So Many Procedures, So Little Time

How to Develop an Effective Schedule of Events for the Rare Disease Clinical Research Network

RARE DISEASES CLINICAL RESEARCH NETWORK

Data Management and Coordinating Center at Cincinnati Children's Hospital Medical Center

Presentation Overview

1. Introduction
2. DMCC Resources Available
3. The “Four Pillars” of an Effective Schedule of Events and Creating a Schedule of Events and Common Issues
4. Questions

Introduction

- Mike Fusakio, PhD
  - Experience in both CRO and Academic regulatory environments leading the submission of IND and NDA projects.
- Nathan Hawk, BSPS
  - Over 14 years of CRO and Academic experience in Data Management.
- Samantha Sonoda, MS, CCRA
  - Experience as a monitoring lead for Investigator-Initiated studies and as an industry CRA.
- Lisa Tully, MA, CCRP
  - Over 15 years experience in Academic regulatory research: over 10 years as a clinical research coordinator and more recently, managing regulatory for multisite studies and IND projects.

DMCC Resources Available

1. DMCC Protocol Template and Checklist
   - Checklist details each section to allow you to decide what is needed.
   - The template provides some standard language to assist in writing certain protocol sections.

2. DMCC Pilot Project Protocol Template
   - Template for small initial studies or studies involving only human samples, existing data, etc.
   - Based on the standard Protocol Template but trimmed down.

3. Grant to Protocol Conversion Document
   - The document highlights key differences between a Grant application and Human Subject Research Protocol.

4. Manual of Procedures (MOP) Template
   - Template document to aid in constructing an effective MOP to aid in the effectiveness of your other study documents.

Effective Schedule of Events

Procedure	Visit 1 (Screening)	Visit 2	Visit 3	Visit 4 (EOT)
Day	-30	0	7	30
Window	(± 5 days)	(± 1 day)	(± 1 day)	(± 5 days)
Informed Consent	X			
Medical History	X			
Review Concomitant Meds		X	X	X
Inclusion/Exclusion Criteria	X			
Physical Exam[1]	X	X	X	X
Randomization		X		
Medicine Distribution		X		
Study Drug Administration		X		
Pregnancy Test (blood)	X	X	X	X
Labs[2]	X	X	X	X
ECG[3]	X	X	X	
Review of Adverse Events		X	X	X

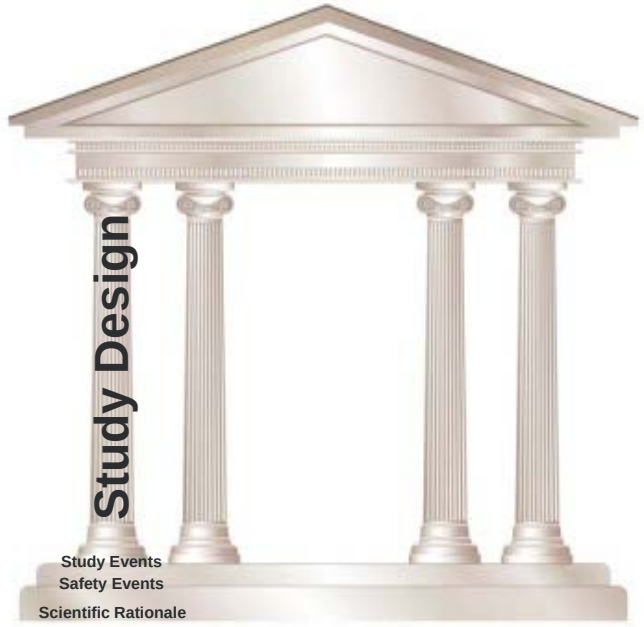
1) Physical exam will include an evaluation of height (cm), weight (kg), vital signs, musculoskeletal assessment, and cardiovascular
2) Labs will include a CBC, a Comprehensive Metabolic Panel, and a Lipid Panel.
3) The ECG will occur after the participant has been resting for approximately 5 minutes and done in triplicate.

- Schedule of Events are a complex portion of your study and require a large amount of input from everyone involved in your study team, including:
  - PIs and Sub-PIs
  - Coordinators
  - Data Management
  - Monitors
  - Statisticians

The “Four Pillars” of an Effective Schedule of Events

- An Effective Schedule of Events will properly address:
  - Study Design
  - Workflow
  - Data Management
  - Quality Assurance
- An effective Schedule of Events that addresses these items will serve as a foundation for the protocol and the overall study.
- These elements of a Schedule of Events are like the pillars of a building, remove one and you are going to struggle to prevent the building from collapsing.

The “First Pillar”: Study Design



- How does the **scientific rationale** affect the SOE?

- **3 Key Sources:**
  - Standard Study Events:
    - Consider elements that should be a part of every study
      - Informed Consent
      - Inclusion/Exclusion Criteria
      - Medical History/Demographics
  - Standard Safety Events:
    - Consider safety elements that should be a part of every study
      - Adverse Events
      - Concomitant Medications
  - Scientific Rationale:
    - Review your Schedule of Events versus your Scientific Rationale for your trial:
      - Are the tests/procedures that must occur to obtain all Endpoints represented in the Schedule of Events?
      - Are there procedures that can encompass multiple elements?
        - Blood Chemistry can be used, but must include an appropriate footnote, to represent several laboratory tests
        - Ensure that it is clear what elements are covered by these procedures
    - When will this information/samples be collected?

Creating a Schedule of Event

- Throughout this talk, we will examine a Schedule of Events that we will develop over the course of several slides by examining some common issues made within each of the “4 Pillars”.

- For this practice example we will consider a trial that has the following parameters:
  - 4 visits: (Screening, Day 0, Day 7, End of Treatment)
  - 2 arms (Placebo and Treatment)
  - Study is looking at whether a drug reduces the levels of Triglycerides (primary endpoint)
  - Several laboratory procedures (ECG, blood draws [CBC, Lipid, Metabolic panel], pregnancy tests [Blood]) that are for Inclusion/Exclusion criteria and safety/efficacy endpoints

Schedule of Events

Procedure	Screening Visit 1	Day 0 Visit 2	Day 7 Visit 3	EoT Visit 4
Inclusion/Exclusion Criteria	X			
Physical Exam	X	X	X	X
Randomization		X		
Medicine Distribution		X		
Study Drug Administration		X		
Pregnancy Test (blood)		X	X	X
Labs	X	X	X	X
ECG	X	X	X	

- The Schedule of Events above has some common issues made in each of the “4 Pillars”.
- We will review each issue, correct it, and progress to final Schedule of Events we showed at the beginning of the talk.

Schedule of Events – Common Study Design Issues

Procedure	Screening Visit 1	Day 0 Visit 2	Day 7 Visit 3	EoT Visit 4
Inclusion/Exclusion Criteria	X			
Physical Exam	X	X	X	X
Randomization		X		
Medicine Distribution		X		
Study Drug Administration		X		
Pregnancy Test (blood)		X	X	X
Labs	X	X	X	X
ECG	X	X	X	

- The 1st Content issue is that Informed Consent, Adverse Events, Medical History, and Concomitant Medications are not listed in the SOE
- The 2nd Content issue is that it is unclear if the Primary Endpoint is being evaluated based on the information provided.

Schedule of Events – Common Study Design Issues Addressed

Procedure	Screening Visit 1	Day 0 Visit 2	Day 7 Visit 3	EoT Visit 4
Informed Consent	X			
Medical History	X			
Review Concomitant Medications		X	X	X
Inclusion/Exclusion Criteria	X			
Physical Exam	X	X	X	X
Randomization		X		
Medicine Distribution		X		
Study Drug Administration		X		
Pregnancy Test (blood)		X	X	X
Labs[1]	X	X	X	X
ECG	X	X	X	
Review of Adverse Events		X	X	X

1) Labs will include a CBC and Lipid Panel.

- We've added rows for Informed Consent, Adverse Events, and Medical History. Other basic elements may be needed (i.e., Demographics)
- The 2nd Content issue has been corrected through the footnote which details the Lipid Panel.

The “Second Pillar”: Workflow

Does the SOE accurately reflect the protocol workflow?

- **3 Key Elements**
  - **Clear**
  - **Consistent**
  - **Concise**

The “Second Pillar”: Workflow

Does the SOE accurately reflect the protocol workflow?

- **3 Key Elements:**
  - **Clear**
    - Coordinators need a clear SOE to ensure study procedures are run correctly, completely, and consistently.
      - Clearly illustrate:
        - Duration of study for individual participants
        - Visit windows
        - Procedures to be completed
  - **Consistent**
    - Section 7: Study Procedures in the protocol template & the SOE must be consistent with each other.
      - Consistently describe:
        - What procedures should be completed & when or in what order?
        - What is included in each procedure?
          - Physical Exam includes what?
        - Terms used are consistent.
          - Example: It’s either screening visit or visit 1 don’t use them interchangeably for the same visit
    - Does the SOE used in the protocol match what is included in the consent?

The “Second Pillar”: Workflow

Does the SOE accurately reflect the protocol workflow?

- **3 Key Elements:**
  - **Concise**
    - The SOE needs to include all pertinent information in an easily discernable manner.
      - Too much can be confusing
      - Too little can create inconsistencies in data collection
    - Concisely define:
      - Abbreviations can be defined in footnotes
      - What procedures happen at which visits
    - Specific details on how to perform procedures or what version of an assessment should be in a MOP.

If the SOE is *not* clear, consistent, and concise it can lead to protocol deviations and missed data, while potentially impacting participant safety.

Schedule of Events – Common Workflow Issues

Procedure	Screening Visit 1	Day 0 Visit 2	Day 7 Visit 3	EoT Visit 4
Informed Consent	X			
Medical History	X			
Review Concomitant Medications		X	X	X
Inclusion/Exclusion Criteria	X			
Physical Exam	X	X	X	X
Randomization		X		
Medicine Distribution		X		
Study Drug Administration		X		
Pregnancy Test (blood)		X	X	X
Labs[1]	X	X	X	X
ECG	X	X	X	
Review Adverse Events		X	X	X
1) Labs will include a CBC and Lipid Panel.				

- The 1st Workflow issue is that visit windows are not provided nor any indication of the time between visits for this SOE
- The 2nd Workflow issue is that the SOE does not specify what is included in a Physical Exam.

Schedule of Events – Common Workflow Issues Addressed

Procedure	Visit 1 (Screening)	Visit 2	Visit 3	Visit 4 (EOT)
Day	-30	0	7	30
Window	(± 5 days)	(± 1 day)	(± 1 day)	(± 5 days)
Informed Consent	X			
Medical History	X			
Review Concomitant Medications		X	X	X
Inclusion/Exclusion Criteria	X			
Physical Exam[1]	X	X	X	X
Randomization		X		
Medicine Distribution		X		
Study Drug Administration		X		
Pregnancy Test (blood)		X	X	X
Labs[2]	X	X	X	X
ECG	X	X	X	
Review of Adverse Events		X	X	X

1) Physical exam will include an evaluation of height (cm), weight (kg), vital signs, musculoskeletal assessment, and cardiovascular

2) Labs will include a CBC and Lipid Panel.

- We've added the windows for each visit and noted time between visits.
- We've included a footnote on the row for Physical exam to specify the procedures to be performed. *Note: We have also updated the footnotes to make them go in order with the SOE.*

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The “Third Pillar”: Data Management

- The following attributes of a SOE are essential for execution of data management responsibilities:
  - Structure
  - Order
  - Granularity
  - Context

The “Third Pillar”: Data Management

- **Structure**
  - Examples:
    - All procedures are represented in the SOE as described in the body of the protocol.
    - Don’t forget Informed Consent, Eligibility, Randomization, and Demographics! These procedure are often missing from the SOE.
  - If data expected to be entered in the database and used for analysis is not listed on the SOE, you run the risk it is not being included in the database.

The “Third Pillar”: Data Management

- **Order**
  - All procedures are in an order consistent with how they will be done in real-time at each visit/event.
    - Examples:
      - If timing of procedures is an important element for the protocol, having the forms listed as they occur chronologically will help ensure data collection is done correctly.
      - Databases are typically built with forms ordered as the appear in the SOE. Listing the procedures in an order consistent with how they will be done at the visit will make data entry more efficient for site personnel.
    - If the order of procedures/forms in the SOE does not match the rest of the protocol, it may create confusion for the person building the database. That confusion ultimately leads to wasted time/money and/or an inaccurate database build.

The “Third Pillar”: Data Management

- **Granularity**
  - Line-items should represent logical domains and should not combine differing concepts or procedures.
    - Example:
      - Do not lump several different domains/procedures into one line-item on the SOE:
        - » Demographics, Medical History, Family History, and Medication History are filed under “Medical History” on the SOE
        - » ECHO, CT, and MRI are just called “Imaging” on the SOE
    - It’s important to separate these domains/procedures/concepts into separate line-items on the SOE to prevent confusion when the database is being built and/or when data is being collected by site personnel.
    - **Alternatively**, if footnotes are provided to define what domains/procedures are done as part of a line-item in the SOE, it’s ok to combine them to save space. Be sure to clearly identify what procedures are done/not done at each visit/event.

The “Third Pillar”: Data Management

- **Context**
  - All context, as applicable, should be described in the SOE.
    - Example:
      - Timing of events and procedures should be clearly defined in the SOE:
        - » If Vital Signs should be done 30 minutes prior to Study Drug Administration, the SOE should note the timing.
        - » Define visit windows in the SOE.
      - If there are multiple types of procedures, specify what kind:
        - » Is it a resting or stress ECG?
        - » What version of a questionnaire should be administered?
        - » Is it arterial or cuff blood pressure?
    - Failing to provide context can lead to inaccurate, mistimed, and/or incomplete data collection.

Schedule of Events – Common Data Management Issues

Procedure	Visit 1 (Screening)	Visit 2	Visit 3	Visit 4 (EOT)
Day	-30	0	7	30
Window	(± 5 days)	(± 1 day)	(± 1 day)	(± 5 days)
Informed Consent	X			
Medical History	X			
Review Concomitant Medications		X	X	X
Inclusion/Exclusion Criteria	X			
Physical Exam[1]	X	X	X	X
Randomization		X		
Medicine Distribution		X		
Study Drug Administration		X		
Pregnancy Test (blood)		X	X	X
Labs[2]	X	X	X	X
ECG	X	X	X	
Review of Adverse Events		X	X	X

1) Physical exam will include an evaluation of height (cm), weight (kg), vital signs, musculoskeletal assessment, and cardiovascular
2) Labs will include a CBC and Lipid Panel.

- 1st Data Management issue, when we initially addressed the Content issue regarding the Study Endpoints, we created a DM issue by not specifying all the labs that will occur.
- 2nd Data Management issue, the SOE calls for an ECG but provide no information on this ECG. Is it a resting ECG? Is it done in triplicate?

Schedule of Events – Common Data Management Issues Addressed

Procedure	Visit 1 (Screening)	Visit 2	Visit 3	Visit 4 (EOT)
Day	-30	0	7	30
Window	(± 5 days)	(± 1 day)	(± 1 day)	(± 5 days)
Informed Consent	X			
Medical History	X			
Review Concomitant Medications		X	X	X
Inclusion/Exclusion Criteria	X			
Physical Exam[1]	X	X	X	X
Randomization		X		
Medicine Distribution		X		
Study Drug Administration		X		
Pregnancy Test (blood)		X	X	X
Labs[2]	X	X	X	X
ECG[3]	X	X	X	
Review of Adverse Events		X	X	X

1) Physical exam will include an evaluation of height (cm), weight (kg), vital signs, musculoskeletal assessment, and cardiovascular
2) Labs will include a CBC, a Comprehensive Metabolic Panel, and Lipid Panel.
3) The ECG will occur after the participant has been resting for 5 minutes and done in triplicate.

- For the 1st Data Management issue, we have added that a metabolic panel will occur as well.
- For the 2nd Data Management issue, we have added details that this is a resting ECG.

The “Fourth Pillar”: Quality Assurance

Study teams can implement and maintain quality assurance by ensuring:

- **Subject Safety**
  - *The rights and well-being of human subjects are protected.*
- **Study Quality and Integrity**
  - *Clinical trial data is accurate, complete, and verifiable from source documents.*
  - *The study protocol provides a consistent and quality approach to the conduct of research among investigative sites.*
- **Compliance**
  - *The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).*

The “Fourth Pillar”: Quality Assurance

Subject Safety

- Are safety procedures conducted at the appropriate timepoints?
  - Safety labs
  - Pregnancy tests
  - Physical exams
  - Medical history review
  - Adverse event/concomitant medication review
  - Vital signs

- Review the Investigator’s Brochure/Package Insert to ensure safety monitoring procedures align with recommended guidance.

The “Fourth Pillar”: Quality Assurance

Study Quality and Integrity

- Do the procedures and SOE exhibit a consistent, quality approach to the conduct of research among investigative sites?
  - Proper performance is outlined, especially regarding study endpoints
  - If a study is multi-site, ensure procedures are applicable to all sites or noted otherwise

The “Fourth Pillar”: Quality Assurance

Compliance

- Would the procedural expectations be clear in the eyes of a monitor or auditor?
  - Timing and specificity for procedures is clearly defined
  - Use footnotes to provide specific details about a procedure

- Ensure Informed Consent is listed within the SOE.

The “Fourth Pillar”: Quality Assurance

Quality Assurance Takeaways:

1. The SOE should be comprehensive and allow for the study team to implement and maintain subject safety, study quality and integrity, and compliance.

2. Study teams should review the SOE through a quality assurance lens to:
   - Identify potential issues that may occur due to *infeasibility*
   - Identify potential issues that may occur due to *inconsistencies* across study documents

Schedule of Events – Common Quality Assurance Issues

Procedure	Visit 1 (Screening)	Visit 2	Visit 3	Visit 4 (EOT)
Day	-30	0	7	30
Window	(± 5 days)	(± 1 day)	(± 1 day)	(± 5 days)
Informed Consent	X			
Medical History	X			
Review Concomitant Medications		X	X	X
Inclusion/Exclusion Criteria	X			
Physical Exam[1]	X	X	X	X
Randomization		X		
Medicine Distribution		X		
Study Drug Administration		X		
Pregnancy Test (blood)		X	X	X
Labs[2]	X	X	X	X
ECG[3]	X	X	X	
Review of Adverse Events		X	X	X

1) Physical exam will include an evaluation of height (cm), weight (kg), vital signs, musculoskeletal assessment, and cardiovascular
2) Labs will include a CBC, a Comprehensive Metabolic Panel, and Lipid Panel.
3) The ECG will occur after the participant has been resting for 5 minutes and done in triplicate.

- The 1st QA issue, the protocol requires a pregnancy test as part of the Inclusion/Exclusion criteria, but we have not included it on the SOE.
- The 2nd QA issue was introduced when addressing the ECG issue. We have created a situation that will lead to protocol deviation by requiring the subject rest for exactly 5 minutes before the ECG occurs.

Schedule of Events – Common Quality Assurance Issues Addressed

Procedure	Visit 1 (Screening)	Visit 2	Visit 3	Visit 4 (EOT)
Day	-30	0	7	30
Window	(± 5 days)	(± 1 day)	(± 1 day)	(± 5 days)
Informed Consent	X			
Medical History	X			
Review Concomitant Medications		X	X	X
Inclusion/Exclusion Criteria	X			
Physical Exam[1]	X	X	X	X
Randomization		X		
Medicine Distribution		X		
Study Drug Administration		X		
Pregnancy Test (blood)	X	X	X	X
Labs[2]	X	X	X	X
ECG[3]	X	X	X	
Review of Adverse Events		X	X	X

1) Physical exam will include an evaluation of height (cm), weight (kg), vital signs, musculoskeletal assessment, and cardiovascular
2) Labs will include a CBC, a Comprehensive Metabolic Panel, and Lipid Panel.
3) The ECG will occur after the participant has been resting for approximately 5 minutes and done in triplicate.

- For the1st QA issue, we noted that it must occur on Visit 1.
- For the 2nd QA issue, we added the term approximately which gives some leeway to prevent protocol deviations.

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Schedule of Events – Room for Improvement

Procedure	Visit 1 (Screening)	Visit 2	Visit 3	Visit 4 (EOT)
Day	-30	0	7	30
Window	(± 5 days)	(± 1 day)	(± 1 day)	(± 5 days)
Informed Consent	X			
Medical History	X			
Review Concomitant Meds		X	X	X
Inclusion/Exclusion Criteria	X			
Physical Exam[1]	X	X	X	X
Randomization		X		
Medicine Distribution		X		
Study Drug Administration		X		
Pregnancy Test (blood)	X	X	X	X
Labs[2]	X	X	X	X
ECG[3]	X	X	X	
Review of Adverse Events		X	X	X

1) Physical exam will include an evaluation of height (cm), weight (kg), vital signs, musculoskeletal assessment, and cardiovascular
2) Labs will include a CBC, a Comprehensive Metabolic Panel, and a Lipid Panel.
3) The ECG will occur after the participant has been resting for approximately 5 minutes and done in triplicate.

- This Schedule of Events is considerably better than its 1st iteration, but there is still room for improvement in respect to the 4 Pillars:
  - Abbreviations are used in the Table but not defined.
  - If subjects terminate early is there an Early Termination visit schedule?
- Schedule of Events are a complex portion of your study and require a large amount of input from everyone involved in your study team.
- The DMCC highly recommends that the protocols sent for review have an SOE that we can review. As you have seen fixing issues in SOEs can introduce new problems. Additional reviews can aid in catching original and new issues in a SOE.

Questions?

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