ClinicalTrials.gov Modernization and How to Provide Your Input

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Agenda

• ClinicalTrials.gov Background
• Modernization Overview
• Request for Information (RFI)
• Provide Your Input
Overview

- 320,000+ registrations
- 40,000+ posted results
- 145,000 unique visitors daily
- 215 million page views per month
Benefits of Comprehensive Registration and Results Reporting

- Honor commitment to participants that their contributions will advance science; support enrollment
- Mitigate publication bias
- Advance stewardship and accountability
  - Identify unmet research needs
  - Facilitate complete reporting
  - Avoid unnecessary study duplication
  - Evaluate research integrity
- Support evidence-based medicine

All contribute to increased public trust in clinical research
ClinicalTrials.gov Modernization

Ensure ClinicalTrials.gov continues to be a trusted and valued premier public health resource that provides maximum value to the public and serves its mission well into the future.
Aim 1: Collect complete and informative information about clinical studies

1. Sponsor Account
2. Registration Information
3. Manual Validation – Quality Control Review
4. Public Posting

Create new study record → Submit study record → Backend Processing (NCT Number Assigned)

Automated Validation

ClinicalTrials.gov

National Library of Medicine
Aim 2: Facilitate use of information to help the public and researchers find studies of interest
ClinicalTrials.gov: Information Scaffold

- Journal Publications
- Results Database
- Conference Abstracts
- Clinical Study Reports

Individual Patient Data (IPD) Repositories
  - Uncoded
  - Coded
  - Analyzable

NCT Number

Summary
  - Results

Other information (e.g., press releases, news articles, editorials)

NCT Number

Full Protocols

Statistical Analysis Plans

Informed Consent Forms

Other Study Documents

National Library of Medicine
ClinicalTrials.gov Key Roles and Principles

• Sponsor or investigator
  • Submits study information directly to ClinicalTrials.gov; keeps up-to-date
  • Responsible for safety and validity of study and following applicable laws and regulations

• NLM conducts a limited quality control (QC) review
  • Identifying apparent errors, deficiencies, or inconsistencies
  • Listing does not mean study itself has been evaluated by U.S. government

• Site lists information for many uses, including research participation
  • Participation is an important personal decision; encourage learning about all options and consulting with health care provider and other trusted advisors

Source: Disclaimer https://clinicaltrials.gov/ct2/about-site/disclaimer
ClinicalTrials.gov Modernization Overview

Current year: Engagement
- Engage with stakeholders to determine and validate approach and specifications
  - Request for Information (RFI) and Public Meeting
- Develop modernization roadmap
- Enhance internal business processes

Future (years 2 – 5): Implementation
- Implement modernization roadmap
  - User testing/evaluation and continue engagement
  - Improvements to support compatibility across clinical trial lifecycle (seamless end-to-end process)
  - Upgrade system infrastructure components
Request for Information (RFI): ClinicalTrials.gov Modernization

Notice Number: NOT-LM-20-003

Key Dates

Response Date: March 14, 2020

Related Announcements

None

Issued by

National Library of Medicine (NLM)

Purpose

Introduction

The purpose of this Request for Information is to solicit public input to guide the National Library of Medicine (NLM) in planning infrastructure enhancements aimed at users and submitters of ClinicalTrials.gov as part of a multi-year modernization initiative.

“... we aim to gather information to help maximize the value of ClinicalTrials.gov to its many users, while continuing to provide essential services to support existing legal and policy requirements.”

- March 14 – responses due

We Request Your Input on These Topics

1. Website functionality
2. Information submission
3. Data standards

Note: RFI not intended to modify existing legal and policy requirements for clinical trial registration and results submission
1. Provide Your Input: Website Functionality

a. Uses that are not currently supported and examples of other good models

b. Resources that should be linked from ClinicalTrials.gov and explanation of why such resources are useful

c. Examples of how you currently use site, what features work well, and what could be improved

d. Describe whether uses are dependent on wide range of studies or more limited and explain any limiting criteria that are useful to you
ClinicalTrials.gov Users by Role

42% Patients and Caregivers, including:
- 24% Patient
- 8% Family/friend of patient
- 5% Healthcare provider
- 5% Healthy person

9% Not Categorized (“Other”)

49% Researchers and Others, including:
- 26% Scientist/researcher
- 8% Clinical research support (e.g., regulatory affairs)
- 6% Clinical trials staff
- 5% Student/educator
- 3% Medical communications
- 2% Librarian or information professional
- <1% IRB or ethics committee member

Source: ClinicalTrials.gov Qualtrics Survey Data: 1 July 2019 – 31 December 2019 (n=3,399)
Recent Website Updates

- Options to improve first search precision
  A. Recruitment status
  B. Location
- Research participation resources and disclaimer
  • Help people learn what ClinicalTrials.gov listing does and doesn’t mean
- Search results options; filters and custom display
Beta API (Application Programming Interface)

• Supports 3rd party electronic use of ClinicalTrials.gov content
• Over 300 search fields available (current API has 24 key fields)
• Formats: XML, JSON, SVI, tree
• Query and Info URLs
• Documentation and interactive training demos
• https://clinicaltrials.gov/api/gui
### Content of ClinicalTrials.gov (as of Jan 10, 2020)

<table>
<thead>
<tr>
<th>Study and Intervention Type</th>
<th>Number Registered Studies (% Total)</th>
<th>No. Studies with Posted Results (% Total) ***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Records</td>
<td>326,612</td>
<td>40,841</td>
</tr>
<tr>
<td>Interventional Studies</td>
<td>257,482 (79%)</td>
<td>38,361 (94%)</td>
</tr>
<tr>
<td>Type of Intervention*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug or biologic</td>
<td>144,503</td>
<td>29,807</td>
</tr>
<tr>
<td>Behavioral, other</td>
<td>83,013</td>
<td>7,279</td>
</tr>
<tr>
<td>Surgical procedure</td>
<td>27,089</td>
<td>2,068</td>
</tr>
<tr>
<td>Device**</td>
<td>32,977</td>
<td>5,063</td>
</tr>
<tr>
<td>Observational Studies</td>
<td>67,671 (21%)</td>
<td>2,480 (6%)</td>
</tr>
<tr>
<td>Expanded Access</td>
<td>603</td>
<td>N/A</td>
</tr>
</tbody>
</table>

* A study may include more than one type of intervention, meaning that a single study may be counted more than once.

** A total of 856 applicable device clinical trials have been submitted as "delayed posting" under FDAAA/Part 11 (i.e., in “lockbox”) and are not included in the counts of trials.

*** Results are required to be submitted only for certain studies.

### Location of Registered Studies (as of Jan 10, 2020)

<table>
<thead>
<tr>
<th>Location of Study Sites</th>
<th>Number Registered Studies (% Total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States (U.S.) only</td>
<td>110,661 (34%)</td>
</tr>
<tr>
<td>Both U.S. and non-U.S.</td>
<td>17,051 (5%)</td>
</tr>
<tr>
<td>Non-U.S. Only</td>
<td>160,085 (49%)</td>
</tr>
<tr>
<td>Not provided</td>
<td>38,815 (12%)</td>
</tr>
<tr>
<td>Total</td>
<td>326,612 (100%)</td>
</tr>
</tbody>
</table>

**Source:** ClinicalTrials.gov Trends, Charts, Maps (Jan 10, 2020) [https://clinicaltrials.gov/ct2/resources/trends](https://clinicaltrials.gov/ct2/resources/trends)
2. Provide Your Input: Information Submission

a. Steps in submission process that would most benefit from improvements
b. Opportunities for alignment with organization processes, such as interoperability with clinical trial management software or tools
c. Novel or emerging methods for enhancing quality and submitted content and displayed on ClinicalTrials.gov
d. Informational materials that would make process easier
e. Ways to credit, incentivize, or recognize efforts of individuals and organizations submitting complete, accurate, and timely information
Basics of Registration Information Submission

**ClinicalTrials.gov PRS**
Protocol Registration and Results System

- Interactive data entry or automated upload
- Anyone can enter data, but “responsible party” must submit
- Content reflects:
  - Legal requirements
  - International standards
  - Good reporting practices
- NIH grant application aligns with subset of content
Basics of Results Information Submission

ClinicalTrials.gov PRS
Protocol Registration and Results System

- Structure supports:
  - Complete reporting
  - Efficient quality review
  - Consistent data display
  - Detailed search and integration of other NLM resources
- Aligns with good reporting practices (CONSORT)
Quality Control Review Process and Volume

• Quality control review focused on identifying apparent errors, deficiencies, or inconsistencies

• Review all registration study records < 5 days
  • ~1,200 new registration records per week (includes new records and previously reviewed records that did not meet QC review criteria)
  • ~6,600 updated registration records per week

• Review all results study records < 25 days
  • ~280 new results records per week (includes new records and previously reviewed records that did not meet QC review criteria)
  • ~140 updated results records per week
Quality Control Review Example

Baseline Measures – Example

<table>
<thead>
<tr>
<th>GOG Performance Status [units: participants]</th>
<th>Drug X</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>48</td>
</tr>
<tr>
<td>1</td>
<td>27</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

Baseline Measures – Example Corrected

<table>
<thead>
<tr>
<th>Gynecological Oncology Group (GOG) Performance Status [units: participants]</th>
<th>Drug X</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – Fully Active</td>
<td>48</td>
</tr>
<tr>
<td>1 – Restricted Strenuous Activity, Ambulatory</td>
<td>27</td>
</tr>
<tr>
<td>2 – Ambulatory, Difficulty Walking</td>
<td>4</td>
</tr>
<tr>
<td>3 – Limited Self-Care, Partly Confined to Bed</td>
<td>0</td>
</tr>
<tr>
<td>4 – Completely Disabled, No Self-Care</td>
<td>0</td>
</tr>
</tbody>
</table>

5-point, ordinal scale specifying patient's ability to perform activities from 0 (fully active) to 4 (completely disabled, no self-care)
Results Submission “Success:”
Industry and Non-Industry Orgs

Sample: initial results submitted > 1 May 2017 and QC reviewed < 30 Sept 2018

<table>
<thead>
<tr>
<th>Org Type</th>
<th># Orgs</th>
<th>#Records</th>
<th>% Success</th>
<th>#Records</th>
<th>% Success</th>
</tr>
</thead>
<tbody>
<tr>
<td>Industry</td>
<td>572</td>
<td>2780</td>
<td>31</td>
<td>2140</td>
<td>77</td>
</tr>
<tr>
<td>Non-Industry</td>
<td>777</td>
<td>3486</td>
<td>17</td>
<td>2359</td>
<td>63</td>
</tr>
<tr>
<td>All</td>
<td>1349</td>
<td>6266</td>
<td>23</td>
<td>4499</td>
<td>70</td>
</tr>
</tbody>
</table>


\[ \text{%Success} = 100\% \times \frac{\text{# Records with no Major Issues}}{\text{# Total Record Submissions}} \]
PRS Guided Tutorials

• Launched August 2019
• Access on ClinicalTrials.gov or PRS
• Results submission content first
  • Registration content expected in early 2020
• Collecting feedback via survey
  • https://bit.ly/2N1mMHV
  • Further evaluation planned
3. Provide Your Input: Data Standards

a. Input on ways to balance use of standards while also retaining flexibility to accurately reflect content of study protocol and statistical analysis plan

b. Name specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov
Clinical Trial Lifecycle Opportunities

Clinical Trial Milestones

1. ID Research Question
2. Finding Funding
3. Designing Study
4. Developing Protocol
5. Obtaining Approval
6. Registration
7. Recruiting Participants
8. Enrolling Participants
9. Collecting Data
10. Updating Study Record
11. Analyzing Data
12. Disseminating Results
13. Reporting
14. Results Reporting
15. Access to Individual Participant Data (IPD)

Time

Before Trial Initiation

During Trial Conduct

After Trial Completion

Trial Start Date

Trial Completion Date

National Library of Medicine
Submitting Feedback

• “The Insider’s Guide to Effective Commenting on NIH Policies” (from the NIH Office of Science Policy)
  - Be specific
  - Provide data
  - Answer the questions
  - Include new ideas
  - Emphasize what matters most

Submitting Feedback - Reminders

• **March 14, 2020** is the deadline for submitting feedback using web-based form accessible from the RFI:

• Submitted responses will be posted publicly without change after the close of the comment period.
  • Do not include proprietary, classified, confidential, or sensitive information
  • Do not include personally identifiable information you do not wish to be made public

• RFI not intended to modify existing legal and policy requirements for clinical trial registration and results submission
Public Meeting – April 30, 2020

• We will share a summary of the RFI responses and initial interpretation of themes and priorities
• Opportunity for further discussion and clarification of topics
• More details on how to register will be available soon
  • Hosted at the NIH in Bethesda, MD and also available by Webcast
Stay up to date with **Hot Off the PRS!**

- E-mail bulletin
- Provides timely updates for PRS users on new information about the PRS and ClinicalTrials.gov

**What’s New?**

Welcome to Hot Off the PRS!

We are excited to share the first Hot Off the PRS bulletin. We are planning to use the bulletin to provide timely announcements about the Protocol Registration and Results System (PRS), including updates on new features planned for the PRS, 42 CFR Part 11 implementation, and resources for PRS users. We will still continue to post announcements of new features and resources when they are available in the What’s New on ClinicalTrials.gov and in the PRS. We hope you find Hot Off the PRS to be a valuable resource for staying informed.

Note: This bulletin replaced the NIH FDAAA Update listserv on Aug. 1, 2019.

**Resources**

Parallel Study Design Example Has Been Updated

The [Example Studies for Results Data Entry](https://bit.ly/33qcZBb) are example study records and study papers that are useful for understanding key concepts for results data entry in the PRS. The Parallel Study Design example has been updated for consistency with the data elements and content in the Final Rule for Clinical Trials Registration and Results Information Submission (42 CFR Part 11). The example also now reflects the current display of study arms Information on ClinicalTrials.gov. More updates for these example...
Thank You

Questions? Submit to the ClinicalTrials.gov Information Team
National Library of Medicine
register@clinicaltrials.gov

ClinicalTrials.gov Modernization Information
https://clinicaltrials.gov/ct2/about-site/modernization

A recording of this presentation will be posted within 7 days.