Guidelines for Assuring Quality in Clinical Research – RPG-12

Guideline

Purpose

During the conduct of clinical research, there can be various sources of human or measurement error, such as inaccurate collection of data, inaccurate transcription or transfer of data including data entry errors, misinterpretation, and measurement instrument error or limitations as well as potential falsification of data. Therefore, every study must include systems to avoid or minimize errors and ensure the integrity of the study.

The purpose of this guideline is to assist investigators in developing and implementing quality systems that will promote the conduct of high quality clinical research. Such quality control and assurance systems provide a checks and examinations that help ensure the quality of clinical research studies. **Note:** This guide is not meant to be exhaustive and each PI must ensure that they are aware of and implement procedures that may be required by their specific study, funding agency, regulatory agency or the institution.

Procedure

The principal investigator is ultimately responsible for developing and overseeing the implementation of a quality plan for their study and ensuring that their study is implemented according to the study protocol as well as any relevant federal or state regulations, institutional policies, and study specific standard operating procedures. This should include proactive measures that are taken to ensure study quality during the planning and development phases, having regular quality assurance activities and checks during the implementation of the study, and having thorough and systematic data-cleaning activities and the conduct of appropriate statistical analyses to support the validity of the findings at the end of the study.

The investigator should engage all appropriate and qualified individuals to assist him or her in writing the study protocol and developing the quality plan and consult with the CHB Education and Quality Improvement Program (EQuIP) for guidance on regulatory related procedures and documentation.

Study Protocol

A well-written protocol is the foundation of good science and should be carefully and thoughtfully developed by every principal investigator. The protocol specifies the research questions and the study design, methods and analyses required to validly answer the research questions and ensure the safety and welfare of research participants. The protocol is reviewed and approved by the Scientific Review Committee and the Institutional Review

© Children's Hospital Boston, 2014 All rights reserved

Board. Where applicable, the protocol is filed with the Food and Drug Administration (FDA). Any changes or amendments to the protocol during the study must be submitted to the IRB for review and approval. Every study should be implemented according to the most recent version of the IRB approved protocol and study compliance should be measured against the approved protocol as well as any study specific Standard Operating Procedures and procedures documents in the study Manual of Operation.

Study Manuals of Operations

The Study Manual of Operations (MOO) is a tool used to ensure accurate and standard implementation of the protocol. The MOO is used for staff training and serves as the guide for study staff on will conduct study procedures. When standard procedures are provided to staff in written form, and kept current through updates as amendments and clarifications are made, the Investigator is better able to guarantee standard implementation for all study procedures across data collectors, across teams, and over time.

Case Report Forms and Form Completion Instructions

The study case report forms (CRF), hard copy or electronic case report forms (eCRF) capture the data and variables needed to answer the research questions in a format that can be entered into the study database. Variables captured on the CRFs should be outlined in the research objectives documented in the IRB approved protocol. Corresponding form completion instructions to ensure consistent documentation and interpretation across data collectors should be included in the MOO and on the forms where applicable. Principal Investigator sign off of final drafts of CRFs provides an important quality control check that the variables required to answer the research questions are included in the study database.

Staff Roles and Responsibilities

While the PI may delegate specific duties to other investigators and/or study staff, the PI is ultimately responsible to ensure study staff is duly qualified, trained, and competent to implement study activities and comply with all applicable regulatory requirements. As such, it is important to clearly define staff roles and responsibilities; conduct start-up training in the protocol, interventions and measures; and establish reliable systems for study and staff communications.

To assure for clarity in responsibilities delegated to study staff, the PI should maintain a current list of all study staff to whom s/he has delegated study specific responsibilities. A complete list would include staff names, qualifications, assigned responsibilities, and relevant contact information. Contact information might include any or all of the following: name, title, study-specific responsibilities, and telephone number. As needed, the list might also include the staff person's page number, fax number, mailing address, and back-up contact person if unavailable. The list should be, i) distributed to all involved parties, ii) easily accessible and iii) kept current when information or responsibilities change.

Research Team Communications

Team Meetings

Study staff should meet routinely to establish priorities, track progress and re-organize when established plans are ineffective. Evidence of a well-organized communications system includes meeting agendas distributed to all team members in advance of the meeting and meeting minutes including a list of attendees, discussion items, decisions made, and action items required with corresponding due dates and person responsible. The PI should chair the meeting or delegate responsibility for meeting chair and recorder. Minutes should be

© Children's Hospital Boston, 2014 All rights reserved

distributed soon after each meeting and maintained in an easily accessible hard copy or electronic study binder or file.

In general, team meetings are needed more frequently during the planning and early implementation phases (e.g. weekly). Although the frequency of team meetings might diminish once study activities become fully established, it is prudent to maintain the habit of a regular team meeting, even if meetings are brief.

Notification of protocol amendments and clarifications

There are several strategies an Investigator can employ to ensure that all study staff are up to date on all study procedures. Common methods include:

Mandatory attendance at regularly scheduled team meetings followed by distribution of minutes including announcements, decisions made, with due dates and specification of responsible parties. Some studies require sign in sheets for meetings.

Distribution of 'Communications Memos', 'Operations Memos' or 'Memos To File' to announce protocol or procedural amendments or modifications. Some studies require staff send an electronic confirmation of receipt or sign a hard copy of such memos. See the EQuIP website for a template for a Memo to File.

Training and certification of research staff

All study staff should receive training on the study protocol and special tests and procedures and demonstrate competencies for same. One of the most important activities that ensure standard implementation of study procedures across all study staff is staff training at start-up. Ideally, all members of the study team (PI, Co-Investigators, Research Nurses, Study Coordinators, intervention and evaluation staff, data managers, and data entry clerks) will participate in a training program at the time of study start-up to review and discuss all study procedures including study design, intervention/treatment procedures, evaluation measurements and standards, CRF completion, reconciliation of data recording errors, data cleaning and data management procedures. Individualized (break-out) training sessions may be offered for intervention and evaluation staff as these teams may be blinded to selected components of the protocol. As required, study-specific randomization and blinding procedures should also be covered thoroughly in the training.

Training sessions are customarily offered as didactic review and discussion of the study protocol with special attention devoted to the science of the treatments, and the primary and secondary outcome measures. Training should also include a review of all treatment and evaluation procedures including a thorough review of related CRFs, surveys and form completion guides. Whenever possible, training may include demonstrations and practice sessions as a means to establish staff competencies in performance of novel and complex interventions and measurements, in addition to those pertaining to primary outcomes. Videotapes may be used to augment study trainings. Baseline training concludes with staff certification. Certification might include return demonstration sessions to document staff meet minimum competencies in study procedures prior to study start up or a short test to demonstrate acceptable levels of knowledge. Minimum standards should be established a priori to evaluate staff performance during return demonstrations.

It is important to maintain evidence of trainings, staff competencies, and staff attendance at team meetings. Staffs are often required to sign and date attendance logs and training logs that are maintained in the study file or study binders.

© Children's Hospital Boston, 2014 All rights reserved

Study staff that joins the study team after start-up should also complete training and certify they meet minimum standards prior to completing interventions or measurements under the protocol.

At least annual re-training and/or re-certification is also recommended to minimize drift away from prescribed study procedures.

Documentation of staff contacts with study subjects

Staff should keep a record of all contacts with study subjects in addition to signed informed consent documentation, completed CRFs and subject completed questionnaire or survey. The location of where study documentation is kept will be study specific. The Principal Investigator should propose the location for storage of study documentation; the IRB will approve the location or make an alternate recommendation. Ultimately, the study informed consent will disclose where such research documentation will be filed. The Investigator should review all documentation procedures with study staff prior to start up. Locations might include: the CHB Medical Record, a Study Specific Worksheet, a study specific research file, study contact record log or progress note, and/or study specific visit log or checklist

Important Note: The IRB may restrict documentation of study events in the CHB medical record for some studies where additional confidentiality has been promised to the subject. Be certain to verify where such notes should be made prior to documentation in the subject's medical record as once documentation is made in a medical record, it cannot be deleted.

Selection, maintenance and calibration of equipment

If equipment is required to conduct measurements for the study, staff should choose equipment based on a thorough review of the literature and equipment selected should last the duration of the study. Equipment should be stored in a protected location to prevent damage and/or theft. A qualified staff person should be assigned responsibility for storage, maintenance and calibration of the equipment. The same person may be responsible for conducting all measurements using that equipment or for training all others who will conduct the measures. If more than one piece of the same type of equipment is used in the investigation, each should be assigned a unique study number and labeled with the number affixed to the equipment, and equipment should be registered in a central file. The ID # of the equipment used to complete the measurement should be documented on the study CRF along with the actual measurement value. The equipment should be calibrated by study staff regularly and Calibration Logs should be maintained for each instrument as evidence that the calibrations were completed. The staff person completing the calibrations should record notes in the Log describing the procedures followed and sign and date the Calibration Log. Some equipment will require checks of other critical functions, e.g. scheduled temperature checks of refrigerators and freezers; routine accuracy checks of scales using standard weights and measures, etc. Logs should be maintained of all checks made including calibration checks completed, breakdown and misuse events, servicing by manufacturer or others, along with signatures and dates.

Study specific procedures for use and care of equipment should be developed and kept in the MOO. The procedure should describe procedures for the care and maintenance of the equipment. The manufacturer's instruction manual should be included in the MOO for easy reference throughout the terms of the study.

© Children's Hospital Boston, 2014 All rights reserved

Selection of database technology and creation of the database

Careful consideration should be given to the selection of the database technology planned for use in the study. Factors to be considered include the volume of data, the complexity of the visit protocol, whether the study is longitudinal, and whether FDA regulatory requirements must be met. Quality of the data can be enhanced by using tools that can monitor data quality at the time of data entry and generate edit queries and reports that can monitor compliance with the study protocol. See the DOC Core section of the CRC website for more information about database and web-survey technologies available at Children's.

Document Organization and Storage

Study staff should maintain a well-organized documentation of all official study documents (approved protocols, manuals, forms, communications, etc.) in hard copy format or electronically in a study specific ring binder, lateral file and/or electronic folders on departmental shared drives. More recently, some CHB Investigators are establishing CHB intranet SharePoint sites to store study reference documents for easy access by all study staff across departments and divisions. See the EQuIP web site for additional guidance regarding clinical research file and document management as well as the recommendations for the content of the Regulatory Binder that is required for FDA regulated trials.

Each study should maintain a well-organized folder on each study subject that includes all the hard copy case report forms and data collected on the subject but with no names or other identifiers in the file. Informed Consents and study ID logs should be maintained in separate locked file cabinets. All files should be stored in secure locations and locked cabinets that are only accessible to authorized study personnel.

Completion of CRFs, data entry and edit resolution

Careful completion of study case report forms is essential for accurate and complete data. Hard copy CRFs or eCRFs should be completed as soon as possible following the study event and/or completion of the intervention or measurement. Codes should be legible and notes should be added for all missing and out-of-range values. All data recorded on case report forms, surveys or questionnaires should be reviewed for completeness and clarity by the person abstracting the data from the source prior to data entry. CRFs should be presented for data entry and errors or omissions should be resolved by the original person who transcribed that case history. Corrections to codes must not obscure the original recordings. Original recordings must never be erased or obscured with a white out. A chief tenant of good data management is "Seven Days to Clean Data", which recommends data should be recorded, entered into the master database and all edits and queries resolved within 7 days from the date a measurement is made or an intervention conducted.

Routine Study and Data Monitoring

The PI should conduct routine monitoring of study implementation activities that are objective, standardized and written (e.g. develop a QC Checklist to be used). Whether monitoring is conducted by the PI along with his or her study staff or an invited independent monitor, monitoring procedures should mimic what an EQuIP quality review or an FDA audit would entail where applicable. The FDA publishes guidance on what to expect from an FDA inspection. See their publication, "Information Sheet Guidance for IRBs, Clinical Investigators and Sponsors, FDA Inspections of Clinical Investigators" as well as a field guide for FDA auditors to conduct inspections, "Compliance Program Guidance Manual Chapter 48- Bioresearch Monitoring Clinical Investigator and Sponsor-Investigators". Routine monitoring conducted by the PI may be sufficient for studies not regulated by the

© Children's Hospital Boston, 2014 All rights reserved

FDA. Investigators who hold their own IND/IDE must arrange for regular independent monitoring of studies. EQuIP staff may serve as independent monitors on arrangement. Monitoring should essentially ensure that study procedures comply with the IRB approved version of the study protocol (which should also be on file with the FDA where applicable), study specific SOP's and any relevant regulations. All or a randomly selected sample of subjects' study documents should be periodically reviewed during the study to verify the following where relevant and other items as appropriate to the particular study:

- Human subjects protections regulations
- Eligibility criteria are met
- Informed consents are present and signed
- Randomization and blinding procedures are strictly adhered to
- Data recorded on CRFs/eCRFs match data in source documents
- Routine safety monitoring is conducted and safety labs are evaluated
- Adverse events are reported in accordance with applicable regulations and institutional policies
- Subjects visits fall within the visit windows in the protocol/manual of operations
- Compliance with prescribed study procedures or SOP's for intervention and evaluation activities.
- Drug accountability and storage

In some cases, regular data management and central monitoring can be used to monitor protocol compliance for trials using Electronic Data Capture Databases especially for multicenter trials where the IND/IDE holder is in charge of monitoring protocol compliance and safety. See "Risk-Based Approach to Monitoring" for more information on using data management and statistical analyses for quality control during the conduct of the study.

In addition to the direct monitoring of study activities, the PI and research team should develop and regularly review data quality reports (see Attachments as Example). (Note: Such reports should be designed so as not to jeopardize unblinding for Blinded Trials). These reports may include but are not limited to reports on:

- Status of screening, recruitment, study drop outs, terminations or losses to follow-up
- Visit window compliance
- Status of expected case report forms and other files of tests or procedures such as electronic images, and/or stored specimens
- Missing Data Rates by Form
- Distributions and Outliers
- Safety Lab Results
- Reports on QC procedures related to data management

Many of these central monitoring systems can be done through use of appropriate data management technology and a qualified data manger. Please see the FDA guidance document on "Risk-Based Approach to Monitoring" for more information.

Data Cleaning and Statistical Analyses

All studies should 1) have systematic data preparation including data cleaning; inspection of data for outliers or obviously miscoded values; and examination of specific data elements for inconsistencies e.g. measurements that show a loss in height over time; 2) develop and document timelines and standardized procedures for database locking/unlocking; 3)

© Children's Hospital Boston, 2014 All rights reserved

procedures for safety/efficacy analyses, reporting of analyses to the study DSMB, and standardized procedures for planned or unexpected unblinding; and 4) procedures for documenting statistical programs so that the analyses and results may be readily replicated by an independent programmer. Statistical analyses should be conducted in accordance with the methods proposed in the IRB approved protocol.

Related Content

Sample Study Reports

(Reported for data collected and entered as of 11/29/11)

Table 1. Summary of Screening and Enrollment (target =70 subjects)

Screened		640
Able to swallow pills (no)	10	
Able to speak English (no)	32	
Allergies (yes)	5	
Moving (yes)	16	
Bleeding disorder or coagulopathy (yes)	1	
Liver disease (yes)	7	
Type 1 or 2 diabetes (yes)	22	
Thyroid disease (yes)	9	
Other significant medical condition or cognitive or psychosocial impairment (yes)	86	
Taking anticoagulant medications (yes)	2	
Taking medications for thyroid condition (yes)	4	
Taking meds for triglyceride, cholesterol, blood glucose, insulin levels (yes)	53	
Taking prescription/OTC omega-3 medications (yes)	29	
Fasting triglycerides 150-1000 mg/dL at screening (no)	10	
Fasting triglycerides 150-1000 mg/dL at baseline (no)	10	
ALT greater than 2 times the upper limit of normal (yes)	1	
Fasting glucose ≥126 mg/dL (yes)	0	
Elevated TSH (yes)	2	
Abnormal PT or PTT (yes)	0	
Low platelet count (yes)	0	
Positive urine pregnancy test (yes)	0	

© Children's Hospital Boston, 2014 All rights reserved

Able to abstain from alcohol use (no)	0	

© Children's Hospital Boston, 2014 All rights reserved

Table 1 cont.

Pregnant or planning to become pregnant (yes)	0	
Currently breastfeeding (yes)	0	
Consistent oral contraceptive use (no)	1	
Consistent statin use (no)	1	
Willing to take study medication (no)	7	
Unable to reach/unable to follow-up	90	
Declined	258	
Participant/parent/legal guardian signed informed consent/assent (no)	592	
Meets eligibility criteria (yes)		25
Randomized (yes)		25

© Children's Hospital Boston, 2014 All rights reserved

Table 2. Safety Lab Distributions through 6-month Follow-up Visit

Measure	Time (mo)	n	Mean±SD	Min	Max
ALT, U/L	x	12	24 ± 10	12	53
	0	25	25 ± 13	10	58
	3	22	26 ± 10	12	49
	6	19	26 ± 17	10	76
AST, U/L	x	8	22 ± 4	17	31
	0	25	22 ± 6	14	43
	3	22	22 ± 6	13	39
	6	19	22 ± 7	14	39
Platelets, K/uL	x	7	298 ± 94	204	455
	0	25	293 ± 78	170	489
	3	22	280 ± 76	196	506
	6	18	293 ± 73	187	466
PT, sec	x	7	10.6 ± 0.4	10.0	11.1
	0	23	10.7 ± 0.5	10.0	12.3
	3	22	10.6 ± 0.5	9.8	11.7
	6	19	10.6 ± 0.3	10.0	11.0
PTT, sec	x	7	28.9 ± 1.7	26.7	31.1
	0	23	28.3 ± 2.0	23.8	31.8
	3	22	28.9 ± 2.0	25.2	33.5
	6	19	27.9 ± 2.5	21.0	31.1
BUN, mg/dL	x	7	11.7 ± 1.1	10	13
	0	25	12.6 ± 2.7	9	18
	3	22	12.7 ± 2.5	9	18
	6	19	12.3 ± 2.2	8	17
Creatinine, mg/dL	x	7	0.6 ± 0.1	0.5	0.8
	0	25	0.6 ± 0.1	0.4	0.9
	3	22	0.6 ± 0.2	0.4	1.0
	6	19	0.6 ± 0.1	0.4	0.9

© Children's Hospital Boston, 2014 All rights reserved

Table 2. ***(continued)***

Measure	Time (mo)	n	Mean±SD	Min	Max
Glucose, mg/dL	x	13	91± 8	77	103
	0	25	88 ± 6	76	100
	3	23	91 ± 7	78	102
	6	19	91± 6	80	103
Triglycerides, mg/dL	x	25	247± 83	160	511
	0	25	231± 52	154	332
	3	23	194 ± 97	74	465
	6	19	196 ± 72	97	342
TSH, uU/mL	x	10	2.4 ±1.3	1.25	5.62
	0	18	2.9 ±1.2	0.82	5.35
Iron,ug/dL	0	11	86 ± 36	45	182
	3	11	76 ± 40	31	183
	6	8	84 ± 28	56	122
Hemoglobin, g/dL	0	14	13.6 ± 1.30	11.9	15.9
	3	11	13.6 ± 1.0	12.4	15.1
	6	8	14.0 ± 1.3	12.4	16.0
Hematocrit, %	0	14	38.5 ± 2.5	34.6	44.2
	3	11	38.3 ± 2.7	34.1	41.8
	6	8	39.7 ± 3.4	34.8	44.1
Urine pregnancy screen, positive	x	0	0	0	0
	0	10	0	0	0
	3	9	0	0	0

© Children's Hospital Boston, 2014 All rights reserved

Table 3. Participant Safety Lab Alert Values

a. AST ≥ 60 U/L - none
b. ALT ≥ 80 U/L - none
c. Platelets < 150 K/uL or > 500 K/uL

ID	Visit	Lab date	Platelets K/uL
	3-month	5/7/09	506

d. PT > 15 sec - none
e. PTT > 50 sec - none
f. BUN > 18 mg/dL - none
g. Creatinine > 1.3 mg/dL - none
h. TSH > 5.7 uU/mL - none
i. Urine pregnancy screen (positive) - none
j. Glucose ≥ 126 mg/dL – none
k. Triglycerides > 1000 mg/dL - none
l. Iron >120 ug/dL (if 12-18 years old) or >175 (if 19 years old)

ID	Visit	Lab date	Iron ug/dL
	6-month	2/19/09	122
	3-month	3/19/09	183
	Baseline	10/16/09	182

m. Hemoglobin < 11 g/dL or > 15 g/dL

ID	Visit	Lab date	Hemoglobin g/dL
	Screening	11/6/08	15.5
	3-month	3/19/09	15.1
	6-month	6/25/09	16.0
	Baseline	10/11/08	15.9
	6-month	4/23/09	15.1
	3-month	1/20/11	15.5

n. Hematocrit < 31% or > 45%

ID	Visit	Lab date	Hematocrit %
	3-month	1/20/11	45.3

© Children's Hospital Boston, 2014 All rights reserved

Table 4: Self Reported Side effects

Measure	Time (mo)	Total respondents (N)	Total reporting the symptom (n)	Most days each week	A few days per week	<1 day per week	About once per month	One time in last 3 months
a. Burping	0	25	10	4	2	0	2	2
	3	23	6	3	2	0	1	0
	6	19	4	3	1	0	0	0
b. Upset stomach	0	25	12	2	0	4	5	1
	3	23	6	1	0	1	2	2
	6	19	6	1	0	1	2	2
c. Abdominal gas	0	25	10	3	3	2	1	1
	3	23	2	1	0	0	1	0
	6	19	2	1	1	0	0	0
d. Bloated feeling	0	25	1	0	0	0	0	1
	3	23	2	0	0	1	1	0
	6	19	1	0	0	1	0	0
e. Unusual taste in mouth	0	25	3	0	0	1	1	1
	3	23	1	0	1	0	0	0
	6	19	2	0	1	0	0	1
f. Stomach pains or cramps	0	25	10	2	0	2	4	2
	3	23	5	0	2	2	1	0
	6	19	5	0	0	2	2	1
g. Loose stools	0	25	4	0	1	0	0	3
	3	23	0	0	0	0	0	0
	6	19	1	0	0	0	0	1
h. Pain in chest	0	25	1	1	0	0	0	0
	3	23	2	1	0	0	1	0
	6	19	2	0	2	0	0	0
i. Pain in back	0	25	4	1	1	0	1	1
	3	23	6	2	0	0	2	2
	6	19	6	3	1	1	0	1
j. Muscle aches	0	25	5	1	1	1	2	0
	3	23	2	1	0	0	0	1
	6	19	3	1	1	1	0	0

© Children's Hospital Boston, 2014 All rights reserved

Table 4 cont.

k. Joint aches	0	25	2	1	0	0	1	0
	3	23	1	0	0	0	1	0
	6	19	3	1	1	0	0	1
l. Skin rash	0	25	2	0	0	0	1	1
	3	23	1	0	0	0	0	1
	6	19	1	0	0	0	0	1
m. Fever and chills	0	25	1	0	0	0	0	1
	3	23	3	0	0	0	0	3
	6	19	0	0	0	0	0	0
n. Infection	0	25	2	0	0	0	0	2
	3	23	2	0	0	0	0	2
	6	19	3	0	0	0	0	3
o. Other health problems	0	25	11*					
	3	23	8**					
	6	19	6***					

*Headache from too much TV; tendonitis from bad shoes & ear/sinus infection 1.5 months ago; flu 2 weeks ago; meniscus injury and complex regional pain syndrome; symptoms due to food allergies/intolerances or side effects from sinus infection medication; heartburn after eating; broken wrist from skateboarding accident; depression; hypertension; runny nose x2 days; seasonal allergies with stuffy nose and chills

**Feces smell like fish; a cold; upper respiratory infection with no fever that lasted 7 days; skin peeling on top of thumb and headache about three days per week for past month; ringworm and middle back muscle strain; hypertension; headache from allergies to pollen; head cold for approximately 4 weeks with low grade fever

***Nose bleeds, though notes pre-existing history of nose bleeds since infancy; cold symptoms; muscular back injury for 3 months; upper respiratory infection lasted one week with no fever; flu; patch of dry skin on arm

Table 5. Pill Compliance through 6-month Follow-up Visit

				Returned		
Measure	**Time (mo)**	**Participants (n)**	**Pills dispensed/ participant**	**Mean±SD**	**Min**	**Max**
Number of pills returned	3	23 *	360 **	60±69	0	269
	6	21 *	360 **	67±52	0	162

* 3 participants failed to return bottles at 3-month visit; 4 participants failed to return bottles at 6-month visit

** Two participants were given 420 pills total due to delayed study visits.

© Children's Hospital Boston, 2014 All rights reserved

Table 6. Study Visit Compliance

Study ID	Screening Visit		Baseline Visit		Randomized		3-month Visit		6-month Visit	
	Complete		Within range (30 days ±14)	Outside range	Within range (7 days)	Outside range	Within range (90 days ±14)	Outside range	Within range (90 days ±14)	Outside range
	X		X		X		X		X	
	X		X		X		X		X	
	X		X		X		X		X	
	X		X		X			X	X	
	X		X		X		X			**
	X		X		X		X		X	
	X			X	X		X		X	
	X		X		X			***		
	X		X		X		X		X	
	X		X			X	X		X	
	X		X		X		X		X	
	X		X		X		X		X	
	X			X	X		X		X	
	X		X		X		X		X	
	X		X		X		X		X	
	X		X		X		X			**
	X		X		X		X		X	
	X		X		X		X		X	
	X			X	X		X		X	
	X		X		X		X		X	
	X		X		X		X		X	
	X		X		X			X		**
	X		X		X		X			
	X			X	X			X		
	X		X		X					

Notes:

101-5: 83 days between screening and baseline due to iron amendment
121-6: 113 days between baseline and 3-month visit due to iron amendment
224-8: 33 days between baseline and randomization due to delay in obtaining complete labs
228-5: 55 days between screening and baseline per mother's scheduling request
335-6: 79 days between screening and baseline per mother's scheduling request
514-3: 111 days between baseline and 3 months per mother's scheduling request
590-1: 64 days between screening and baseline due to stopping because of placebo rancidity
590-1: 101 days between baseline and 3 months (1 week outside range) due to patient's febrile illness

** Lost to follow-up
*** Terminated from study

© Children's Hospital Boston, 2014 All rights reserved

Table 7. Case Report Form Completion Rates of Participants

	Visit							
	Screening		**Baseline**		**3-Month**		**6-Month**	
Form	Received	Expected	Received	Expected	Received	Expected	Received	Expected
Screening and eligibility Form	640	640						
Sociodemographic questionnaire	25	25						
Screening medical history and exam	25	25						
Medical history and exam			25	25	23	23	19	19
Participant lifestyle questionnaire			25	25	23	23	19	19
Anthropometric form			25	25	23	23	19	19
Laboratory form	25	25	25	25	23	23	19	19
Fish intake form			25	25	23	23	19	19
3-day food record			21	25	20	23	17	19
Side effects form			25	25	23	23	19	19
Vascular testing form			25	25	23	23	19	19
Pill count form					23	23	19	19

© Children's Hospital Boston, 2014 All rights reserved

Table 8. Distributions of Baseline Characteristics of Enrolled Participants and Missing Data Rates

Characteristic		N	Mean ± SD	Min	Max
Age, yr		25	14.0 ± 2.6	10.1	19.3
Height, cm		25	160.7 ± 12.8	141.8	184.3
Weight, kg		25	80.9 ± 20.6	54.0	127.3
Waist circumference, cm		25	100.3 ± 12.0	80.3	126.5
BMI, kg/m^2		25	30.9 ± 4.4	24.3	40.5
BMI z-score		25	2.09 ± 0.36	1.18	2.69
Blood pressure, mmHg	Systolic	25	111 ± 12	95	135
	Diastolic	25	71 ± 8	57	91
Triglycerides, mg/dL		25	231± 52	154	332
Insulin, mcIU/mL		25	23.4 ± 10.9	8.7	50.2

			n	%
Gender, male		25	14	56.0 %
Race		25		
Caucasian			19	76.0%
Black/African American			1	4.0%
Asian			0	0.0%
American Indian/Alaskan native			0	0.0%
Native Hawaiian/Pacific Islander			0	0.0%
Multiple			0	0.0%
Other			5	20.0%
Unknown			0	0.0%
Hispanic ethnicity		25	5	20.0%
Family history		16-21		
Hypertriglyceridemia	1st degree relative		6	24.0
	2nd degree relative		2	8.0%
	Both		8	32.0%
Hypercholesterolemia	1st degree relative		1	4.0%
	2nd degree relative		5	20.0%
	Both		15	60.0%
Early heart disease	1st degree relative		1	4.0%
	2nd degree relative		9	36.0%
	Both		1	4.0%
Hypertension	1st degree relative		2	8.0%
	2nd degree relative		10	40.0%
	Both		10	40.0%
Type 2 diabetes	1st degree relative		1	4.0%
	2nd degree relative		12	48.0%
	Both		3	12.0%
Obesity	1st degree relative		3	12.0%
	2nd degree relative		5	20.0%
	Both		13	52.0%

© Children's Hospital Boston, 2014 All rights reserved

Mother Education		25		
	Less than high school		1	4.0%
	Some high school		0	0.0%
	High school graduate		3	12.0%
	Trade school		2	8.0%
	Some college		7	28.0%
	College graduate		9	36.0%
	Post graduate degree		3	12.0%
Father Education		25		
	Less than high school		0	0.0%
	Some high school		0	0.0%
	High school graduate		8	32.0%
	Trade school		2	8.0%
	Some college		3	12.0%
	College graduate		5	20.0%
	Post graduate degree		4	16.0%
	Not applicable		3	12.0%
Income		25		
	Below $20,000		1	4.0%
	$20-29,000		1	4.0%
	$30-39,000		2	8.0%
	$40-49,000		1	4.0%
	$50-59,000		4	16.0%
	$60-69,000		3	12.0%
	$70-79,000		3	12.0%
	$80-89,000		3	12.0%
	$90-99,000		0	0.0%
	Above $100,000		4	16.0%
	Declined		3	12.0%

© Children's Hospital Boston, 2014 All rights reserved

Table 9: Specimen Tracking Log

ID	Initials	Baseline	Red Cells	3 month	Red Cells	6 month	Red Cells	Notes
		8/11/2008	2 tubes 0.5 mL each	11/13/2008	NONE	2/19/2009	2 tubes 0.5 mL each	**Complete**
		10/11/2008	2 tubes 0.5 mL each	1/10/2009	2 tubes 0.5 mL each	4/23/2009	2 tubes 0.5 mL each	**Complete**
		10/9/2008	2 tubes 0.5 mL each	1/23/2009	2 tubes 0.5 mL each	4/9/2009	2 tubes 0.5 mL each	**Complete**
		11/17/2008	2 tubes 0.5 mL each	2/26/2009	2 tubes 0.5 mL each	No Show		**Lost to Follow Up after 3 Months**
		11/5/2008	2 tubes 0.5 mL each	2/26/2009	2 tubes 0.5 mL each	6/1/2009	2 tubes 0.5 mL each	**Complete**
		12/5/2008	2 tubes 0.5 mL each	3/19/2009	2 tubes 0.5 mL each	6/25/2009	2 tubes 0.5 mL each	**Complete**
		2/4/2009	2 tubes 0.5 mL each	5/7/2009	2 tubes 0.5 mL each	7/30/2009	2 tubes 0.5 mL each	**Complete**
		4/1/2009	2 tubes 0.5 mL each	N/A		N/A		**Terminated From Study**
		5/14/2009	2 tubes 0.5 mL each	8/4/2009	2 tubes 0.5 mL each	11/2/2009	2 tubes 0.5 mL each	**Complete**
		5/22/2009	NOT DRAWN; DEVIATION	10/1/2009	2 tubes 0.5 mL each	1/14/2010	2 tubes 0.5 mL each	**Complete**
		7/2/2009	2 tubes 0.5 mL each	10/6/2009	2 tubes 0.5 mL each	12/30/2009	2 tubes 0.5 mL each	**Complete**

© Children's Hospital Boston, 2014 All rights reserved

Table 9 cont.

ID	Initials	Baseline	Red Cells	3 month	Red Cells	6 month	Red Cells	Notes
		7/22/2009	2 tubes 0.5 mL each	10/22/2009	NONE	1/20/2010	2 tubes 0.5 mL each	**Complete**
		8/20/2009	2 tubes 0.5 mL each	12/3/2009	2 tubes 0.5 mL each	3/17/2010	2 tubes 0.5 mL each	**Complete**
		8/25/2009	2 tubes 0.5 mL each	12/2/2009	2 tubes 0.5 mL each	3/4/2010	2 tubes 0.5 mL each	**Complete**
		10/16/2009	2 tubes 0.5 mL each	1/20/2010	2 tubes 0.5 mL each	3/18/2010	2 tubes 0.5 mL each	**Complete**
		11/16/2009	2 tubes 0.5 mL each	2/25/2010	2 tubes 0.5 mL each	N/A		**Lost to Follow Up after 3 Months**
		12/23/2009	2 tubes 0.5 mL each	3/24/2010	2 tubes 0.5 mL each	7/7/2010	2 tubes 0.5 mL each	**Complete**
		1/13/2010	2 tubes 0.5 mL each	4/14/2010	2 tubes 0.5 mL each	7/2/2010	2 tubes 0.5 mL each	**Complete**
		1/21/2010	2 tubes 0.5 mL each	4/29/2010	2 tubes 0.5 mL each	8/5/2010	2 tubes 0.5 mL each	**Complete**
		5/25/2010	2 tubes 0.5 mL each	8/26/2010	2 tubes 0.5 mL each	11/22/2010	2 tubes of 0.5 mL each	**Complete**
		9/16/2010	2 tubes 0.5 mL each	12/10/2010	2 tubes 0.5 mL each	3/4/2011	2 tubes of 0.5 mL each	**Complete**
		10/27/2010	2 tubes 0.5 mL each	2/16/2011	2 tubes of 0.5 mL each	N/A		**Withdrawn prior to 6 month visit**

© Children's Hospital Boston, 2014 All rights reserved

Table 9 cont.

ID	Initials	Baseline	Red Cells	3 month	Red Cells	6 month	Red Cells	Notes
		11/8/2010	2 tubes 0.5 mL each	1/20/2011	2 tubes of 0.5 mL each	4/29/2011	2 tubes of 0.5 mL each	**Complete**
		7/15/2011	2 tubes 0.5 mL each	10/27/2011	2 tubes of 0.5 mL each	N/A		**Enrolled**
		9/20/2011	2 tubes of 0.5 mL each	N/A		N/A		**Enrolled**

© Children's Hospital Boston, 2014 All rights reserved

References

Guidance for Data Quality Assurance. April 2001. National Heart, Lung, and Blood Institute, National Institutes of Health. 6 April 2009
http://www.nhlbi.nih.gov/funding/policies/dataqual.htm

International Conference on Harmonisation. Guidance E6. Consolidated Guidelines.

(***http://www.ninds.nih.gov/research/clinical_research/policies/quality_assurance_guidelines.htm***)

The Society for Clinical Data Management. "Assuring Quality Data" June 2008. Good Clinical Data Management Practices. 6 April 2009

The Society for Clinical Data Management. "Measuring Data Quality" June 2008. Good Clinical Data Management Practices. 6 April 2009

Valania, Martin. Quality Control and Quality Assurance in Clinical Research. March 1, 2006. Pharmanet. 6 April 2009
http://www.pharmanet.com/pdf/whitepapers/QCQA.pdf

Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring August 2011
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf

Compliance Program Guidance Manual For FDA Staff: Compliance Program 7348.811: Bioresearch Monitoring: Clinical Investigators
http://www.fda.gov/downloads/ICECI/EnforcementActions/BioresearchMonitoring/UCM133773.pdf

Document Attributes

Title	**Guidelines for Assuring Quality in Clinical Research – RPG-12**		
Author	Colette Hendricks, MSW, MBA	**Date of Origin**	January 2012
Reviewed/ Revised by	n/a	**Dates Reviewed/Revised**	January 2012
Copyright	©Children's Hospital Boston, 2014	**Last Modified**	1/5/2012
Approved	**Signature on File** Stavroula Osganian, MD, ScD, MPH Co-Chief, Clinical Research Center		

Disclaimer: Should Hospital and CRC policies conflict, Hospital policy will supersede CRC policy in all cases.

© Children's Hospital Boston, 2014 All rights reserved