ClinicalTrials.gov Modernization

Rebecca J. Williams, Acting Director of ClinicalTrials.gov

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.
Welcome and Introduction

Carrie D. Wolinetz, PhD
Associate Director for
Science Policy, NIH
General Agenda

9:30 a.m. Welcome and Introduction
9:45 a.m. Overview of ClinicalTrials.gov Modernization Effort and High-level Summary of Request for Information (RFI) Public Comments
NLM Welcome and Introduction to Board of Regents Public Service Working Group
10:30 a.m. Information Submission Panel
11:15 a.m. Break
11:30 a.m. Website Functionality Panel
12:20 p.m. Summary and Next Steps
12:30 p.m. Adjourn
Overview of ClinicalTrials.gov Modernization Effort

Rebecca J. Williams, PharmD, MPH
Acting Director of ClinicalTrials.gov
Goals of the Public Meeting

Provide an overview of ClinicalTrials.gov Modernization
Share high-level summary of Request for Information (RFI) comments and key themes
Gather diverse stakeholders to share interests and needs
Obtain further information on RFI themes and topic areas
Overview

330,000+ registrations

42,000+ posted results

3.5 million visitors monthly

Benefits of Comprehensive Registration and Results Reporting

All contribute to increased public trust in clinical research

- 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
ClinicalTrials.gov Aims

Two primary aims in support of realizing the intended benefits of comprehensive registration and results reporting

• Aim 1: Collect complete and informative information about clinical studies

• Aim 2: Facilitate use of information to help the public and researchers find studies of interest
Aim 1: Collect complete and informative information about clinical studies

1. Sponsor Account
   - Create new study record

2. Registration Information
   - Automated Validation
   - Submit study record

3. Manual Validation – Quality Control Review
   - Backend processing (NCT number assigned)

4. Public Posting

See Submit Studies on ClinicalTrials.gov for information on how to apply for an account, how to register your study, and how to submit results.
Submission Review Process and Volume

- Automated validation rules detect issues before submission
- Manual quality control (QC) review after submission focuses on identifying apparent errors, deficiencies, or inconsistencies
- NLM staff review registration study records within 2 to 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
- NLM staff 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
Overall and COVID-19-Related New Study Registrations Jan 1, 2020 – Apr 22, 2020

Cumulative Count of Study Registrations

<table>
<thead>
<tr>
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<th>Number of Non-COVID-19 Study Records</th>
<th>Number of COVID-19-Related Study Records</th>
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<td>22-Apr-2020</td>
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Submission Support Materials

- PRS User’s Guide
- PRS Guided Tutorials (shown on right)
- Data Element Definitions
- Templates and Submission Checklists
- Study Design Examples
- Frequently Asked Questions (FAQs)
- Legal, Regulatory, and Policy Requirements Information
COVID-19: Submitter Information

Issued new support materials to address top questions (updated as needed)


What's New

2020

April 2, 2020

- Answers to Questions from Responsible Parties on Submitting Information to ClinicalTrials.gov Related to Coronavirus (COVID-19) Available: Questions about submitting information to the ClinicalTrials.gov Protocol Registration and Results System (PRS) have been addressed in Responses to Top Questions from Responsible Parties Related to Coronavirus (COVID-19) (PDF). COVID-19 is an emerging, rapidly evolving situation. These responses will be updated as needed. Document is available on the Support Materials page.
Aim 2: Facilitate use of information to help the public and researchers find studies of interest

ClinicalTrials.gov is a database of privately and publicly funded clinical studies conducted around the world.

Explore 333,173 research studies in all 50 states and in 209 countries.

Clinical Trials.gov is a resource provided by the U.S. National Library of Medicine.

IMPORTANT: Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

Before participating in a study, talk to your health care provider and learn about the risks and potential benefits.

Find a trial that's right for you

Breast Cancer Trials

Healthcare Professionals

Find a Trial That's Right for You

Browse Trials

Match to Study

Healthcare Professionals

Learn how NCT can work for you

Search

Advanced Search
ClinicalTrials.gov Search Statistics:

This year

10.2 million clicks

Compared to Last Year

7.7 million clicks

This year

65.6 million page visits

13.1 million users

20.9 million sessions

Last Year

46.8 million page visits

9.1 million users

15 million sessions
COVID-19: Added related resources and link to registered studies
NIH does not endorse or recommend any commercial products, processes, or services.
COVID-19 has rapidly developed into a worldwide pandemic with a significant health and economic burden. There are currently no approved treatments or preventative therapeutic strategies. Hundreds of clinical studies have been registered with the intention of discovering effective treatments. Here, we review currently registered interventional clinical trials for the treatment and prevention of COVID-19 to provide an overall summary and insight into the global response.

Keywords: #2019-ncov #covid-19 #sars-cov-2 #coronavirus #pandemic
Mitigate Publication Bias

Publication of NIH-Funded Clinical Trials (Ross et al. *BMJ* 2012)

- 46% NIH-funded trials published within 30 months of completion
- A third of trials remained unpublished after a median of 51 months after completion

ClinicalTrials.gov is a unique source of results

- ~50% of posted results are not yet published in a journal
ClinicalTrials.gov: Information Scaffold

- Journal Publications
- Results Database
- Conference Abstracts
- Clinical Study Reports
- Individual Patient Data (IPD) Repositories
  - Uncoded
  - Coded
  - Analyzable
  - NCT Number
- Other information (e.g., press releases, news articles, editorials)
  - NCT Number
- ClinicalTrials.gov
- Full Protocols
- Statistical Analysis Plans
- Informed Consent Forms
- Other Study Documents
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.
Who is Modernization for?

**Internal**
- Information specialists, reviewers, developers
- Management, policy, oversight

**External**
- Patients, healthcare providers, and related organizations
- Data submitters (investigators, sponsors, 3rd party services)
- Researchers and journal editors
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
Infrastructure Accomplishments 2020

- Migrated development, test, and production environments from NLM’s Lister Hill National Center for Biomedical Communications to NLM’s National Center for Biotechnology Information (NCBI)
  - Note: ClinicalTrials.gov program was organizationally shifted several years ago
- New server hardware
- Upgraded operating system, servers, version control system, software components, database
- Adopted NCBI security posture, including network, firewall, and patching methodology
- Pilot projects to evaluate cloud infrastructure approaches
Clinical Trial Lifecycle Opportunities

Before Trial Initiation
- ID Research Question
- Find Funding
- Design Study
- Develop Protocol
- Obtain Approvals

During Trial Conduct
- Enroll Participants
- Collect Data
- Update Study Records at ClinicalTrials.gov
- Registration at ClinicalTrials.gov

After Trial Completion
- Recruit Participation
- Analyze Data
- Disseminate Results
- Report Results at ClinicalTrials.gov
- Access to IPD

Time
- Trial Start Date
- Trial End Date

Before Trial Initiation
- Trial Start Date
- Trial End Date
- After Trial Completion

National Library of Medicine
Patricia Flatley Brennan, RN, PhD

Director of National Library of Medicine (NLM)

NLM Welcome and Introduction to Board of Regents Public Service Working Group
NLM Response to COVID-19: Resources

• **PubMed Central**
  • Expanding access to ~40k AI-ready articles, 2M accesses

• **Exploiting machine-readable COVID-19 literature**
  • Kaggle - challenge AI-fueled insights from literature
  • TREC-COVID challenge to search engines
  • LitCOVID - AI-curated literature hub organizing and exploring scientific information

• **ClinicalTrials.gov**
  • >900 clinical studies
  • Display of studies listed in WHO portal with >900 studies

• **GenBank**
  • Fully automated 24-hour submission and release of data

• **Standards and Terminologies**
  • C19 updates to UMLS, MeSH, RxNorm, LOINC, Common Data Elements Repository, VSAC

• **NLM support of libraries virtually engaging their communities**
Enhancing Access to COVID-19 Literature and Molecular Data Resources

Developing and strengthening infrastructure, mechanisms, and tools to **ensure continued access to high quality literature** when libraries are closed during public health events.

Supporting chemical editing for **MeSH** and **ChemIDplus** to cover COVID-19/Coronavirus SARS/MERS-related drugs and chemicals.

**Ensuring NLM Collection Materials for COVID-19** are available electronically.

Extending **PMC submission workstreams** to facilitate AI/machine learning.

Developing a **PubMed portal** for COVID-19 literature collected through **LitCOVID text mining**.

Ensuring rapid sequence submission and access through **GenBank** and **VirusHub**.

Using **SRA** in the cloud for viral surveillance and discovery.
Improving Quality of Clinical Data for Research and Care

• Implementation guidelines, training for standardization, and addition of codes to support COVID-19-related laboratory tests within LOINC

• Value Set Authority Center (VSAC) FHIR API development to enable standardized sharing of COVID-19 terminology updates
Accelerating Research: Deep Phenotyping, Text-mining, and Real-time Surveillance

• Mining clinical data for ‘deep phenotyping’ models that can be used to identify or predict presence of COVID-19
• AI/Machine Learning, analytics, and visualization of image and clinical data to support clinical decisions in real time
• Public health surveillance using virus genomics, health data, and social media data to identify spread

CoronavirusStaffQuery@od.nih.gov
National Library of Medicine Board of Regents

The NLM Board of Regents was established in 1956 by the same Act that created the National Library of Medicine.

Serves as advisory body to the Secretary, HHS

Serves as advisory body to the Assistant Secretary for Health and others

Meets three times a year
Summary of Working Group Charge

The NLM Board of Regents Public Service Working Group is charged to explore topics related to ClinicalTrials.gov modernization such as, but not limited to, ways NLM can:

- Maintain the *integrity* of ClinicalTrials.gov as a trusted resource
- Maximize the *utility* of the growing corpus of information
- Connect with stakeholders through *engagement* to ensure evolving needs are understood and considered

Report regularly in open session to the NLM Board of Regents
“Thanks everyone for joining the meeting today, we are excited about this initiative. At a time when robust science needs to inform our path forward, our task is more important than ever. ClinicalTrials.gov is a powerful tool to help us evaluate clinical evidence. Our modernization efforts must be focused on you and all the stakeholders you represent. Let’s make the most of our time together today.”
Rebecca (Becky) J. Williams, PharmD, MPH
Working Group Executive Secretary
National Library of Medicine, NIH

Lourdes Baezconde-Garbanati, PhD, MPH
University of Southern California
Kent J. DeZee, MD, MPH, FACP, COL, MC
U.S. Army Office of the Surgeon General

Gary A. Puckrein, PhD
National Minority Quality Forum
External Members

Public Service Working Group on ClinicalTrials.gov Modernization

Carrie Dykes, PhD
University of Rochester Medical Center

Alissa Gentile, MSN, RN
The Leukemia and Lymphoma Society

Sally A. Gore, MS, MS LIS
University of Massachusetts Medical School

Barbara Kress, BSN, RN
Merck
NLM
Board of Regents

External Members

Public Service Working Group on ClinicalTrials.gov Modernization

Seth A. Morgan, MD
National Multiple Sclerosis Society

Joseph S. Ross, MD, MHS
Yale School of Medicine

Stephen J. Rosenfeld, MD, MBA
Secretary’s Advisory Committee on Human Research Protections (SACHRP)

Steven Woloshin, MD
The Dartmouth Institute
Lyric A. Jorgenson, PhD
Office of Science Policy

Pamela Reed Kearney, MD
Office of Extramural Research
Learn More

Additional link to materials for NLM Board of Regents and the Public Service Working Group on ClinicalTrials.gov Modernization

High-level Summary of Request for Information (RFI) Public Comments

Rebecca J. Williams, PharmD, MPH
Acting Director of ClinicalTrials.gov
Request for Information (RFI): ClinicalTrials.gov Modernization

**Goal:** To obtain public input to guide the National Library of Medicine (NLM) in planning infrastructure enhancements aimed at users and submitters of ClinicalTrials.gov

**Timing:** 75-day comment period (Dec 30, 2019 – Mar 14, 2020)

**Collection Method:** Web-based form with 3 main topic areas and 11 specific sub-question prompts; upload of attachments also permitted

**Guide Notice (NOT-LM-20-003):**
Overview of RFI Main Topic Areas

Note: RFI not intended to modify existing legal and policy requirements for clinical trial registration and results submission.

1. **Website functionality** of ClinicalTrials.gov website and application programming interface (API)

2. **Information submission** using the ClinicalTrials.gov Protocol Registration and Results System (PRS)

3. **Data standards** that may support submission, management, or use of information content
RFI Informed by Input from NIH

NLM held 12 sessions with 20 Institutes and Centers (ICs) from July to Dec 2019

Shared current status and general plans for ClinicalTrials.gov modernization

Requested input on issues important to ICs

High-Level Themes from NIH IC Sessions

- **Engagement** – ensure broad representation
- **Mission** – clarify and enhance communication re: benefits of reporting
- **Inclusion** – reinforce importance and standardize reporting
- **Value** – participant enrollment and scientific aspects of clinical research lifecycle
- **Study-specific issues** – for example, basic science, observational/natural history
- **Results submission** – address challenges
- **Systems and standards** – integration and discovery with NIH systems; data standards
Modernization External Activities FY2020

NLM Board of Regents Public Service Working Group

Transparent, bi-directional forum to communicate and receive input about modernization and support validation of ClinicalTrials.gov modernization roadmap

Dec 13
Kick-off Webinar

Dec 20
Webinar
Feb 3
Meeting
May 1
Meeting
Sept 14 or 15
Meeting


Dec 30 Request for Information (RFI) Comments Start
Mar 14 Request for Information (RFI) Comments End
Apr 30 Public Meeting
Host meeting with stakeholders to share high-level summary from RFI and obtain further input

NIH Institutes and Centers (IC) Engagement
Met with 20+ NIH ICs (including Directors) to learn IC needs

RFI External Engagement
Organization-hosted web meetings to engage key stakeholders directly

External Engagement Continued
Participate in conferences and other stakeholder meetings; further share and validate roadmap

NIH/NLM Activities

NIH IC Engagement: Continue engaging NIH points of contact monthly

ClinicalTrials.gov
RFI External Engagement Strategy
January – April 2020

Directly inform stakeholders of modernization effort and opportunity to submit comments to RFI

Audience
• Patients, Advocacy and Healthcare Providers
• Investigators and Sponsors
• Researchers and Journal Editors

Core Materials
• Request for Information (RFI) Guide Notice
• NLM and NIH OER Blogs
• Modernization Banner and Webpage

Method
• Targeted Emails
• Public Webinars
• Social Media
• Hot Off the Press! e-bulletin
• Organization Meetings
• Stakeholders
• Public Meeting

Reach
• 3,000+ subscribers to e-bulletin
• 1,200+ webinar participants
• Direct emails to 60+ organizations
• Over 10 web meetings hosted by organizations
RFI Comments by Role

268 submissions received; apparent role of submitter assigned by NLM reviewer

Breakdown of Roles

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<th>Percent</th>
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<td>29</td>
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<tr>
<td>Patient</td>
<td>31%</td>
<td>16</td>
</tr>
<tr>
<td>Health Care Provider</td>
<td>13%</td>
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<table>
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<th>Researchers &amp; Others</th>
<th>Percent</th>
<th>Number</th>
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<tr>
<td>Data Provider</td>
<td>58%</td>
<td>76</td>
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<tr>
<td>Scientist/Researcher</td>
<td>27%</td>
<td>35</td>
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<tr>
<td>Other (e.g., IRB)</td>
<td>11%</td>
<td>14</td>
</tr>
<tr>
<td>Clinical Research Support</td>
<td>4%</td>
<td>5</td>
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<tr>
<td>Medical Librarian or Info Specialist</td>
<td>2%</td>
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RFI Comments Initial Analysis Approach

• Downloaded all comments
  • Note: Full comment set available on ClinicalTrials.gov Modernization webpage

• Review of comments performed by NLM subject matter experts

• Developed high-level “domain codes” and lower-level “issue codes” based on review of responses; approximately 200 domain-issue code pairs

• Assigned one or more domain and issue code pairs to each response; assignment also reviewed by a second reviewer

• Summarized number of responses by domain and issue code
Number of Respondents by Sub-question
(259 unique respondents)

1. Website Functionality
   1a. New uses: 111
   1b. Resources for linking: 73
   1c. Current uses: 123
   1d. Scope of primary uses: 76

2. Information Submission
   2a. PRS improvements: 110
   2b. Align PRS with other processes: 24
   2c. Novel methods to enhance content: 9
   2d. Useful support materials: 29
   2e. Incentives for results submission: 50

3. Data Standards
   3a. Balance standards and flexibility: 15
   3b. Useful standards: 37
The ClinicalTrials.gov site provides an important public service, and it’s invaluable to have the registry information freely available to the public. As the ClinicalTrials.gov platform continues to evolve, in both form and function, it will become even more widely used and beneficial to the patient, research, and funding communities. Thank you for your efforts on this project!
Example: Comments from Different Roles

Contact information for study sponsors and sites

“Need to ensure sponsors provide the name of each institution participating in a trial (not just a postcode), along with the name of the investigator at that site, and an email address to contact him/her or their delegate”

“Clinical trials.gov is a huge headache for PI's in resource-limited small towns… All I get from ClinicalTrials.gov is emails from people from other regions of the country/world (who are ineligible to participate) inquiring if they can participate in my study which takes even more of my time.”
Coming Up…

10:30 a.m. – 11:15 a.m.

Information Submission Panel

- Heather Dobbins, ClinicalTrials.gov
- Carrie Dykes, University of Rochester Medical Center
- Sally A. Gore, University of Massachusetts Medical School
- Barbara Kress, Merck