Everything You Wanted to Know About ClinicalTrials.gov*

Deborah A. Zarin, MD
Director, ClinicalTrials.gov
National Library of Medicine

(*But Were Afraid to Ask)
DISCLAIMER

Views are mine and do not necessarily represent views of NIH or HHS
Key Concepts:

- **Registration**: the process for making key summary information about interventional studies using human volunteers accessible to the public via a web-based system, from study initiation to completion

- **Results Reporting**: making summary results information available in a structured, publicly accessible web-based database

Source: https://clinicaltrials.gov/ct2/about-studies/glossary
Motivating Problems

• One practical problem:
  • Potential participants had trouble finding trials.

• Three scientific problems:
  • Not all trials are published
  • Not all outcome measures (or adverse events) are published
  • Changes to protocols are not always acknowledged
Kaplan-Meier estimates for ulcer complications according to traditional definition. Results are truncated after 12 months, no ulcer complications occurred after this period. (Adapted from Lu 2001.)
Publication of NIH funded trials registered in ClinicalTrials.gov: cross sectional analysis

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Why is Registration Important?

• Human Subject Protections
  • Allows potential participants to find studies
  • Assists ethical review boards and others to determine appropriateness of studies being reviewed (e.g., harms, benefits, redundancy)
  • Promote fulfillment of ethical responsibility to human volunteers – research contributes to medical knowledge

• Research Integrity
  • Facilitates tracking of protocol changes
  • Increases transparency of research enterprise

• Evidence Based Medicine
  • Facilitates tracking of studies and outcome measures
  • Allows for more complete identification of relevant studies

• Allocation of Resources
  • Promotes more efficient allocation of resources
Clinical Trial Registration: A Statement from the International Committee of Medical Journal Editors

Altruism and trust lie at the heart of research on human subjects. Altruistic individuals volunteer for research because they trust that their participation will contribute to improved health for others and that researchers will minimize risks to participants. In return for the altruism and trust that make clinical research possible, the research enterprise has an obligation to conduct research ethically and to report it honestly. Honest reporting begins with revealing the existence of all clinical studies, even those that reflect unfavorably on a research sponsor’s product.

Unfortunately, selective reporting of trials does occur, and it distorts the body of evidence available for clinical decision-making. Researchers (and journal editors) are generally most enthusiastic about the publication of trials that show either a large effect of a new treatment (positive trials) or equivalence of two approaches to treatment (non-inferiority). Other researchers, and experts who write practice guidelines or decide on insurance-coverage policy. If all trials are registered in a public repository at their inception, every trial’s existence is part of the public record and the many stakeholders in clinical research can explore the full range of clinical evidence. We are far from this ideal at present, since trial registration is largely voluntary, registry data sets and public access to them varies, and registries contain only a small proportion of trials. In this editorial, published simultaneously in all member journals, the International Committee of Medical Journal Editors (ICMJE) proposes comprehensive trials registration as a solution to the problem of selective awareness and announces that all eleven ICMJE member journals will adopt a trials-registration policy to promote this goal.

The ICMJE member journals will require, as a

42 CFR Part 11
Clinical Trials Registration and Results Information Submission; Final Rule

Part II

Department of Health and Human Services

Subpart D—Additional Submission of Clinical Trial Information

§ 11.60 What requirements apply to the voluntary submission of clinical trial information for clinical trials of FDA-regulated drug products (including biological products) and device products?

§ 11.62 What requirements apply to applicable clinical trials for which submission of clinical trial information has been determined by the Director to be necessary to protect the public health?

Subpart E—Potential Legal Consequences of Non-Compliance

§ 11.66 What are potential legal consequences of not complying with the requirements of this part?


Subpart A—General Provisions

§ 11.2 What is the purpose of this part?

This part implements section 422(j) of the Public Health Service Act (42 U.S.C. 282) by providing requirements and procedures for the submission of clinical trial information for certain applicable clinical trials and other clinical trials to the Director of the National Institutes of Health (NIH) to be made publicly available via ClinicalTrials.gov, the Internet-accessible clinical trial registry and results data bank established by the National Library of Medicine (NLM) at https://clinicaltrials.gov.

§ 11.4 To whom does this part apply?

(a) This part applies to the responsible party for an applicable clinical trial that is required to be registered under § 11.22, a clinical trial for which clinical trial registration information or clinical trial results information is submitted voluntarily in accordance with § 11.60, or an applicable clinical trial that is required by the Director to have clinical trial information submitted to protect the public health under § 11.62.

(b) The responsible party must communicate the identity and contact information of the responsible party to the Director by submitting a Responsible Party Contact Information data element under § 11.22(a)(2)(III)(ii) and (a)(2)(IV)(F) as part of the clinical trial information submitted at the time of registration. Changes must be communicated to the Director by updating information in accordance with § 11.64(a).
ClinicalTrials.gov
The Basics
About ClinicalTrials.gov

• Clinical studies registry and results database
  • Over 253,000 studies (trials & observational studies)
  • Studies with locations in all 50 states and 200 countries
  • Privately and publicly funded studies involving humans
  • Study information submitted by study sponsors or investigators

• Web Site & registry launched in February 2000
  • Results database, in September 2008
  • Over 28,000 studies with posted results

• Intended Audience
  • Registry: Public
  • Results Database: Readers of the medical literature

• Usage
  • 76,000 unique visitors per day
Content of a Study Record (Minimum Information Requirements)

• **Registration section**
  – Submitted at trial initiation
  – Summarizes information from trial protocol: e.g.,
    – Condition
    – Interventions
    – Study Design
  – Includes recruitment information (e.g., eligibility, locations)

• **Results section**
  • Submitted after trial completion
  • Summarizes trial results
    • Participant flow
    • Baseline characteristics
    • Outcome measures (including statistical analyses)
    • Adverse events
    • All cause Mortality
  • Full Protocols & SAPs
Archival Data:
Tracking Changes in the Record

- Each record is expected to be corrected or updated throughout the trial's life cycle, and all changes are tracked on a public archive site that is accessible from each record (through a “History of Changes” link).

- Tabular View
  - Current Outcome Measures
  - Original (First Registered) Outcome Measures

Inhaled Aztreonam Lysine for Chronic Airway Pseudomonas aeruginosa in Cystic Fibrosis

Karen S. McCoy1, Alexandra L. Quittner2, Christopher M. Oermann3, Ronald L. Gibson4, George Z. Retsch-Bogart5, and A. Bruce Montgomery6

1Ohio State University, Columbus, Ohio; 2University of Miami, Coral Gables, Florida; 3Baylor College of Medicine, Houston, Texas; 4Children’s Hospital and Regional Medical Center, Seattle, Washington; 5University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; and 6Gilead Sciences, Inc., Seattle, Washington

Abstract

RATIONAL: The effectiveness and safety of aztreonam lysine for inhalation (AZLI) in patients with cystic fibrosis (CF) on maintenance treatment for Pseudomonas aeruginosa (PA) airway infection was evaluated in this randomized, double-blind, placebo-controlled study.

OBJECTIVES: To evaluate the safety and efficacy of inhaled aztreonam lysine in controlling PA infection in patients with CF.

METHODS: After randomization and a 28-day course of tobramycin inhalation solution (TIS), patients (n = 219; >6 yr; >3 TIS courses within previous year; FEV1 > 25% and <75% predicted values) were treated with 75 mg AZLI or placebo, twice or three times daily for 28 days, then monitored for 56 days. The primary efficacy endpoint was time to need for additional inhaled or intravenous antipseudomonal antibiotics. Secondary endpoints included changes in respiratory symptoms (CF Questionnaire Revised [CFQ-R] Respiratory Scale), pulmonary function (FEV1), and sputum PA density. Adverse events and minimum inhibitory concentrations of aztreonam for PA were monitored.

Measurements and Main Results: AZLI treatment increased median time to need for additional antipseudomonal antibiotics for symptoms of pulmonary exacerbation by 21 days, compared with placebo (AZLI, 92 d; placebo, 71 d; P = 0.007). AZLI improved mean CFQ-R respiratory scores (5.01 points, P = 0.02), FEV1 (6.3%, P = 0.001), and sputum PA density (-0.66 log[10] cfu/g, P = 0.006) compared with placebo; no AZLI dose-response was observed. Adverse events reported for AZLI and placebo were comparable and consistent with CF lung disease. Susceptibility of PA to aztreonam at baseline and end of therapy were similar.

Conclusions: AZLI was effective in patients with CF using frequent TIS therapy. AZLI delayed time to need for inhaled or intravenous antipseudomonal antibiotics, improved respiratory symptoms and pulmonary function and was well tolerated.

Clinical trial registered with www.clinicaltrials.gov (NCT 00104520).
ClinicalTrials.gov: Informational Scaffold

Individual participant data (IPD)

Journal publications
Results database entries
Conference abstracts

ClinicalTrials.gov Record

Full protocols
SAPs
Other study documents

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

# Key Clinical Trial Reporting Requirements

<table>
<thead>
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<tbody>
<tr>
<td>Scope</td>
<td>Registration</td>
<td>Registration &amp; Results Reporting</td>
<td>Registration &amp; Results Reporting</td>
</tr>
<tr>
<td>Funding Source</td>
<td>Any</td>
<td>Any</td>
<td>NIH</td>
</tr>
<tr>
<td>Intervention Type</td>
<td>All</td>
<td>Drugs, Biologics, &amp; Devices regulated by the FDA (Except Phase 1)</td>
<td>All (e.g., including Phase 1, behavioral interventions)</td>
</tr>
<tr>
<td>Submission Timing</td>
<td>Before enrollment of first participant</td>
<td>Registration: Within 21 days after first participant</td>
<td>Registration: Within 21 days after first participant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Results: Not later than 1 year after Primary Completion Date (some Delays permitted)</td>
<td>Results: Not later than 1 year after Primary Completion Date (some Delays permitted)</td>
</tr>
<tr>
<td>Enforcement</td>
<td>Refusal to publish</td>
<td>Criminal proceedings and civil penalties (up to $10,000/day); Loss of HHS funding to grantee institution</td>
<td>Loss of NIH funding (term and condition of award)</td>
</tr>
</tbody>
</table>
Fig 2. Schematic depicting the functions of the three key components of the [Trial Reporting System] TRS.

IPD Sharing
- Provides audit trail for summary results reporting
- Enables re-analyses of trial data
- Enables combining of trial data with other data for novel investigations

Summary Results Reporting
- Provides "minimum results reporting set" for each trial based on registered protocol information
- Structured data enable accurate search and retrieval based on elements of study design

Prospective Registration
- Documents existence and enables tracking of ongoing and completed trials
- Allows verification of key protocol information and tracking of changes
- Provides survey of research landscape (e.g., by topic or across the clinical research enterprise)
Other Selected US Policies

- **Center for Medicare and Medicaid Services (CMS)** requires NCT Number for coverage of routine costs of qualifying clinical trials
- **U.S. Department of Veterans Affairs (VA)** requires registration and results reporting of clinical trials funded by the VA Office of Research & Development
- **PCORI** requires registration and results reporting for interventional studies that it funds
Other Selected International Policies

- **European Union** requires registration and results reporting of certain European Medicines Agency (EMA)-regulated drug and biologic clinical trials.

- **Declaration of Helsinki** states that all research studies involving human subjects must be registered & researchers have a responsibility to make research results publicly available.

- **World Health Organization (WHO)** considers registration a “scientific, ethical and moral responsibility” and states that there is an ethical imperative to report results.
The Results Database

- FDAAA enacted in September 2007
  - Results Database launched in September 2008
  - Over 28,000 posted entries

- Design
  - Based on statutory requirements
  - Informed by CONSORT and other relevant standards
  - Requires “minimum data set” specified in protocol
  - Uses a tabular format for data with minimal narrative

- About 60% of entries do not have corresponding publications
- About 50% of entries are not required by FDAAA
4 Scientific Modules

- Participant Flow
- Baseline Characteristics
- Outcome Measures
- Adverse Events
- Other, including “Certain Agreements”
Minimum Results Information

- Baseline Characteristics
  - One table, for each arm and overall
  - Age (continuous or categorical)
  - Gender
- Participant Flow
  - # Started and # completed each arm
- Full Protocols & SAPs

- Outcome Measures
  - Summary data for each prespecified Primary and Secondary Outcome Measure (per arm)

- Adverse Events
  - Table of all Serious Adverse Events (per arm)
  - Table of “other” Adverse Events that occur in more than 5% of participants (per arm)

- All-cause Mortality
General Review Criteria

• Protocol and results must be clear and informative

• Review focuses on:
  • Logic and internal consistency
  • Apparent validity
  • Meaningful entries
  • Formatting, including appropriate use of database structure

• Differs in important ways from peer review;

Evidence of Benefits
Update on Trial Registration 11 Years after the ICMJE Policy Was Established

Deborah A. Zarin, M.D., Tony Tse, Ph.D., Rebecca J. Williams, Pharm.D., M.P.H., and Thiyagu Rajakannan, Ph.D.

Laws and policies to establish a global trial reporting system have greatly increased the transparency and accountability of the clinical research enterprise. The three components of the trial reporting system are trial registration, reporting of aggregate results, and sharing of individual participant data. Trial registration is foundational to our understanding and interpretation of trial results, because it requires that information be provided about all relevant clinical trials (to put results in a broad context) and their prespecified protocol details (to ensure adherence to the scientific plan).

In this article, we describe the current trial registration landscape and summarize evidence of its effect on the clinical research enterprise to date. We then present the results of analyses that were performed with the use of ClinicalTrials.gov data to provide additional evidence regarding the degree to which current practices are fulfilling certain key goals initially envisioned for trial registration. Finally, we identify challenges and suggest potential responses for the next decade.

EVOLUTION OF THE GLOBAL TRIAL REPORTING SYSTEM

After the announcement of the International Committee of Medical Journal Editors (ICMJE) trial registration policy in September 2004, a series of related laws and policies were implemented in the United States and internationally that increased the scope and content of mandatory prospective trial registration. The World Health Organization International Clinical Trials Registry Platform established the Trial Registration Data Set standard, which is the minimum set of data to be provided during trial registration.
Summary of Key Benefits

• Reporting volume
  • ~600 new registrations/week
  • ~140 new summary results/week
    • 50% not published

• Journal editors depend on registration records to ensure fidelity to the study protocol

• Evidence that ClinicalTrials.gov is filling the “gaps” in the public evidence base

• Funders increasingly use ClinicalTrials.gov to inform funding decisions

• Critical database for characterizing and analyzing the clinical research enterprise
Sample Uses of ClinicalTrials.gov
Basic Uses of ClinicalTrials.gov

• Identify trials of potential interest for an individual
  • Including to specific user communities

• Track progress of a specific trial, including availability of summary results

• Identify all trials that are completed or ongoing for a specific set of conditions/interventions
  • Complement to literature review
  • Useful in planning stages of a new protocol

• Identify investigators and/or research centers of relevance to a specific set of conditions/interventions
For those concerned with human subjects protections...

- Complete list of ongoing and completed trials of relevance
- Assurance that information about the trial of interest
  - is in the public domain
  - for some trials, results will become public
For those with medical conditions...

- Finding a trial in which to participate
- Finding an expanded access drug
- Finding a center of research for a given condition/intervention
ClinicalTrials.gov Apps

Find Trials
Please select your search criteria using one or more of the fields below:

Condition (ie, \text{“colon cancer”})
\begin{itemize}
  \item All conditions
\end{itemize}

Treatment (\text{drug, procedure, device being tested})
\begin{itemize}
  \item All treatments
\end{itemize}

Location
\begin{itemize}
  \item Current location
\end{itemize}

Phase
\begin{itemize}
  \item All
  \item Phase I
  \item Phase II
  \item Phase III
  \item Phase IV
\end{itemize}

Sponsor
\begin{itemize}
  \item All trials
\end{itemize}

Results
33280 trials matched your search.
Tap any trial for more information or select any trial result to view it on a map or e-mail it.

Select all

A Study to Evaluate the Efficacy and Safety of IV Peramivir in Addition to Standard of Care...
- Phase: Phase 3
- Distance: 2.01 miles
- Sponsor: BioCryst Pharmaceuticals

An Observational Study to Evaluate the Safety and Efficacy of FOLFIRI / FOLFOX Plus Cetuximab as...
- Phase: N/A
- Distance: 2.20 miles
- Sponsor: Merck KGaA

A Post Marketing Surveillance Study to Assess the Safety and Efficacy of Cetuximab Plus...
- Phase: N/A
- Distance: 2.20 miles
- Sponsor: Merck KGaA

Cardiovascular Risk Reduction Study (Reduction in Recurrent Major CV Disease Events)
- Phase: Phase 3
- Distance: 2.20 miles
Learn About Breast Cancer Trials

Every advance in breast cancer prevention and care has been the result of a clinical trial.

Learn More

Find A Trial
That’s Right For You

Browse Trials

or

Match to Trials

Healthcare Professionals
Learn how BCT can work for you

Researchers
Care Providers
Sponsors
Navigators

New to BCT

An easy-to-use tool specifically for patients with metastatic breast cancer.

Get Started

Join the BCT Trial Alert Service

Our Trial Alert Service is an easy way to learn about newly listed trials that match your situation. Create a BCT profile to subscribe.

Start Now

BCT In the News!

NEW TOOL PAIRS WOMEN WITH BREAST CANCER TRIALS

A powerful new tool is helping women access clinical trials that offer the latest treatments for breast cancer.

ABC News
For those concerned with research integrity and methods...

• Relatively complete list of trials
• Description of protocol
• Tracking of changes to protocols
• Identifying all outcome measures
• Providing results, regardless of journal publication status
• Provides method of overseeing types of trial methods being used, e.g.
  • OM specification; non-inferiority designs; single-arm studies;
For those seeking study findings/results...

- Linkages to PubMed
- Summary Results in database
  - About 60% not available in PubMed
- Results for all prespecified outcome measures
- Standardized format facilitating comparisons
Conclusions: Our results highlight the need to search ClinicalTrials.gov for both unpublished and published trials. Trial results, especially serious adverse events, are more completely reported at ClinicalTrials.gov than in the published article.
For those seeking to use aggregate data...

• Search engine allows one to identify all trials that meet certain criteria
  • Search results are listed by relevance
• Must understand nuances of database
• May be best to call for help
• Alternative site to find ClinicalTrials.gov data; CTTI:
For characterizing and analyzing the clinical research landscape...
Use of Trial Registries for Systematic Reviews

• “Sources of grey literature including regulatory data, clinical trial registries and conference abstracts should be searched in addition to bibliographic databases.”
  
  • AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Jan 2014 Update

  • Trials registers and trials results registers are an important source of ongoing and unpublished trials.”
  
  • Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]
Conclusion Clinical trials registered in ClinicalTrials.gov are dominated by small trials and contain significant heterogeneity in methodological approaches, including reported use of randomization, blinding, and DMCs.
PERSPECTIVE: “ClinicalTrials.gov registry enables researchers to get a snapshot of a specific field and observe changes over time in trial design, including numbers of subjects accrued, and it can inform clinical trial design...”
Trials in Acute Kidney Injury (AKI)

• 126 ongoing trials registered in ClinicalTrials.gov
  • 65% (n=82) prevention trials

• Appropriate Sample Size with Adequate Power?
  • Accurate estimate of incidence of AKI in group studied
  • Realistic estimate of the effect of the intervention

• Outcome: No Studies with Sufficient Power
  • Estimated that 822 participants per arm needed
  • Only 3 of 28 contrast studies and 3 of 30 cardiac surgery studies had more than 800 participants TOTAL

Sample Landscape Analysis: Trials Studying the Tau Protein as a Biomarker in Alzheimer Disease

<table>
<thead>
<tr>
<th>Row</th>
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<th>Status</th>
<th>Study Title</th>
<th>Conditions</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>☐</td>
<td>Not yet recruiting</td>
<td>Evaluation of (18\text{F})MNI-958 as a Potential PET Radioligand for Imaging Tau Protein in the Brain</td>
<td>• Alzheimer Disease</td>
<td>• Drug: [(18\text{F})MNI-958]</td>
</tr>
<tr>
<td>2</td>
<td>☐</td>
<td>Recruiting</td>
<td>Phase 0 Evaluation of [(18\text{F})MNI-958 as a Potential PET Radioligand for Imaging Tau Protein in the Brain</td>
<td>• Alzheimer Disease • Healthy Volunteers • Progressive Supranuclear Palsy</td>
<td>• Drug: [(18\text{F})MNI-958] • Drug: [(18\text{F})Florbetapir] • Drug: DaTscan</td>
</tr>
<tr>
<td>3</td>
<td>☐</td>
<td>Recruiting</td>
<td>Evaluation of [(18\text{F})MNI-952 as a Potential PET Radioligand for Imaging Tau Protein in the Brain</td>
<td>• Progressive Supranuclear Palsy • Alzheimer Disease • Healthy Volunteers</td>
<td>• Drug: [(18\text{F})MNI-952] • Drug: [(18\text{F})Florbetapir]</td>
</tr>
<tr>
<td>4</td>
<td>☐</td>
<td>Completed</td>
<td>18-months Safety Follow-up Study of AADvac1, an Active Tau Vaccine for Alzheimer’s Disease</td>
<td>• Alzheimer’s Disease</td>
<td>• Drug: AADvac1</td>
</tr>
</tbody>
</table>
11 Studies found for:

"tau protein" | Completed, Terminated, Withdrawn Studies | Interventional Studies | "Alzheimer Disease"

<table>
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<th>Row</th>
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<th>Status</th>
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<th>Conditions</th>
<th>Interventions</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>Completed</td>
<td>18-months Safety Follow-up Study of AADvac1, an Active Tau Vaccine for Alzheimer’s Disease</td>
<td>• Alzheimer’s Disease</td>
<td>• Drug: AADvac1</td>
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<tr>
<td>2</td>
<td></td>
<td>Completed</td>
<td>Evaluation of [18F]MNI-815 as a Potential PET Radioligand for Imaging Tau Protein in the Brain of Patients With Tauopathies</td>
<td>• Alzheimer’s Disease (AD)</td>
<td>• Drug: [18F]MNI-815 (MNI-815)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Progressive Supranuclear Palsy (PSP)</td>
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<td></td>
<td></td>
<td>• Cortical Basal Syndrome (CBS)</td>
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<td>(and 1 more...)</td>
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</tr>
<tr>
<td>3</td>
<td></td>
<td>Completed</td>
<td>Safety Study of AADvac1, a Tau Peptide-KLH-Conjugate Active Vaccine to Treat Alzheimer’s Disease</td>
<td>• Alzheimer Disease</td>
<td>• Biological: AADvac1</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>• Other: Placebo</td>
</tr>
</tbody>
</table>
30 Studies found for:
"tau protein" | Interventional Studies | "Alzheimer Disease"

A similar map is available for all studies in ClinicalTrials.gov
Click on the map below to show a more detailed map (when available) or search for studies (when map not available).

Colors indicate the number of studies with locations in that region.
Least
Labels give the exact number of studies.
Most

Source: https://ClinicalTrials.gov
30 Studies found for:
"tau protein" | Interventional Studies | "Alzheimer Disease"

**Sponsor/Collaborators related to search results**

<table>
<thead>
<tr>
<th>Sponsor/Collaborators</th>
<th>Studies</th>
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<tbody>
<tr>
<td>Molecular Neuromaging</td>
<td>4</td>
</tr>
<tr>
<td>Assistance Publique - Hôpitaux de Paris</td>
<td>3</td>
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<tr>
<td>Axon Neuroscience SE</td>
<td>3</td>
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<tr>
<td>University Hospital, Tours</td>
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</tr>
<tr>
<td>University Hospital, Grenoble</td>
<td>2</td>
</tr>
<tr>
<td>Asan Foundation</td>
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<td>Asan Medical Center</td>
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<tr>
<td>Avid Radiopharmaceuticals</td>
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<tr>
<td>Biopolis S.L.</td>
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</tbody>
</table>
Update on Trial Registration 11 Years after the ICMJE Policy Was Established

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KEY GOALS OF TRIAL REGISTRATION IN THE TRIAL REPORTING SYSTEM

Trial registration involves the submission of descriptive information about a clinical trial to a publicly accessible, Web-based registry. Two key goals underlie the registration requirements. The first goal is to establish a publicly accessible and searchable database for disseminating a minimum set of structured information about all ongoing and completed trials. Trial registries are designed to publicly document all biomedical or health-related experiments involving humans, facilitate the identification of trials for potential participants, and permit the incorporation of clinical research findings into the medical evidence base. The second goal is to provide access to date-stamped protocol amendments that occur during the trial. Access to structured archival information allows the public to track the progress of individual studies and assess whether reported results are consistent with the prespecified protocol or statistical analysis plan.

After the announcement of the International Committee of Medical Journal Editors (ICMJE) trial registration policy in September 2004, a series of related laws and policies were implemented in the United States and internationally that increased the scope and content of mandatory prospective trial registration. The World Health Organization International Clinical Trials Registry Platform established the Trial Registration Data Set standard, which is the minimum set of data to be provided during trial registration, and continues to coordinate a global network of trial registries (Table 1). To address biases in results disclosure, which are well documented in the published literature, governing bodies and organizations subsequently enacted laws and policies requiring the systematic reporting of aggregate results in publicly accessible results databases. In the United States, the Food and Drug Administration Amendments Act of 2007 (FDAAA) established a legal mandate requiring those responsible for initiating certain clinical trials of drugs, biologics, and devices to register the trials and report summary results. In response, the National Institutes of Health (NIH) launched the ClinicalTrials.gov results database in September 2008. In September 2016,

Sharing Individual Participant Data (IPD) within the Context of the Trial Reporting System (TRS)

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Summary Points

- The role of individual participant data (IPD) sharing can best be understood as part of an overall three-level trial reporting system (TRS) framework.
- Different "types" of IPD, which reflect varying degrees of information granularity, have different potential benefits and harms.
- Study 329 of Paxil (paroxetine) in children with depression is used as a case study to highlight the potential value of different components of the TRS.

The Institute of Medicine (IOM) [1], journal editors [2,3], and many others [4–6] have called for more widespread, third-party access to the individual participant data (IPD) and associated documentation from clinical trials (i.e., "IPD sharing"). Advocates assert that access to trial IPD will help to address well-established flaws in the current system of communicating trial results, including nonpublication, selective reporting, and lack of reproducibility [2]. Additional proposed benefits include the ability to reanalyze study data (e.g., validation and/or correction of previously published findings [4]) and to combine data from multiple studies (e.g., IPD-level meta-analyses [5]). Others note the burdens and costs associated with preparing IPD and associated documentation for sharing, the need to ensure participant privacy, and the risk of invalid analyses [6].

We do not attempt to replicate the more comprehensive analysis of IPD sharing that was conducted by the recent IOM panel [1]. However, we believe that it would be helpful at this pivotal time to consider the implications of IPD sharing within the context of the "trial reporting system" (TRS), which encompasses existing efforts to enhance access to information about trials and their findings and to improve the transparency of the clinical research enterprise (CRE) [1,1]. In this essay, we attempt to add precision to the ongoing discussion by examining the range of information granularity associated with different types of IPD. We then consider IPD sharing within a three-level TRS framework and illustrate the roles of these levels with a case study.

The ClinicalTrials.gov Results Database — Update and Key Issues

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ABSTRACT

BACKGROUND
The ClinicalTrials.gov trial registry was expanded in 2008 to include a database for reporting summary results. We summarize the structure and contents of the results database, provide an update of relevant policies, and show how the data can be used to gain insight into the state of clinical research.

METHODS
We analyzed ClinicalTrials.gov data that were publicly available between September 2009 and September 2010.

RESULTS
As of September 27, 2010, ClinicalTrials.gov received approximately 330 new and 2000 revised registrations each week, along with 30 new and 80 revised results submissions. We characterized the 79,413 registry and 2178 results of trial records available as of September 2010. From a sample cohort of results records, 78 of 150 (52%) had associated publications within 2 years after posting. Of results records available publicly, 20% reported more than two primary outcome measures and 5% reported more than five. Of a sample of 100 registry record outcome measures, 61% lacked specificity in describing the metric used in the planned analysis. In a sample of 700 results records, the mean number of different analysis populations per study group was 2.5 (median, 1; range, 1 to 25). Of these trials, 24% reported results for 90% or less of their participants.

CONCLUSIONS
ClinicalTrials.gov provides access to study results not otherwise available to the public. Although the database allows examination of various aspects of ongoing and completed clinical trials, its ultimate usefulness depends on the research community to submit accurate, informative data.