1
- No..... 0
- C2. Was the patient pre-medicated with a non-steroidal anti-inflammatory drug?
- Yes..... 1
- No..... 0
- C3. Was the patient pre-medicated with an antihistamine?
- Yes..... 1
- No..... 0
- C4. Was the patient pre-medicated with an antiemetic?
- Yes..... 1
- No..... 0
- C5. Was the patient pre-medicated with a corticosteroid?
- Yes..... 1
- No..... 0
- C6. Was the patient pre-medicated with another drug?
- Yes..... 1 C6a. Specify drug: _____
- No..... 0 (GO TO SECTION D)

SECTION D: INFUSION INFORMATION

- D1. Did the patient have a change in gamma globulin product from the previous infusion?
- Yes..... 1
- No..... 0

Subject ID: _____

D2. Which product did the patient receive for this infusion?

- IVIG..... 1
- SCIG..... 2

D3. Select the brand name of the drug administered at this infusion:

- | | |
|---------------------------|----------------------------|
| Carimune NF..... 1 | Iveegam EN 12 |
| Flebogamma 5%..... 2 | Octagam 5% 13 |
| Gamimune N 5%..... 3 | Panglobulin NF..... 14 |
| Gamimune N 10%..... 4 | Polygam S/D 5%..... 15 |
| Gamimune N S/D 5%..... 5 | Polygam S/D 10%..... 16 |
| Gamimune N S/D 10%..... 6 | Sandoglobulin 17 |
| Gammagard Liquid..... 7 | Venoglobulin-I 18 |
| Gammagard S/D 5%..... 8 | Venoglobulin-S..... 19 |
| Gammagard S/D 10%..... 9 | Venoglobulin-S 5%..... 20 |
| Gammar-P I.V. 10 | Venoglobulin-S 10%..... 21 |
| Gamunex 10% 11 | Vivaglobin..... 22 |

D4. Record the Lot Number of the product given: _____

D5. Record the concentration of the product given: _____ % weight/volume

D6. Record the maximum infusion rate: _____ . _____ mg/kg/min

D7. Record the total dose infused: _____ mg/kg

D8. Record the infusion end time: _____ : _____ (HH:MM)

D9. Record the total infusion time: _____ : _____ (HH:MM)

SECTION E: ADVERSE EVENTS

E1. Did the patient have any significant infusion-related reactions during this infusion?

- Yes..... 1 (GO TO E2)
- No 0 (END OF FORM)

E2. Reaction severity grade:

- Mild 1
- Moderate..... 2
- Severe 3

E3. Reaction type:

- Acute..... 1
- Delayed..... 2

References

Document Attributes					
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Copyright	©Children’s Hospital Boston, 2011	Last Modified	08/28/2013		
Approved	<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none; vertical-align: top;"> <u>SIGNATURE ON FILE</u> Stavroula Osganian, MD, ScD, MPH Co-Chief, Clinical Research Center </td> <td style="width: 50%; border: none; vertical-align: top;"> <u>SIGNATURE ON FILE</u> Ellis Neufeld, MD, PhD Associate Chief, Division of Hematology/Oncology </td> </tr> </table>			<u>SIGNATURE ON FILE</u> Stavroula Osganian, MD, ScD, MPH Co-Chief, Clinical Research Center	<u>SIGNATURE ON FILE</u> Ellis Neufeld, MD, PhD Associate Chief, Division of Hematology/Oncology
<u>SIGNATURE ON FILE</u> Stavroula Osganian, MD, ScD, MPH Co-Chief, Clinical Research Center	<u>SIGNATURE ON FILE</u> Ellis Neufeld, MD, PhD Associate Chief, Division of Hematology/Oncology				

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