ClinicalTrials.gov
Updated Quality Control and Posting Procedures

October 15, 2019
Outline

1. Background
   Current process and regulation

2. Procedures
   Examples

3. Implementation
   Initial scope and timeline
Current: Results information submission

1. Sponsor Account

2. Update study record
   - Responsible Party
   - Registration Information
   - Results Information
   - Automated Validation
   - Address QC Review Issues
   - QC Review Comments

3. Submit study record
   - QC Review Staff
   - Manual Validation
   - Quality Control Review
   - No "Major" Issues
   - "Major" Issues

4. Backend Processing
   - Public Posting
Quality Control (QC) Review Process

Two-part review process for submitted study records

**Before submission:** Automated validation rules in the Protocol Registration and Results System (PRS)

**After submission:** Manual review by NLM staff using established review criteria to identify apparent errors, deficiencies, and inconsistencies.
- “Major” issues must be addressed
- “Advisory” issues are suggestions to help improve the clarity of the record and are optional to address
## PRS: Example of Automated Validation Rule

### ERROR – Information is missing

<table>
<thead>
<tr>
<th>Edit</th>
<th>Arm/Group Title</th>
<th>Remuverol</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edit</td>
<td>Arm/Group Description</td>
<td>Participants received Remuverol 15 ...</td>
<td>Participants received Remuverol placebo</td>
<td></td>
</tr>
<tr>
<td>Edit</td>
<td>Overall Number of Baseline Participants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Baseline Analysis Population Description</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **ERROR**: The Overall Number of Baseline Participants has not been entered.

### CORRECTED – Missing information added

<table>
<thead>
<tr>
<th>Edit</th>
<th>Arm/Group Title</th>
<th>Remuverol</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edit</td>
<td>Arm/Group Description</td>
<td>Participants received Remuverol 15 ...</td>
<td>Participants received Remuverol placebo</td>
<td></td>
</tr>
<tr>
<td>Edit</td>
<td>Overall Number of Baseline Participants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Baseline Analysis Population Description</td>
<td>101</td>
<td>99</td>
<td>200</td>
</tr>
</tbody>
</table>
Public View: Example of Submitted Results

Results Submitted – Not Posted on ClinicalTrials.gov

Results information has been submitted to ClinicalTrials.gov by the sponsor or investigator, but is not yet publicly available (or "posted") on ClinicalTrials.gov. The submitted information may not be available if it is pending Quality Control (QC) Review by the National Library of Medicine (NLM) or if issues identified during QC review are being addressed or corrected by the sponsor or investigator. NLM's limited QC review assesses for apparent errors, deficiencies, or inconsistencies. NLM staff do not verify the scientific validity or relevance of the submitted information.

<table>
<thead>
<tr>
<th>Recruitment Status</th>
<th>Completed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actual Primary Completion Date</td>
<td>January 25, 2019</td>
</tr>
<tr>
<td>Actual Study Completion Date</td>
<td>January 25, 2019</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Submission Cycle</th>
<th>Results Submitted to ClinicalTrials.gov</th>
<th>Results Returned after Quality Control Review</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>January 18, 2020</td>
<td></td>
</tr>
</tbody>
</table>
QC Review Criteria

Review Identifies Apparent:

✓ Errors
✓ Deficiencies
✓ Inconsistencies

Protocol Registration and Results Review Criteria:
https://prsinfo.clinicaltrials.gov/ResultsDetailedReviewItems.pdf
### Baseline Measure

<table>
<thead>
<tr>
<th>Measure Type: Count of Participants</th>
<th>Number Analyzed</th>
<th>Remuverol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance Status</td>
<td>29 participants</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

#### Standard QC Review Comment

Quality Control Review Comment provided by the National Library of Medicine [1]:

**Major Issues:** 1) Information about the scale used in this measure appears to be missing. Additional information about the scale is typically needed to interpret measure data.

The Measure includes a scale. Please briefly describe the criteria for each indicated Category AND/OR please complete the scale information:

- Specify Full Scale Name and Construct (i.e., indicate what the scale measures if not clear from name)
- Specify minimum and maximum possible values and specify which values are considered better or worse outcome
- If a series of subscales are combined for a TOTAL overall score, specify TOTAL possible minimum and maximum values.
- Use "Units on a scale" or "Scores on a scale" if no other units apply.

For additional information about entering results, see Helpful Hints and Common Errors.
### Example of QC Review Comment Addressed

<table>
<thead>
<tr>
<th>Baseline Measure</th>
<th>Arm/Group Title</th>
<th>Remuverol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Performance Status</strong></td>
<td>Number Analyzed</td>
<td>29 participants</td>
</tr>
<tr>
<td>Measure Type: Count of Participants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unit of measure: participants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 – Fully active</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>1 – Restricted strenuous activity, ambulatory</td>
<td></td>
<td>23</td>
</tr>
<tr>
<td>2 – Ambulatory, difficulty walking</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>3 – Limited self-care, partly confined to bed</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>4 – Completely disabled, no self-care</td>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>

[1] 5-point, ordinal scale specifying patient’s ability to perform activities from 0 (fully active) to 4 (completely disabled, no self-care)
Regulation

- **42 CFR 11.44** When must clinical trial results information be submitted for applicable clinical trials ...?
  - Standard submission deadline - results information must be submitted no later than 1 year after the Primary Completion Date
    - Delayed submission of results information permitted in specific circumstances

- **42 CFR 11.52** By when will the NIH Director post submitted clinical trial results information?
  - “… will post publicly clinical trial results information on ClinicalTrials.gov not later than 30 calendar days after the date of submission.”
Final Rule: Posting and Quality Control

- Intend to continue a form of quality control (QC) review at time of submission that is similar to procedures we have been using
  - (1) automated validation rules; (2) manual review (81 FR 65064)
- Interpret the statutory posting deadline to be a clearly delineated timeline between submission and posting (81 FR 65101)
  - Information will be posted even if QC review process has not concluded
  - Posted record will contain information to make clear process has not concluded
  - Will evaluate ways posted record could specify data elements that may contain errors, deficiencies, and/or inconsistencies
42 CFR 11.64(b) When must clinical trial information submitted to ClinicalTrials.gov be updated or corrected?

• Director may provide electronic notification to the responsible party of apparent errors, deficiencies, and/or inconsistencies that are identified by established quality control review procedures.

• The responsible party must correct or address all apparent errors, deficiencies, and/or inconsistencies in clinical trial results information not later than 25 calendar days after the date of electronic notification.
Summary

NIH is required to post clinical trial information for applicable clinical trials on ClinicalTrials.gov within 30 days of submission, regardless of whether the quality control review process is complete.
Procedures

Note: Examples are intended for explanatory purposes. Specific wording and appearance may not reflect actual implementation.
Posting Results Within 30 Days

• Will post study record with results information following each QC review

• If QC review process has not concluded, include two types of information:
  1. General notice that QC review process has not concluded
  2. Brief, standard QC review comment (“major” issue) identifying relevant section and data element

• Responsible party will continue to receive in the PRS the QC review comments with additional details about the “major” issue and any “advisory” issues

• Will post all versions of QC reviewed record until process concludes (no “major” issues)

• Archive site will provide access to all posted versions (History of Changes), including those with QC review issues, consistent with current practices
Results Information Submission

1. Sponsor Account
2. Responsible Party
   - Registration Information
   - Automated Validation
3. QC Review Staff
   - Manual Validation
   - Quality Control Review
   - No "Major" Issues
   - "Major" Issues
4. Public Posting
   - General Notice and Standard QC Review Comments
Scope: Posting Results Within 30 Days

- Will apply to the following applicable clinical trials (ACTs) submitted with results information
  - Study Start Date on or after January 18, 2017 (Final Rule Effective Date); AND
  - Results information first submitted after implementation date (estimate January 2020)
### Results Baseline Characteristics

<table>
<thead>
<tr>
<th>Measure Type: Count of Participants</th>
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**Quality Control Review Comment provided by the National Library of Medicine [1]:**

**Major Issues:** 1) Information about the scale used in this measure appears to be missing. Additional information about the scale is typically needed to interpret measure data.

The Measure includes a scale. Please briefly describe the criteria for each indicated Category AND/OR please complete the scale information:
- Specify Full Scale Name and Construct (i.e., indicate what the scale measures if not clear from name)
- Specify minimum and maximum possible values and specify which values are considered better or worse outcome
- If a series of subscales are combined for a TOTAL overall score, specify TOTAL possible minimum and maximum values.
- Use "Units on a scale" or "Scores on a scale" if no other units apply.

For additional information about entering results, see Helpful Hints and Common Errors.
Results Submitted – Quality Control Review Process Has Not Concluded

Results information for an applicable clinical trial (ACT) is posted within 30 days of submission even if the submission has not completed the ClinicalTrials.gov quality control (QC) review process. Results information is submitted to ClinicalTrials.gov by the sponsor or investigator, and NLM staff assess for apparent errors, deficiencies, or inconsistencies. NLM staff do not verify the scientific validity or relevance of the submitted information.

All versions of ACT results information submissions, that have not completed the QC review process are posted on ClinicalTrials.gov (since January 2020). After the QC review process is completed, the results information is posted without QC review comments and previous versions are archived.

<table>
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<tbody>
<tr>
<td>1</td>
<td>January 18, 2020</td>
<td>February 17, 2020 Submission with QC Comments</td>
</tr>
<tr>
<td>2</td>
<td>March 10, 2020</td>
<td></td>
</tr>
</tbody>
</table>
Quality Control Review Has Not Concluded

Note: The results information displayed below has not completed the quality control (QC) review process. ClinicalTrials.gov must post results information for applicable clinical trials (ACTs) within 30 days of submission, even if the submission has not completed the QC review process. The study sponsor or investigator is responsible for ensuring the results information meets the QC review criteria.

This submission includes brief standardized QC review comments added by the National Library of Medicine. These comments indicate the location of apparent errors, deficiencies, or inconsistencies.

For more information, see the Final Rule (42 CFR Part 11) Information page.

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Implementation
Other Supporting Steps

• Revised QC review commenting approach to distinguish “major” and “advisory” issues
• Updated QC Review Criteria documents
• Shared data on QC review cycles and common “major” issues
• Reached staffing goals and eliminated results backlog
• Launched additional training resources
• **Pending** – Make available list of brief, standard QC review comments used to identify “major” issues
PRS Guided Tutorials (Beta)

• Launched August 13\textsuperscript{th}
• Access on ClinicalTrials.gov or PRS
• Results submission content
• Registration content expected in late 2019 or early 2020
• Feedback needed \textit{via} survey: https://bit.ly/2N1mMHV
• Further evaluation planned
Communication

We will inform you of further updates using:

• “What’s New”
  • PRSTest, PRS, and ClinicalTrials.gov
• Hot Off thePRS! email bulletin
  • Provides timely updates for submitters
  • Sign up: https://bit.ly/33qcZBb
Results Information Submission

1. Sponsor Account
   - Update study record

2. Responsible Party
   - Registration Information
   - Automated Validation
   - Address QC Review Issues

3. QC Review Staff
   - Manual Validation
   - Quality Control Review
   - QC Review Comments

4. Public Posting
   - General Notice and Standard QC Review Comments

ClinicalTrials.gov
Implementation Plan

This procedure applies as follows:

1. Applicable Clinical Trial (ACT)
2. Study Start Date on or after January 18, 2017
3. Results information first submitted after January 2020 (specific day TBD)
4. Posted within 30 days (with or without QC Review Comments)
Questions?

Contact
register@clinicaltrials.gov

For more information see: https://prsinfo.clinicaltrials.gov

Sign up for the email bulletin *Hot off the PRS!*

https://bit.ly/33qcZBb