Submitting Results to ClinicalTrials.gov
(including some Practical Helpful Hints)

Heather Dobbins, PhD
Lead Results Analyst, ClinicalTrials.gov
National Library of Medicine, NIH
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http://ClinicalTrials.gov

Disclaimer!

In this presentation, I may paraphrase or talk about FDAAA 801, but this is not meant to be legal advice and should not be interpreted as such. Information about FDAMA 113 and FDAAA 801 can be found on ClinicalTrials.gov and legal council should be sought from other appropriate sources.

ClinicalTrials.gov
Background
ClinicalTrials.gov Brief Timeline

- FDAMA 113 (1997) mandates registry
  - Investigational New Drug application (IND) trials for serious and life-threatening diseases or conditions
- ClinicalTrials.gov launched in February 2000
- Calls for increased transparency of clinical trials
  - Maine State Law: State Attorneys General
- ClinicalTrials.gov accommodates other policies
- FDAAA Section 801 (2007): Expands registry & adds results database

Why the need for a public database?

- Give patients access to information about clinical trials
- Reduce/eliminate publication bias
- Publically acknowledge all prespecified outcome measures
- Publically display any changes made to a trial protocol that could affect the interpretation of the findings
  - e.g., changes to prespecified outcome measures

Why should trials register and report results?

- Human Subjects and Public Health Benefits
  - Allows potential participants to find studies
  - Access to trial results influences medical decisions
  - Assists ethical review boards and others to evaluate studies (e.g., harms, benefits, redundancy)
  - Promote fulfillment of ethical responsibility to human volunteers – all research contributes to medical knowledge
- Scientific Research Integrity
  - Increasing transparency creates trust in research enterprise
  - Disclosure of protocol changes allows for contextualized interpretation of results
  - Keeping the existence of trials and their results hidden impedes scientific progress
  - Promotes more efficient allocation of resources
...and did we mention?

- FDAAA 801 enforcement provisions
  - Notices of non-compliance
  - Civil monetary penalties up to $10,000/day
  - Withholding of NIH grant funds
- the ability to publish research
  - ICMJE policy

Registering and Submitting Results to ClinicalTrials.gov

Which studies? Who is supposed to register and submit results?

- Applicable Clinical Trials*
  - Interventionsal studies of drugs, biologics & devices
  - Not Phase 1 (drugs/biologics), not small feasibility (devices)
  - US FDA jurisdiction (e.g., IND/IDE or US site)
  - ACTs initiated on or after 9/27/07 or if initiated after 09/27/07, "ongoing" as of 12/26/07
- Responsible Party*
  - Sponsor [only one per trial]
  - Sponsor may designate the Principal Investigator (PI) [only one per trial]

When do I register and submit results?

- **When to register**
  - FDAAA 801: No later than 21 days after the first participant is enrolled
  - ICMJE: before the first participant is enrolled

- **When to submit results**
  - FDAAA 801: Generally, submission within 12 months of Primary Completion Date (the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome) or use official mechanisms for Delayed Submission of Results
https://register.clinicaltrials.gov

What does it look like?

What results do I submit?

- Participant Flow
- Baseline and Demographic Characteristics
- Outcome Measures
- Adverse Events (summary data)
- Other Information
  - "Certain Agreements" related to Restrictions on Results Disclosure
  - Overall Limitations and Caveats
  - Results Point of Contact

Helpful Hint: Use the Simple Results Templates (On ClinicalTrials.gov, under Submit Studies, Support Materials) to organize your information before starting PRS data entry
Basic Results: Data Elements

http://prsinfo.clinicaltrials.gov/results_definitions.html

ClinicalTrials.gov "Basic Results" Data Element Definitions (DRAFT)

September 28, 2009

Go to ClinicalTrials.gov
→ Submit Studies
→ Support Materials
→ Protocol Registration System (PRS) Information
→ Data Element Definitions

Participant Flow

“A table ..., including the number of patients who dropped out of the clinical trial and the number of patients excluded from the analysis, if any.”
[Sec. 282(j)(3)(C)(i)]
What if I have a complicated Participant Flow?

Helpful Hints: The number of Arm/Groups is generally equal to the number of “experiences” to which a participant could be randomized/assigned. (e.g., number of sequences in a crossover, number of interventions in a parallel study, number of doses in a dose escalation, etc.) Although, this can be a little more nuanced if you have multiple randomizations/assignments.

We have some study design examples on ClinicalTrials.gov under → Submit Studies → Training Materials → Results Database Train-the-Trainer Workshop → Example Studies for Results Data Entry

OR email us: register@clinicaltrials.gov

Some Participant Flow Data Elements of Note

Period(s)
Definition: Discrete stages of a clinical trial during which numbers of participants at specific significant events or points of time are reported. If only one period, use Overall Study for “Period Title.”

Milestone(s)
Definition: Specific events or time points in the trial when the numbers of participants are reported. While there is no limit to the number of milestones that may be used in a single period, data are required for two milestones, STARTED and COMPLETED, within each period.

From ClinicalTrials.gov “Basic Results” Data Elements Definitions (DRAFT)
Outcome Measure

“…a table of values for each of the primary and secondary outcome measures for each arm of the clinical trial…”
[Sec. 282(j)(3)(C)(ii)]

Statistical Analysis

“…a table of values for each of the primary and secondary outcome measures…, including the results of scientifically appropriate tests of the statistical significance of such outcome measures.”
[Sec. 282(j)(3)(C)(ii)]
Per FDAAA 801: Collected data for all Primary and Secondary Outcome Measures are required to be reported for an Applicable Clinical Trial whether or not the trial was terminated.

**Helpful Hint:** You can include an “Other Pre-specified” Outcome Measure Type in Registration and/or Results, and you can include a “Post-hoc” Outcome Measure Type in Results.

**Specific Example:** What if a publication includes other Outcome Measures or analyses that were not pre-specified?

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**Are there any shortcuts for entering data?**

**Helpful Hints:** You can “Copy” any Outcome Measure, and only edit the data elements that are different. Sometimes it is possible to use Categories to present multiple “rows” of the same type of data. We have an XML upload feature, and a separate adverse events upload feature.
Are Statistical Analyses Required?

Per FDAAA 801: If the trial is an Applicable Clinical Trial, then you should submit “the results of scientifically appropriate tests of the statistical significance of,” Primary and Secondary Outcome Measures.

Note: We do not review for compliance! We will post a record without statistical analysis sections, but this is not a determination of compliance or even “good practice”.

Serious Adverse Events

“A table of anticipated and unanticipated serious adverse events grouped by organ system, with number and frequency of such event in each arm of the clinical trial.”

[Sec. 282(j)(3)(I)(iii)(I)]
Frequent Adverse Events

“A table of anticipated and unanticipated adverse events that are not included in the [Serious Adverse Events] table … that exceed a frequency of 5 percent within any arm of the clinical trial, grouped by organ system, with number and frequency of such event in each arm of the clinical trial.”

[Sec. 282(j)(3)(I)(iii)(II)]

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>Deltamethrin 6.5 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total, other (not including serious) adverse events</td>
<td>1151/9236 (7.70%)</td>
<td>1206/9105 (6.67%)</td>
</tr>
<tr>
<td>Any adverse drug-related event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>221/810 (7.70%)</td>
<td>170/910 (1.88%)</td>
</tr>
<tr>
<td>Any leading drug-related event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>97/630 (15.37%)</td>
<td>115/630 (18.27%)</td>
</tr>
<tr>
<td>Any serious event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucocutaneous and connective tissue disorders</td>
<td>158/630 (24.92%)</td>
<td>220/630 (34.88%)</td>
</tr>
<tr>
<td>Back pain, %</td>
<td>234/630 (36.97%)</td>
<td>340/630 (53.98%)</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genitourinary dysfunction, %</td>
<td>261/630 (41.36%)</td>
<td>466/630 (73.89%)</td>
</tr>
</tbody>
</table>

† Indicates events were collected by systematic assessment.
A Teratome vocabulary, NCI-CDEA.

Why is organ system required?

FDAAA 801 says that both the Serious and Other (Non-Serious) Adverse Events tables should be “grouped by organ system”

Helpful hint: You can upload Adverse Events from a tab delimited spreadsheet (this can be organized using Excel), if you explicitly follow the instructions

Link located in “Adverse Event Overview”

Download or Upload Adverse Events (BETA)
This is the beta version of a feature for downloading and uploading adverse event tables in a Tab Delimited file format.
How can I provide more contextual information for adverse events?

**Helpful Hint:** Use the Additional Description free text for the Adverse Event Module and/or Adverse Event Term to provide more information!

**Specific Example:** How do I convey adverse event severity and attribution?

<table>
<thead>
<tr>
<th>Time Frame</th>
<th>Duration of study plus follow-up, approximately 2 years total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Additional</strong></td>
<td>Safety population includes all participants who received at least one dose. All adverse events are included whether or not they were attributed to the study intervention.</td>
</tr>
<tr>
<td><strong>Description</strong></td>
<td>Safety population includes all participants who received at least one dose. All adverse events are included whether or not they were attributed to the study intervention.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serious Adverse Events</th>
<th>Placebo</th>
<th>Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular disorders</td>
<td>0/23 (0%)</td>
<td>1/24 (4.17%)</td>
</tr>
<tr>
<td>Hypertension [1]</td>
<td>0/23 (0%)</td>
<td>1/24 (4.17%)</td>
</tr>
</tbody>
</table>

[1] Grade 3 (SBP ≥ 180 mmHg or DBP ≥ 110 mmHg)

Are there examples available that are similar to my trial design?

**Helpful Hint:** Do a search on ClinicalTrials.gov!

**Specific Example:** How do I report a Phase I Study with Pharmacokinetic Outcome Measures?

Who is the Audience?

PI and Clinical Research Team

Other Medical Researchers in same field

Other Medical Researchers in other fields

General Readers of the medical literature

Science Writers

Lay Public (readers of consumer health literature)

**Helpful Hint:** From the “Edit Protocol Record” screen, use the “Preview” link to see the public view in its entirety.
How can I link to manuscript(s) with Results for more info?

Located in “Edit Protocol Record” screen:

- Click “Edit” next to Citations
- Click “Add” a Citation
- Search for the manuscript, enter the PMID, or manually enter the citation text
- Select “Yes” from the “Results Reference” drop down menu

**NOTE!** This can be done in addition to but NOT in lieu of entering data into PRS

How can I provide disclaimers or caveats for the submitted data?

**Helpful Hint:** Use the free text fields to provide contextual information, particularly the Limitations and Caveats data element.

**Specific Example:** What if my study was terminated and I am reporting for transparency, but know that the data are not significant?

**Limitations and Caveats:** Limitations of the study, such as early termination leading to small numbers of subjects analyzed and technical issues with measurement leading to unreliable or uninterpretable data.

Study was terminated due to lack of funding before power analysis target accrual was met. Results are reported for transparency only, and should not be used to extrapolate significant conclusions.

Protocol and Results Review

- Protocol and results must be clear and informative
- Review focuses on:
  - Logic and internal consistency
  - Apparent validity
  - Meaningful entries
  - Formatting
- **Note:** Review is NOT “peer review” and is NOT a determination of compliance
Results QA Review
(i.e., What kinds of things are we trying to prevent in QA Review?)

1. Primary Outcome Measure:
   Measure Title: Six-minute Walk Test
   Measure Description: Patient is instructed to walk as fast as she can. The distance covered during 6 minutes is documented.
   Time Frame: 15 weeks
   Safety Issue: No
   Description: Arm A: Exercise
   The intervention group participated in Nordic walking
   Arm B: Active Comparator
   The active comparison group participated in low-intensity walks.

   Reporting Groups
   Number of Participants Analyzed: 29
   Six-minute Walk Test
   Mean ± Standard Deviation: 37.7 ± 41.6

Example 1
Participant Flow and Outcome Measure Before QA Review

<table>
<thead>
<tr>
<th>Reporting Groups</th>
<th>Description</th>
<th>Overall Study</th>
<th>A. High Intensive Exercise</th>
<th>B. Low Intensive Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Started</td>
<td>34</td>
<td>33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completed</td>
<td>29</td>
<td>29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Completed</td>
<td>5</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lost to Follow-up</td>
<td>5</td>
<td>4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Example 1
Outcome Measure After QA Review
1. Primary Outcome Measure:  
**Measure Title:** Change in Biomarkers of Breast Cancer and Cancer Progression 
**Measure Description:** 
**Time Frame:** Typically 4-6 weeks 
**Safety Issue?** No 

**Group 1** 

<table>
<thead>
<tr>
<th>Measured Values</th>
<th>Group 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Participants Analyzed</td>
<td>32</td>
</tr>
<tr>
<td>Change in Biomarkers of Breast Cancer and Cancer Progression (units: participants)</td>
<td>19</td>
</tr>
</tbody>
</table>

1. Primary Outcome Measure:  
**Measure Title:** Change in Serum VEGF in Breast Cancer 
**Measure Description:** Change in serum VEGF from baseline to post treatment with polyphenon E. 
**Time Frame:** Baseline and 4 to 6 weeks 
**Safety Issue?** No 

**ECGC and Breast Cancer** 

- Single arm for a phase II study of EGCG and breast cancer. Subjects are asked to take 4 polyphenon E (200mg) capsules daily with a meal for the duration of the study. Biomarkers are measured at baseline and then again at post-surgery, the end point for the study. 

<table>
<thead>
<tr>
<th>Measured Values</th>
<th>ECGC and Breast Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Participants Analyzed</td>
<td>58</td>
</tr>
<tr>
<td>Change in Serum VEGF in Breast Cancer (units: pg/ml)</td>
<td>Median (Inter-Quartile Range) 270 (-142.5 to 581.25)</td>
</tr>
</tbody>
</table>

1. Primary Outcome Measure:  
**Measure Title:** Compare the Change in Hemoglobin A1c and the Proportion of Patients Achieving A1C < 7% 
**Measure Description:** 
**Time Frame:** 24 weeks 
**Safety Issue?** Yes 

**Sitagliptin Pioglitazone** 

- Sitagliptin: add sitagliptin 100mg/d to pre-study OADs 
- Pioglitazone: add pioglitazone 30mg/d to pre-study OADs 

<table>
<thead>
<tr>
<th>Measured Values</th>
<th>Sitagliptin Pioglitazone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Participants Analyzed</td>
<td>60 59</td>
</tr>
<tr>
<td>Compare the Change in Hemoglobin A1c and the Proportion of Patients Achieving A1C &lt; 7% (units: participants %)</td>
<td>Least Squares Mean ± Standard Error -0.71 ± 0.12 -0.94 ± 0.12</td>
</tr>
</tbody>
</table>
1. Primary Outcome Measure:
   **Measure Title**: Mean Change in Glycosylated Hemoglobin (A1C)
   **Measure Description**: A1C change from baseline to 24 weeks
   **Time Frame**: 24 weeks
   **Safety Issue?**: Yes
   **Description**:
   - Sitagliptin: add sitagliptin 100mg/d to pre-study OADs
   - Pioglitazone: add pioglitazone 30mg/d to pre-study OADs

   **Reporting Groups**:
   - Sitagliptin
   - Pioglitazone

   **Number of Participants Analyzed**: 60
   **Mean Change in Glycosylated Hemoglobin (A1C)**:
   - **Least Squares Mean ± Standard Error**:
     - Sitagliptin: -0.71 ± 0.12
     - Pioglitazone: -0.94 ± 0.12

2. Primary Outcome Measure:
   **Measure Title**: Adherence (MMAS and Pharmacy Refill Data)
   **Measure Description**: Q 4 Months
   **Safety Issue?**: No
   **Description**:
   - **Intervention**: UC Home Automated Telemanagement
   - **Control**: Best Available Care

   **Reporting Groups**:
   - Intervention
   - Control

   **Number of Participants Analyzed**: 25
   **Adherence (MMAS and Pharmacy Refill Data)**:
   - **Percent** 57

3. Primary Outcome Measure:
   **Measure Title**: Percentage of Participants Adherent to Therapy
   **Measure Description**: Adherence was assessed using the Morisky Medication Adherence Score, a 4 item survey in which participants self-report medication taking behavior. Each question is answered with a No receives a score of 1. The possible scoring range is therefore 0 to 4. Higher scores correlate with better medical adherence. For the purpose of evaluating percent of participants adherent to therapy, the variable was dichotomized to “Adherent” or “Non-adherent”. Any response of Yes to one of the 4 items was scored as “Non-
   **Time Frame**: 12 Months
   **Safety Issue?**: No
   **Description**:
   - **Intervention**: UC Home Automated Telemanagement
   - **Control**: Best Available Care

   **Reporting Groups**:
   - Intervention
   - Control

   **Number of Participants Analyzed**: 25
   **Percentage of Participants Adherent to Therapy**:
   - **Percent** 67
Example 5
Baseline Measure Before QA Review

Baseline Measures

<table>
<thead>
<tr>
<th>Age Continuous [units: years]</th>
<th>Women Pregnant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± Standard Deviation</td>
<td>288 ± .01</td>
</tr>
</tbody>
</table>

Example 5
Baseline Measure After QA Review

Baseline Measures

<table>
<thead>
<tr>
<th>Age Continuous [units: years]</th>
<th>Women Pregnant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± Standard Deviation</td>
<td>27.26 ± 5.81</td>
</tr>
</tbody>
</table>

Example 5
Outcome Measure Before QA Review

Outcome Measure

<table>
<thead>
<tr>
<th>Measure Title</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women Pregnant</td>
<td>Healthy pregnant women between 15 or greater weeks gestation reporting with signs or symptoms of rupture of membranes.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time Frame</th>
<th>Safety Issue</th>
<th>Reporting Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 weeks</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of Participants Analyzed</th>
<th>285</th>
</tr>
</thead>
</table>
Example 5
Outcome Measure After QA Review

<table>
<thead>
<tr>
<th>Measure Title</th>
<th>Measure Description</th>
<th>Reported Measure Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive and Negative for Membrane Rupture Measured Via Clinical Assessment, Chart Review and ROM Plus</td>
<td>Patients underwent two assessments to determine positive or negative membrane rupture status: (1) Standard clinical assessment using fetal leaking from the cul-de-sac, pooling, positive nitrazine test, or ferning and (2) a new combination immunoassay ROM Plus containing a combination of monoclonal and polyclonal antibodies to Placental Protein 12 (PP12) and Alpha-fetoprotein (AFP). The clinical diagnosis of rupture of membranes was confirmed on review of the medical chart records. The Surrogate Markers, the assayed absolute CD+ T cells numbers on participants were measured. The number of participants who were received a daily regimen of 0.200 mg &quot;Kallunk oxide. The powder form 0.200 mg dosage was used as a carrier of Kallunk oxide molecules. The Botanical name of the herb's seed, naturally occurring a herb's seed, was also used as a carrier of Kallunk oxide molecules. The Kallunk oxide safe dose 0.200 mg was studied.</td>
<td>Positive and Negative for Membrane Rupture Measured Via Clinical Assessment, Chart Review and ROM Plus</td>
</tr>
</tbody>
</table>

| Number of Participants Analyzed | 295 | 29 |
| True Positive Membrane Rupture | 285 | 285 |
| False Positive Membrane Rupture | 10 | 10 |
| False Negative Membrane Rupture | 160 | 160 |
| True Negative Membrane Rupture | 95 | 95 |

Example 6
Outcome Measure Before QA Review

<table>
<thead>
<tr>
<th>Measure Title</th>
<th>Measure Description</th>
<th>Reported Measure Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Assayed Absolute Immune Cells Count (CD3, CD4, and CD8+ T Cells Numbers)</td>
<td>The &quot;Arm 1&quot; participants were received one drug that is a combination of a traditional alternative (CAM) medicine &quot;Kallunk Oxide&quot;. The number of participants who were received the drug for once daily dose in 5 days treatment. The powder form 0.200 mg dosage was used as a carrier of Kallunk oxide molecules. The Botanical name of the antidote is &quot;Piper Longum&quot;. The number of participants who were received a daily regimen of 0.200 mg &quot;Kallunk oxide. The powder form 0.200 mg dosage was used as a carrier of Kallunk oxide molecules. The Botanical name of the herb's seed, naturally occurring a herb's seed, was also used as a carrier of Kallunk oxide molecules. The Kallunk oxide safe dose 0.200 mg was studied.</td>
<td>Reported Measure Group (Clinical Assessment, Chart Review)</td>
</tr>
</tbody>
</table>

| Number of Participants Analyzed | 40 | 40 |
| The Assayed Absolute Immune Cells Count (CD3, CD4, and CD8+ T Cells Numbers) | 38 (1 to 40) | 38 (1 to 40) |

Example 6
Outcome Measure After QA Review

<table>
<thead>
<tr>
<th>Measure Title</th>
<th>Measure Description</th>
<th>Reported Measure Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD3+ T Cell Change</td>
<td>The &quot;Arm 1&quot; participant's blood samples were analyzed. The study was depended on contrast between absolute CD3+ T cells count and the later absolute CD3+ T cell count was measured. Flow Cytometry laboratory analysis was performed.</td>
<td>Reported Measure Group (Clinical Assessment, Chart Review)</td>
</tr>
</tbody>
</table>

| Number of Participants Analyzed | 40 |
| CD3+ T Cell Change | 175 ± 30 | 175 ± 30 |
Where can I get information?

www.clinicaltrials.gov

• General info about Submitting studies:
  http://clinicaltrials.gov/ct2/manage-recs

Where do I send questions?

register@clinicaltrials.gov

Questions?

National Library of Medicine & Lister Hill Center for Biomedical Communications
Bethesda, MD