Case Report Forms

A Critical Link to the Success of Your Research Study

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Alice Bisbee, MPH
Assistant Director, Data Management
BUSPH Data Coordinating Center

Outline

1. Introduction
2. Planning
3. Which data to include
4. The anatomy of a CRF
5. How to ask the questions
6. Examples
7. Review of general design principles
8. Final thought

1. INTRODUCTION

Why is this topic important?

- Sloppy CRFs… sloppy research
- Collect too much data… or too little… or the wrong data
- Study questions can't be answered
- Annoyed Study Coordinator

What happens when you do it right?

Data will be:

- Complete
- Accurate
- Analyzable
- Answer the scientific questions

What makes a GOOD form?

1. User-friendly, uncluttered, well organized
2. Provides clear instructions for completion
3. Terminology familiar to person filling out
4. Reading level matches study participants and or evaluators

What makes a GOOD form?

continued

5. Easy for subjects/clinic staff to fill out
6. Questions only asked in one place
7. Easy to refer back and clean data
8. Assists analyst in understanding data

2. PLANNING

Decisions

- Paper vs. web
- Spreadsheets vs. database
- Self-key vs. contract out vs. scan

Create draft versions

- Allow plenty of time
- Review the drafts with your study team
  - Investigators
  - Clinical experts
  - Study Coordinator
  - Data Manager
  - Programmer
  - Statistician
  - Data collectors (RA's, interviewers, clinicians)

Example: draft #2

MEDICAL HISTORY

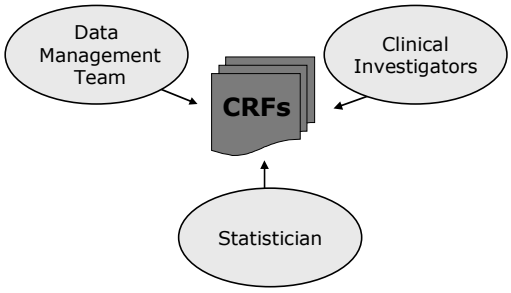
Cardiovascular Status

Documented CAD	Y,N , (MI, cath, + ETT)
Angina	Y,N , class I, II, III or IV *Canadian CVS Funct classif scale, will provide in Manual*
MI (most recent)	Y,N, date
Percutaneous Coronary Intervention	Y,N, ☐ PTCA ☐ stent ☐ DCA ☐ Rotablator ☐ TEC ☐ laser atherectomy
CABG	Y,N, specify graft _____
CVA (most recent)	Y,N, date
CHF	Y,N, NYHA class ☐ I ☐ II ☐ III ☐ IV
Echocardiogram	Y,N ☐ Dobutamine ☐ Doppler ☐ TEE ☐ other _____ Ejection fraction %_____

Example: draft #99

	Yes	No	DK	If Yes, details
1. Documented CAD	1☐	2☐	3☐	1☐ History of previous MI 2☐ catheterization 3☐ positive treadmill testing results
2. Prior MI	1☐	2☐	7☐	1☐ Occurred more than 30 days prior to enrollment 2☐ Occurred within 30 days of enrollment **Stop. Patient ineligible.**
3. Angina	1☐	2☐	7☐	Unstable angina within 30 days prior to enrollment? 1☐ Yes **Stop. Patient ineligible.** 2☐ No
4. Percutaneous Coronary Intervention	1☐	2☐	7☐	☐ PTCA ☐ stent ☐ DCA ☐ TEC ☐ Rotablator ☐ laser atherectomy
5. CABG	1☐	2☐	7☐	Specify graft: _____
6. CVA	1☐	2☐	7☐	1☐ Occurred more than 30 days prior to enrollment 2☐ Occurred within 30 days of enrollment **Stop. Patient ineligible.**
7. Congestive Heart Failure	1☐	2☐	7☐	Decompensated heart failure within 30 days prior to enrollment? 1☐ Yes **Stop. Patient ineligible.** 2☐ No

Use your study team!



Keep the User in mind

- Data collectors: logical, accurate, etc.
- Database programmers: database structures, edit checks, etc.
- Data analysts: coding, reference
- Auditors: will use CRFs to assess quality assurance
- CRFs as archival documents

Pilot Forms

- Tested by intended study population/clinicians
  - Age group (elders, teenagers)
  - Language/Literacy level
  - Clinicians: can this form be used to report results?
- All corrections made prior to start of study
- Do not start data collection prior to finalizing study forms
- Pilot the data entry process

Re-evaluate: Adjust Accordingly

- Are any items generating a high non-response rate?
  - Reword/drop question
- Is useful information being obtained from open-ended questions?
  - Categorize/code
- Are the "skip" instructions being followed correctly?
  - Train clinic personnel/revise forms

3. WHICH DATA TO INCLUDE?

CRF

- Protocol dictates data collection
- Compliance with regulatory requirements
- Designed so that in 10 years you know what happened in your study

Types of Data to Include

- Collect data listed in protocol
- Regulatory data
  - Informed consent, adverse events, …
- Administrative data
  - Sample tracking, visits missed, …
- Should not include data that won't be analyzed.
  - Clearly indicate which data will not be included in the database.

CRFs as Source Documents

- Controversial, but allowable
- Protocol must identify CRFs that are used as source documents (ICH GCP 6.4.9)

Read the protocol!

Know exactly what data need to be collected… and when.

VARIABLE	1M	3M	12M
liver function tests	☐	☐	☐
HbA1c	☐		
echocardiogram	☐		☐
concomitant medications	☐	☐	☐

Data Collection should follow the flow of the study

When →	SCREEN	ENROLL-MENT	1 M	3 M	6 M	12 M	18 M	24 M	DRUG STOPPED	OTHER
Where →	SITE	SITE	PCP	PCP	SITE	SITE	PCP	SITE		
SCREENING	4									
DEMOGRAPHICS	5									
SCREENING LABS	6									
STUDY PROGRESS					30	39		56	67	
PHYSICAL EXAM		10	20	26	32	41	51	58	69	
LABS & TESTING		12			34	43		60	71	
COMMENTS										77
ADVERSE EVENTS										78
TREATMENT DISCONTINUATION								66	66	

4. THE ANATOMY OF A CRF

Anatomy of a CRF

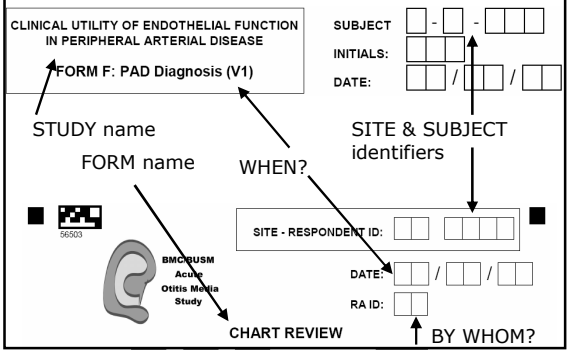
Header

Modules

- Safety Data: *demographics, AEs, medical history/physical exam, vital signs, concomitant meds, enrollment date*
- Efficacy Data: *baseline, 1° and 2° outcome variables*

Footer

Header



Subject Identifier

- The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirements (ICH GCP 2.11)
- The sponsor should use an unambiguous subject identification code that allows identification of all the data reported for each subject (ICH GCP 5.5.5)

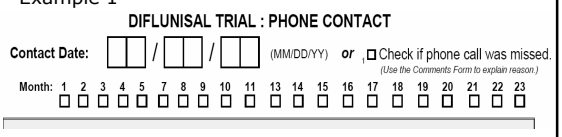
ID Assignment

- Needs to appear on every form & page
- Links paper form with specific record in database
  - Multiple forms: ID="merge key" in database
- Must be UNIQUE for each subject
- May be multi-part: 100102

1=female 001=unique subject # 02=site

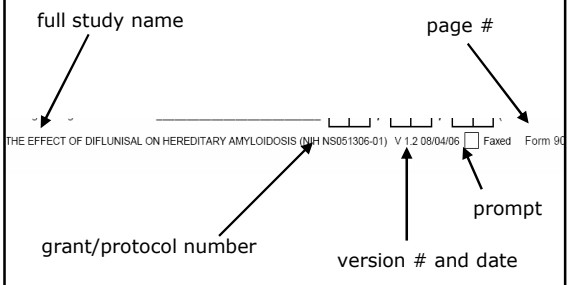
Multiple Contacts

Example 1



Example 2

Footer



5. HOW TO ASK THE QUESTIONS

Layout of Text: Visual Clarity

1. During the past 30 days, how often did pain interfere with your daily activities?
1) All of the time 3) A little of the time 4) None of the time
2) Some of the time

1. During the past 30 days, how often did pain interfere with your daily activities? (select one)

1☐ All of the time
2☐ Some of the time
3☐ A little of the time
4☐ None of the time

Avoid Open-ended & Include Response Measure

1. What is your date of birth? _____
2. How much do you weigh? _____
3. How tall are you? _____
4. Record subject's temperature ____

Unit of Measurement: Clearly Defined

1. Date of Birth? ___ __/__ __/__ __ __ __
MM DD YYYY
2. How much do you weigh? __ __ __.__ (pounds)
3. How tall are you? ___ (feet) __ __ (inches)
4. Record subject's temperature __ __ __. __ (°F)

Avoid Open Ended

Frequency

1. How often do you use an inhaler? _____

1. How often do you use an inhaler? *(Choose one.)*
1☐ QD (daily)
2☐ QAM (every AM)
3☐ BID (2x/day)
4☐ PRN (as needed)
5☐ If none of the above, how often?: _____

Include Clear Instructions

What is your race/ethnicity? **(Check one)**
1☐ Caucasian
2☐ African American/Black
3☐ Asian, Pacific Islander
4☐ Native American
5☐ Other (specify): _____

What is your race/ethnicity? **(Check all that apply)**
1☐ Caucasian
1☐ African American/Black
1☐ Asian, Pacific Islander
1☐ Native American
1☐ Other (specify): _____

Example

D2. For each immediate family member who has had cancer, please mark their relationship to you and write in the type of cancer they had.

☒ Mother ☒ Sister/Half-Sister ☐ Daughter	☐ Father ☐ Brother/Half-Brother ☐ Son	*Breast and colon* Write in type(s) of cancer
☐ Mother ☐ Sister/Half-Sister ☐ Daughter	☐ Father ☐ Brother/Half-Brother ☐ Son	Write in type(s) of cancer
☐ Mother ☐ Sister/Half-Sister ☐ Daughter	☐ Father ☐ Brother/Half-Brother ☐ Son	Write in type(s) of cancer

f. Depression ☒ Yes ☐ No → **If No, Go to g** ☐ Don't Know → **If Don't Know, Go to g**	☐ Mother ☐ Sister/Half-Sister ☐ Daughter	☒ Father ☐ Brother/Half-Brother ☒ Son
g. Chronic Fatigue Syndrome ☐ Yes ☒ No → **If No, Go to h** ☐ Don't Know → **If Don't Know, Go to h**	☐ Mother ☐ Sister/Half-Sister ☐ Daughter	☐ Father ☐ Brother/Half-Brother ☐ Son

Units

Alcoholic Beverages
Serving Sizes

A 12-ounce bottle or can of beer = 1 serving | A 1-1.5 ounce shot of liquor straight or in a mixed drink = 1 serving | a 5-ounce glass of wine = 1 serving

Keep in mind that alcoholic drinks may contain more than one serving of alcohol.

How many servings of alcoholic beverages did you drink?

	1-24 Hours Preceding Gout Attack	25-48 Hours Preceding Gout Attack
***Beer**	Please Select	Please Select
***Wine**	Please Select	Please Select
***Spirits**	Please Select	Please Select

Submit

Beverages

Use the diagrams below as a guideline for the following questions about quantity of beverages consumed. If you had a half serving please round to the nearest whole number.

Non-Alcoholic Beverages
Serving Sizes

1 cup/8 ounces = 1 serving | 20-ounce soda = 2.5 servings | 12-ounce soda = 1.5 servings

Keep in mind that typical drink containers may hold more than one serving.

General Serving Sizes

- A serving of meat or chicken is 3 oz which is about the size of a deck of cards.
- A serving of fish is about the size of a checkbook.

Remember: Typical portions may contain more than one serving.

Please fill out the chart below.

1. Did you eat any of the following animal products? If so, how many servings did you eat?

Eggs, Meat, and Fish	Serving Size	1-24 Hours Preceding Gout Attack	25-48 Hours Preceding Gout Attack
***Beef, Pork, or Bacon** (excluding liver, heart or other organ meat)	3 oz.	Please Select	Please Select
***Beef or Pork Liver or other organ meat**	3 oz.	Please Select	Please Select
***Canned Tuna Fish**	one-half can	Please Select	Please Select
***Chicken, Turkey or Duck**	3 oz.	Please Select	Please Select
***Egg** (or egg substitute)	1 large egg	Please Select	Please Select
***Selected Fish** (Anchovies, Mackerel, Salmon, Sardines, Squid)	5 oz.	Please Select	Please Select

Codes For Every Field

1. Have you been treated in the past for any of these medical problems?

Read each condition, then select Yes of No.

	Yes	No
a. High Blood Pressure	1☐	2☐
b. Heart Disease	1☐	2☐
c. Diabetes	1☐	2☐
d. Cancer	1☐	2☐
e. Lung Disease	1☐	2☐

Account For Missing Data

CBC	Unit	Value
1. Hemoglobin	g/dl	__ __.__
2. Hematocrit	%	__ __.__
3. RBC	M/mm^3	__ __.__

Revised to…

CBC	Unit	Value	
1. Hemoglobin	g/dl	__ __.__	☐ Not Done
2. Hematocrit	%	__ __.__	☐ Not Done
3. RBC	M/mm^3	__ __.__	☐ Not Done

Item In-a-Series Format: Long, wordy

1. To what extent do you consider a lack of rental housing to a problem in this community?

□ Not a problem
□ Small problem
□ Moderate problem
□ Serious problem

2. To what extent do you consider poor road and street repair to be a problem in this community?

□ Not a problem
□ Small problem
□ Moderate problem
□ Serious problem

Revised To…

1. Do you consider each of the following to be a Serious problem, Small Problem, or Not A problem in this community? (Please check one answer for each)

	Serious Problem	Moderate Problem	Small Problem	Not A Problem
a. A lack of rental housing	□	□	□	□
b. Poor road and street repair	□	□	□	□

Always Consider the "Other" Category

1. Major admitting diagnoses **(Check all that apply)**
   a. ☐ Post Operative
   b. ☐ Trauma
   c. ☐ Neurological
   d. ☐ Cardiovascular
   e. ☐ Respiratory
   f. ☐ Other _____

Inclusion of "OTHER"

- Might cut down on items left blank
- Position "Other" last in list of possible responses
  - Ensures all anticipated responses considered 1st
- Continue to monitor "Other"
  - Was common response category overlooked?

Missing Responses

What level of precision is needed?

Unknown
Not Available
Not Applicable
Not Done
Refuse

→ Without it, left blank or respondent guesses

→ With it, provides a means of opting out

Illustrate Skip Patterns

15. Do you work out every day?

□ Yes (Go to Q.16) □ No (Go to Q.18)

16. About how many minutes per day do you workout?

___ ___ ___ minutes per day

15. Do you work out every day?
□ No (Skip to Q.18)
□ Yes

16. About how many minutes per day do you workout?
___ ___ ___ minutes per day

"Skip to Question 18" NOT "Skip questions 16 and 17."

When Open Ended Cannot Be Avoided:

- Check data as it comes in
- Create new categories where appropriate
- Re-evaluate continuously
- May require new versions of forms

Coding Manuals: Open Ended

1. In what country were you born (check one)?
   - ☐ USA
   - ☐ Guatamala
   - ☐ Mexico
   - ☐ Dominican Republic
   - ☐ Other ☐

Coding Manuals: Open Ended

1. After 10-20 forms completed, compile list of open-ended responses to open-ended question
2. Group into common themes, categories (e.g., countries)
3. Assign numeric code to each of these categories to create a "coding scheme" or codebook

6. EXAMPLES

Anatomy of a CRF

Header

Modules

- Demographics
- Screening / IC
- Adverse events
- Labs
- Medical history
- Medications
- Procedures
- Signatures
- Study completion
- Discontinuation

Footer

Demographics

1. Gender: ☐ Male ☐ Female

2. DOB: ☐☐ / ☐☐ / ☐☐☐☐ (MM/DD/YY)

3. Ethnicity: Is the patient of Hispanic (Latino/Mexican/Puerto Rican/ Central or South American) origin or descent?

   ☐ No, not Hispanic ☐ Yes, Hispanic ☐ Don't Know / No Response

4. Race (*check all that apply*)

   ☐ American Indian/Alaskan Native ☐ White
   ☐ Asian ☐ Other (Specify) _____
   ☐ Black ☐ Don't Know / No Response
   ☐ Native Hawaiian or other Pacific Islander

Screening

59082

Eligibility Form SITE:

Any shaded item disqualifies a patient for the study. RA ID:

Date: / /

☐ Check if no patients were screened on this date.	1		2		3		4		5	
	Y	N	Y	N	Y	N	Y	N	Y	N
Has this child ever been enrolled in the ☐ study? *(If Yes, use the flow chart to ascertain the next enrollment procedure.)*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
1 Are you this child's legal guardian?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
2 Was the child diagnosed with ☐ today?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Screening Date: / / (MM/DD/YY)

INCLUSION CRITERIA		
1. Age ≥ 18 and ≤ 75 years?	1☐ Yes	2☐ No
2. Congo Red stain-proven amyloid deposition?	1☐ Yes	2☐ No
3. Genotyping of variant TTR?	1☐ Yes	2☐ No
4. Signs of mild/moderate peripheral or autonomic neuropathy?	1☐ Yes	2☐ No
5. Performance status ≤ 3?	1☐ Yes	2☐ No
6. Negative HCG testing and contraception for sexually active women of child-bearing potential? (Record test results on lab form.)	1☐ Yes	2☐ No / 3☐ NA
*If NO to any of the Inclusion Criteria listed, this patient is **INELIGIBLE** to participate in this study.*		
EXCLUSION CRITERIA		
7. Use of non-study NSAIDs?	1☐ Yes	2☐ No
17. Thrombocytopenia (platelets < 100,000/mm³)?	1☐ Yes	2☐ No
18. Previously participated in this study?	1☐ Yes	2☐ No
*If YES to any of the Exclusion Criteria listed, this patient is **INELIGIBLE** to participate in this study.*		

Result of Screening: ☐ Eligible, enrolled 2☐ Eligible, refused 3☐ Ineligible

Enrollment Date (date of prescription): / /

Date patient notified: / /

Has the patient SIGNED and DATED the Consent Form? 1☐ Yes 2☐ No*

*If No, study activities must NOT start.

Informed Consent

date time

F. Was Informed Consent Obtained?

☐1 Yes: Date: / / Time: :

→ Draw baseline labs and if applicable, serum HCG. Continue with section G.

☐2 No: Give reason informed consent was not obtained (check one).

☐1 1. Patient/representative refused

☐2 2. Not approached: patient is a participant of another clinical trial

☐3 3. Not approached: social/logistical reasons

☐4 4. Not approached: other: _____

→ **Stop here.** Patient is ineligible.

Signatures

I, _____ have seen and reviewed these data.
Print name and study title

Investigator signature and date: _____ / / (MM/DD/YY)

signature date

E. I certify that I have reviewed the Case Report Forms for this study participant, and find the data to be complete and accurate, as of the date below. I also certify that all treatment-emergent adverse events for this study participant have been resolved or a stable clinical end-point has been reached.

_____ / / /
Investigator's signature Date (mm/dd/yy)

_____
Investigator's PRINTED name

Physical

BODY HEIGHT & WEIGHT				
1. Body weight:	. kg	*or*	lb	oz
2. Body height:	. cm	*or*	.	inches

VITAL SIGNS/ORTHOSTATIC BLOOD PRESSURE (BP)			
Position	**Blood Pressure (mm Hg)**		**Pulse Rate**
3. **Supine**	Systolic / Diastolic		bpm
4. **Standing** after 3 minutes upright	Systolic / Diastolic		bpm

1☐ Measurement not performed; patient unable to stand.

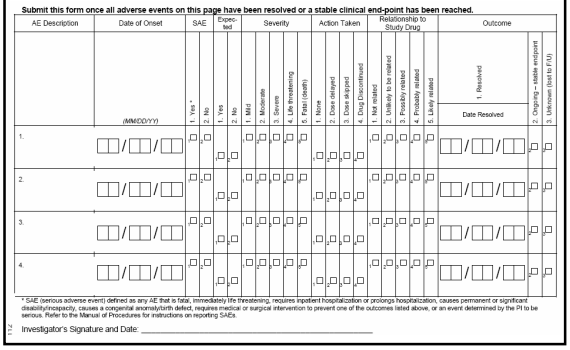
Labs

1. Specimen / Draw Date: / / (MM/DD/YY)

LABS & TESTING	VALUE OBTAINED	UNITS **	Not Done
2. BUN		mg/dL	1☐
3. Hemoglobin	.	g/dL	1☐
4. Hematocrit	.	%	1☐
5. WBC	.	K/uL	1☐
6. Serum Albumin	.	g/dL	1☐
7. BNP		pg/ml	1☐
8. HbA1C	.	%	1☐
9. Beta-HCG	1☐ Positive 2☐ Negative		1☐

*** If any units differ from those stated, check this box and correct the units above.* 1☐

Adverse Events



Submit this form once all adverse events on this page have been resolved or a stable clinical end-point has been reached.

AE Description	Date of Onset (MM/DD/YY)	SAE	Expec-ted	Severity					Action Taken					Relationship to Study Drug					Outcome		
		1. Yes * 2. No	1. Yes 2. No	1. Mild	2. Moderate	3. Severe	4. Life threatening	5. Fatal (death)	1. None	2. Dose delayed	3. Dose adjusted	4. Drug Discontinued		1. Not related	2. Unlikely to be related	3. Possibly related	4. Probably related	5. Likely related	1. Resolved Date Resolved	2. Ongoing – stable endpoint	3. Unknown (date for F/U)
1.	/ /																		/ /		
2.	/ /																		/ /		
3.	/ /																		/ /		
4.	/ /																		/ /		

* SAE (serious adverse event) defined as any AE that is fatal, immediately life threatening, requires inpatient hospitalization or prolongs hospitalization, causes permanent or significant disability/incapacity, causes a congenital anomaly/birth defect, requires medical or surgical intervention to prevent one of the outcomes listed above, or an event determined by the PI to be serious. Refer to the Manual of Procedures for instructions on reporting SAEs.

1.1.2

Investigator's Signature and Date: _____

Comments Form

Date Recorded: ☐☐ / ☐☐ / ☐☐ (MM/DD/YY)

TO BE RECORDED BY THE INVESTIGATOR OR DESIGNEE

This page should be used to provide additional information, clarification concerning the patient, or explanation for protocol deviations.

Contact Date (MM/DD/YY)	Page Number	COMMENTS	Initials	Date (MM/DD/YY)

7. REVIEW OF GENERAL DESIGN PRINCIPLES

Review of design principles #1

- Modular design
- Follow the flow of the treatment schedule of the protocol
- Define the data entry (units)
- Data entry instructions/tips (supplementary documentation?)
- One page forms
- Subject identifiers on every page

Review of design principles #2

- Ask questions in only one place
- Ways to opt out: none / not done / NA
- Instructions ('see protocol' vs. most recent HCT $\geq$ 38%)
- One form per contact
- Consistent coding; coding marks

Review of design principles #3

- Uses data entry boxes as visual clues
- Use italics for instructions (& bolding)
- Avoid free text
- Skip patterns:
  - Don't use *"Skip question X"*
  - Use *"Skip to question Y"*
- Be consistent in positioning data entry fields

8. FINAL THOUGHT

"Perfection is attained by slow degrees;

it requires the hand of time."

- Voltaire