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

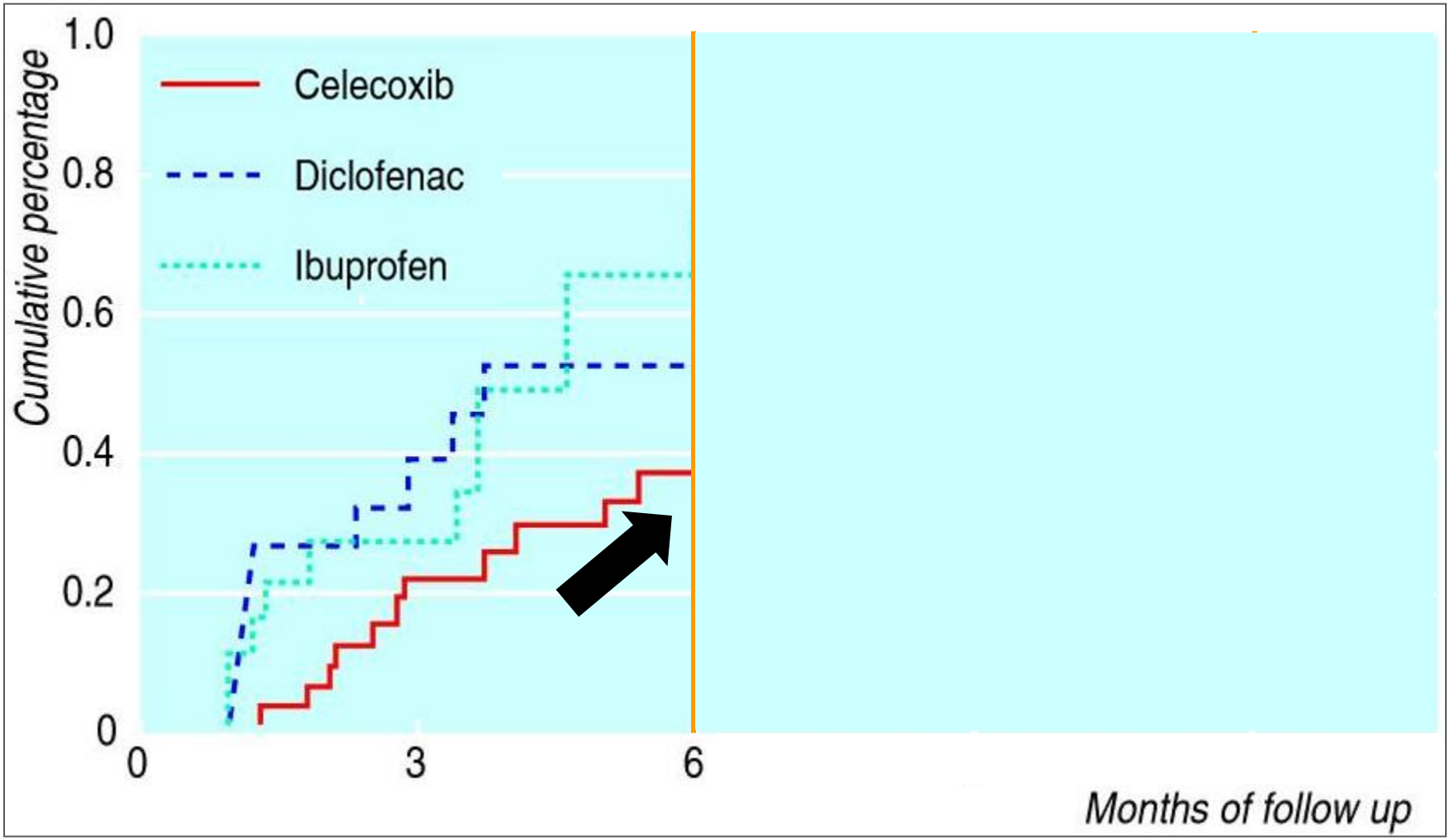
ClinicalTrials.gov

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

ClinicalTrials.gov

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.)



Jüni P, Rutjes AW, Dieppe PA. *BMJ*. 2002 Jun 1;324(7349):1287-8.

BMJ

BMJ 2011;344:d7292 doi: 10.1136/bmj.d7292 (Published 3 January 2012)

RESEARCH

Publication of NIH funded trials registered in ClinicalTrials.gov: cross sectional analysis

Joseph S Ross *assistant professor of medicine*[1 2], Tony Tse *program analyst at ClinicalTrials.gov*[3], Deborah A Zarin *director of ClinicalTrials.gov*[3], Hui Xu *postgraduate house staff trainee*[4], Lei Zhou *postgraduate house staff trainee*[4], Harlan M Krumholz *Harold H Hines Jr professor of medicine and professor of investigative medicine and of public health*[2 5 6]

[1]Section of General Internal Medicine, Department of Medicine, Yale University School of Medicine, New Haven, CT, USA; [2]Center for Outcomes Research and Evaluation, Yale-New Haven Hospital, New Haven, CT; [3]Lister Hill National Center for Biomedical Communications, National Library of Medicine, National Institutes of Health, Bethesda, MD, USA; [4]Fuwai Hospital and Cardiovascular Institute, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [5]Robert Wood Johnson Clinical Scholars Program and Section of Cardiovascular Medicine, Department of Medicine, Yale University School of Medicine, New Haven, CT; [6]Section of Health Policy and Administration, Yale University School of Epidemiology and Public Health, New Haven, CT

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

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

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-inferior-

cians, 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

Source: De Angelis C et al. *N Engl J Med*. 2004 Sep 16;351(12):1250-1

ClinicalTrials.gov

FEDERAL REGISTER

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Part II

Department of Health and Human Services

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

make-sure-you-meet-sba-size-standards/table-small-business-size-standards.
121. U.S. Census Bureau Official Site [Internet]. Washington (DC): Economic census; 2012 [cited 2016 Aug 10]. Available from: *https://www.census.gov/econ/census/.*
122. U.S. Census Bureau Official Site [Internet]. Washington (DC): American FactFinder database; 2012 [cited 2016 Aug 10]. Available from: *http://factfinder.census.gov/faces/tableservices/jsf/pages/productview.xhtml?pid=ECN_2012_US_31SG2&prodType=table.*

List of Subjects in 42 CFR Part 11

Biologics, Clinical trial, Data bank, Drugs, Human subjects research, Medical devices, Medical research, Registry, Reporting and recordkeeping requirements, Results information.

Regulatory Text

For the reasons stated in this preamble, the U.S. Department of Health and Human Services amends Title 42, Chapter I of the Code of Federal Regulations by adding Part 11 to subchapter A to read as follows:

PART 11—CLINICAL TRIALS REGISTRATION AND RESULTS INFORMATION SUBMISSION

Subpart A—General Provisions

Sec.

Subpart B—Registration

Subpart C—Results Information Submission

Subpart D—Additional Submission of Clinical Trial Information

Subpart E—Potential Legal Consequences of Non-Compliance

Authority: 42 U.S.C. 282(i); 42 U.S.C. 282(j); 5 U.S.C. 301; 42 U.S.C. 286(a); 42 U.S.C. 241(a); 42 U.S.C. 216(b).

Subpart A—General Provisions

§ 11.2 What is the purpose of this part?

This part implements section 402(j) of the Public Health Service Act (42 U.S.C. 282(j)) 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.

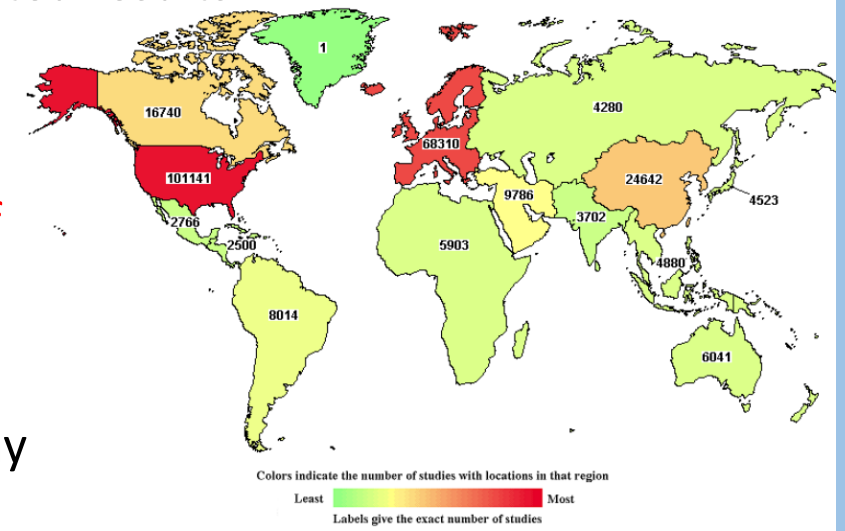
(b) The responsible party must communicate the identity and contact information of the responsible party to the Director by submitting the Responsible Party, by Official Title and Responsible Party Contact Information data elements under § 11.28(a)(2)(iii)(B) and (a)(2)(iv)(F) as part of the clinical trial information submitted at the time of registration. Changes must be communicated to the Director by updating information in accordance with § 11.64(a).

Available from: *https://www.sba.gov/contracting/getting-started-contractor/*

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



Source:https://ClinicalTrials.gov

ClinicalTrials.gov

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

ClinicalTrials.gov

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

Source: Zarin et al. *N Engl J Med* 2011; 364:852-60.

ClinicalTrials.gov

Safety and Efficacy Stu… Aeruginosa (AIR-CF2)

This study has been comple…

Sponsor:
Gilead Sciences

Information provided by:
Gilead Sciences

Full Text View | Tabula…

Purpose

The purpose of this study was to … lung infection due to Pseudomon…

Condition
Cystic Fibrosis

More Information

No publications provided by Gilea…

Additional publications automatica…

McCoy KS, Quittner AL, Oermann… aeruginosa in cystic fibrosis. Am …

NCBI Resour…

PubMed.gov
US National Library of Med…
National Institutes of Healt…

Display Settings:

Am J Respir Crit Care M…

Inhaled aztreon… fibrosis.

McCoy KS[1], Quittner …

Author informa…

Abstract

RATIONALE: The ef… (CF) on maintenanc… randomized, double-…

OBJECTIVES: To ev… with CF.

METHODS: After ra… =6 yr; > or =3 TIS c… with 75 mg AZLI or … endpoint was time t… included changes in… function (FEV(1)), a… PA were monitored.

MEASUREMENTS …

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), FEV(1) (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).

Inhaled Aztreonam Lysine for Chronic Airway *Pseudomonas aeruginosa* in Cystic Fibrosis

Karen S. McCoy[1], Alexandra L. Quittner[2], Christopher M. Oermann[3], Ronald L. Gibson[4], George Z. Retsch-Bogart[5], and A. Bruce Montgomery[6]

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

Rationale: 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 = 211; ≥6 yr; ≥3 TIS courses within previous year; FEV_1 ≥ 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 (FEV_1), 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, $P = 0.02$), FEV_1 (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).

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Cystic fibrosis is a chronic disease often involving endobronchial infection with *Pseudomonas aeruginosa*, which is difficult to treat.

What This Study Adds to the Field

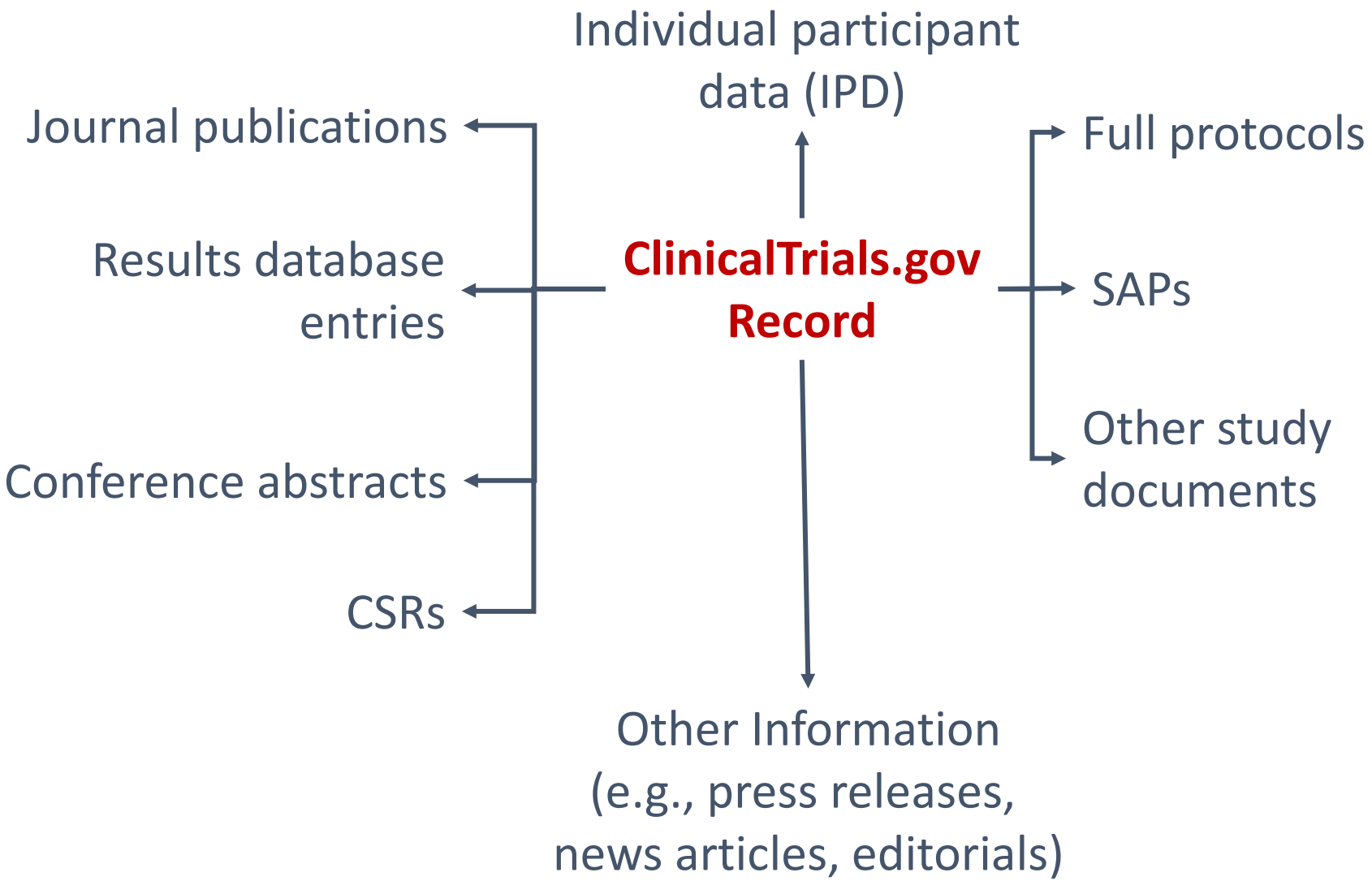
Safety and efficacy data on inhaled aztreonam show that this new formulation may be an alternative treatment option for patients with cystic fibrosis and chronic *P. aeruginosa* infection.

older patients, the most common pathogen in CF airway infections is *Pseudomonas aeruginosa* (PA); these infections are associated with an accelerated decline in pulmonary function and increased mortality (2–4).

Over the past 15 years, management of patients with CF has improved (1, 2, 5–8). However, antimicrobial treatment options for chronic PA airway infections remain limited and additional therapies are needed to augment improvements in clinical outcomes.

Aztreonam lysine for inhalation (AZLI) is an aerosolized formulation of the monobactam antibiotic aztreonam and lysine (9). The intravenous aztreonam formulation contains arginine, which can cause airway inflammation after chronic inhalation therapy in patients with CF (10, 11). The study described herein included patients with CF who frequently used antibiotics for PA

ClinicalTrials.gov: Informational Scaffold

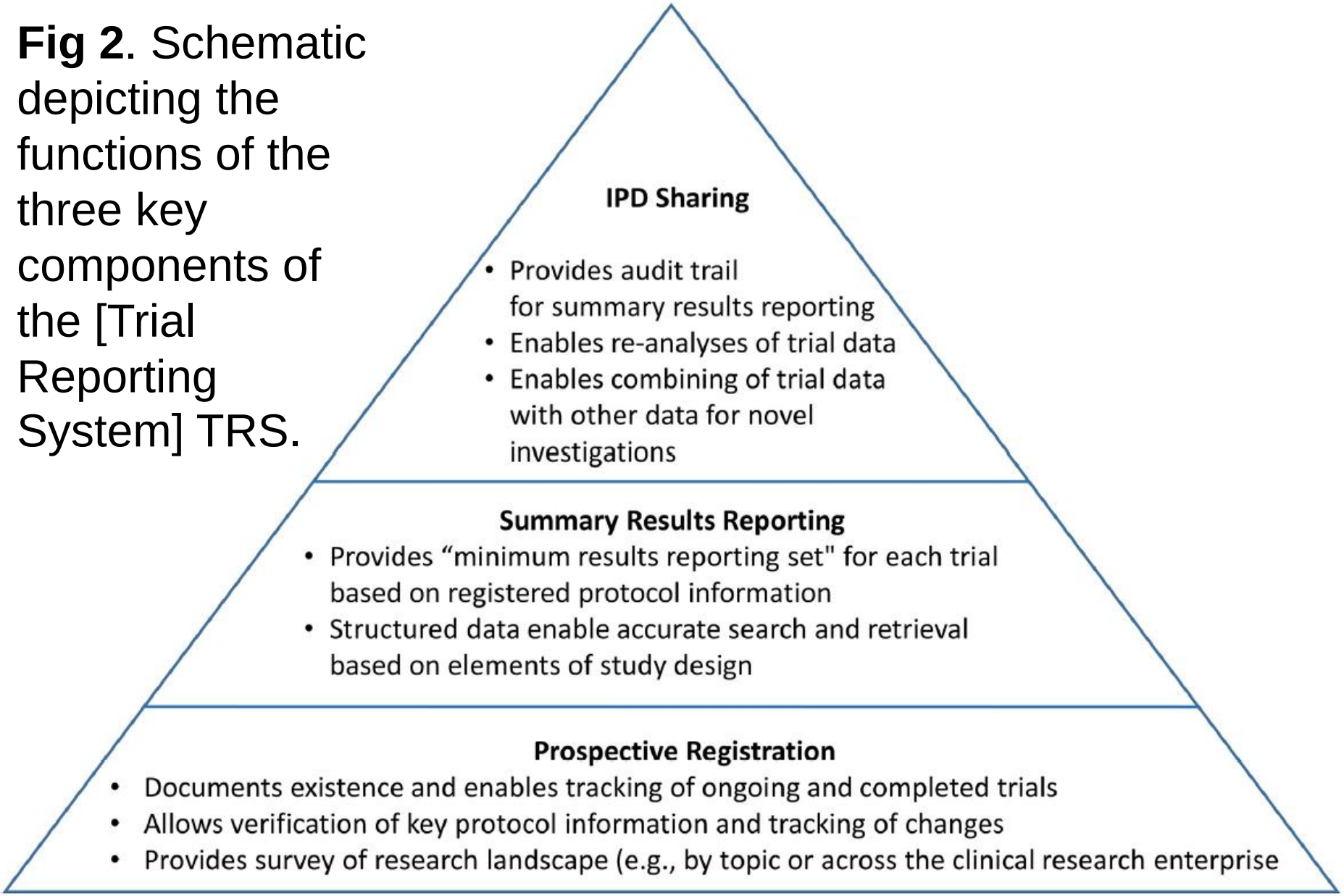


Source: Zarin & Tse. *PLoS Med*. 2016 Jan 19;13(1):e100194.

Key Clinical Trial Reporting Requirements

Reporting Requirement	ICMJE Policy (Effective in 2005)	FDAAA Final Rule (Issued in 2016)	Final NIH Policy (Issued in 2016)
Scope	Registration	Registration & Results Reporting	Registration & Results Reporting
Funding Source	Any	Any	NIH
Intervention Type	All	Drugs, Biologics, & Devices regulated by the FDA (Except Phase 1)	All (e.g., including Phase 1, behavioral interventions)
Submission Timing	Before enrollment of first participant	Registration: Within 21 days after first participant Results: Not later than 1 year after Primary Completion Date (some Delays permitted)	Registration: Within 21 days after first participant Results: Not later than 1 year after Primary Completion Date (some Delays permitted)
Enforcement	Refusal to publish	Criminal proceedings and civil penalties (up to $10,000/day); Loss of HHS funding to grantee institution	Loss of NIH funding (term and condition of award)

Fig 2. Schematic depicting the functions of the three key components of the [Trial Reporting System] TRS.



Zarin DA, Tse T. *PLoS Med*. 2016.

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

Full Text View | Tabular View | Study Results | Related Studies

Brief Descriptive Title of Clinical Trial

Study Recruitment Status

Information provided by Organization

Study Type:	Interventional
Study Design:	Randomized, Double Masked, Placebo Control, Parallel Assignment
Interventions:	Drug: Drug A; Drug: Drug B

Participant Flow

Recruitment Details – Key information relevant to the recruitment process for the overall study, such as dates of the recruitment.

Pre-Assignment Detail – Significant events and approaches for the overall study following participant enrollment, but prior to assignment.

Overall Study

	Drug A	Drug B	Placebo
STARTED			
COMPLETED			
Not Completed			
Lost to Follow-up			
Adverse Event			

Baseline Characteristics

	Drug A	Drug B	Placebo	Total
Number of Participants				
Age				
Gender				
Female				
Male				

Outcome Measures

Primary Outcome Measure

Measure Name	
Measure Description	
Time Frame	

Population Description – Explanation of how the number of participants for analysis was determined.

Measured Values

	Drug A	Drug B	Placebo
Number of Subjects			
Primary Outcome Measure			

Statistical Analysis for Primary Outcome Measure

Groups	
Method	
P-Value	
Mean Difference	
95% Confidence Interval	

Additional Details About the Analysis – e.g., null hypothesis, power calculation, and whether the p-value is adjusted for multiple comparisons

More Information

Certain Agreements – Information about restrictions on the ability of the principal investigator to disseminate trial data after trial completion

Limitations and Caveats – Limitations of the study, such as early termination leading to small numbers of subjects analyzed

Results Point of Contact – Phone and/or email for additional information about the results

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

ClinicalTrials.gov

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;

Review Criteria: http://clinicaltrials.gov/ct2/manage-recs/resources

ClinicalTrials.gov

Evidence of Benefits

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL REPORT

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.[1] 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.

tion 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.

EVOLUTION OF THE GLOBAL TRIAL REPORTING SYSTEM

After the announcement of the International Committee of Medical Journal Editors (ICMJE) trial registration policy[2] in September 2004, a series of related laws and policies were implemented in the United States[3] and internationally[4] 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,[5] which is the minimum set of data to be provided during trial registra-

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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

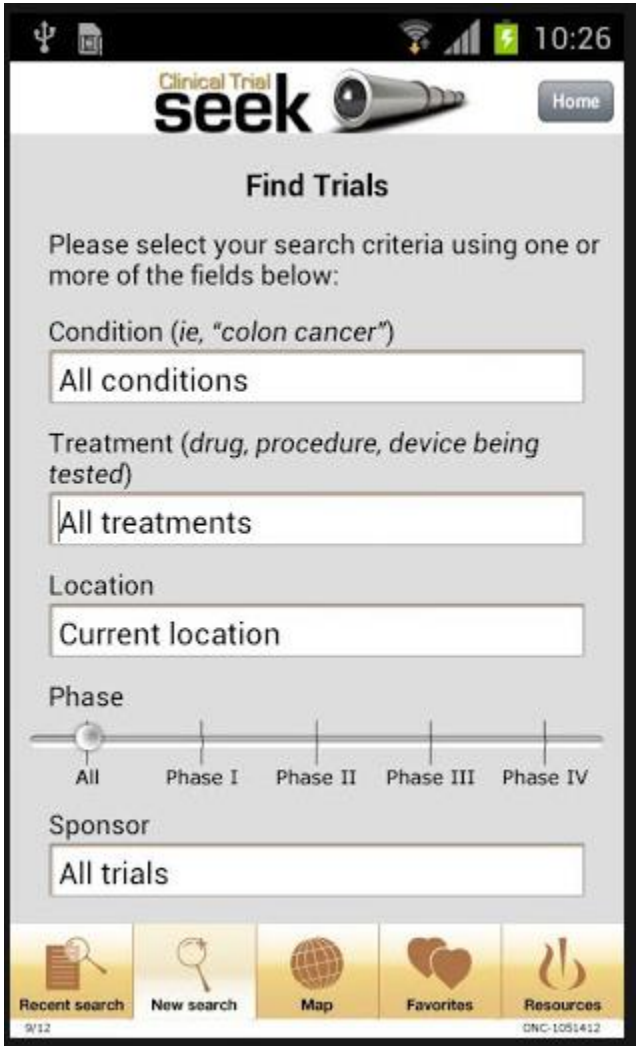
ClinicalTrials.gov

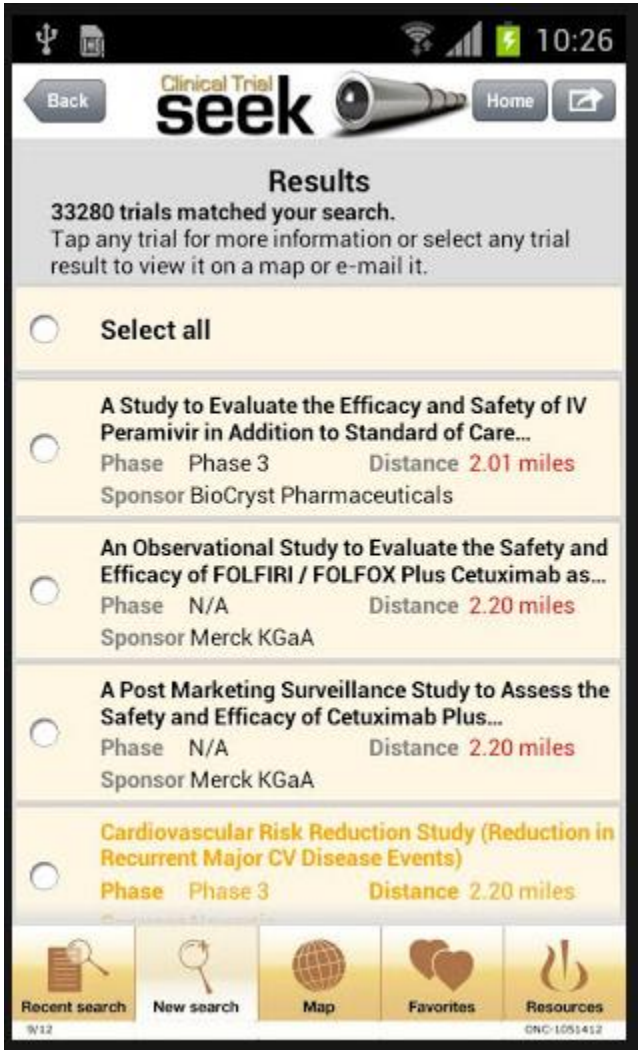
For those with medical conditions…

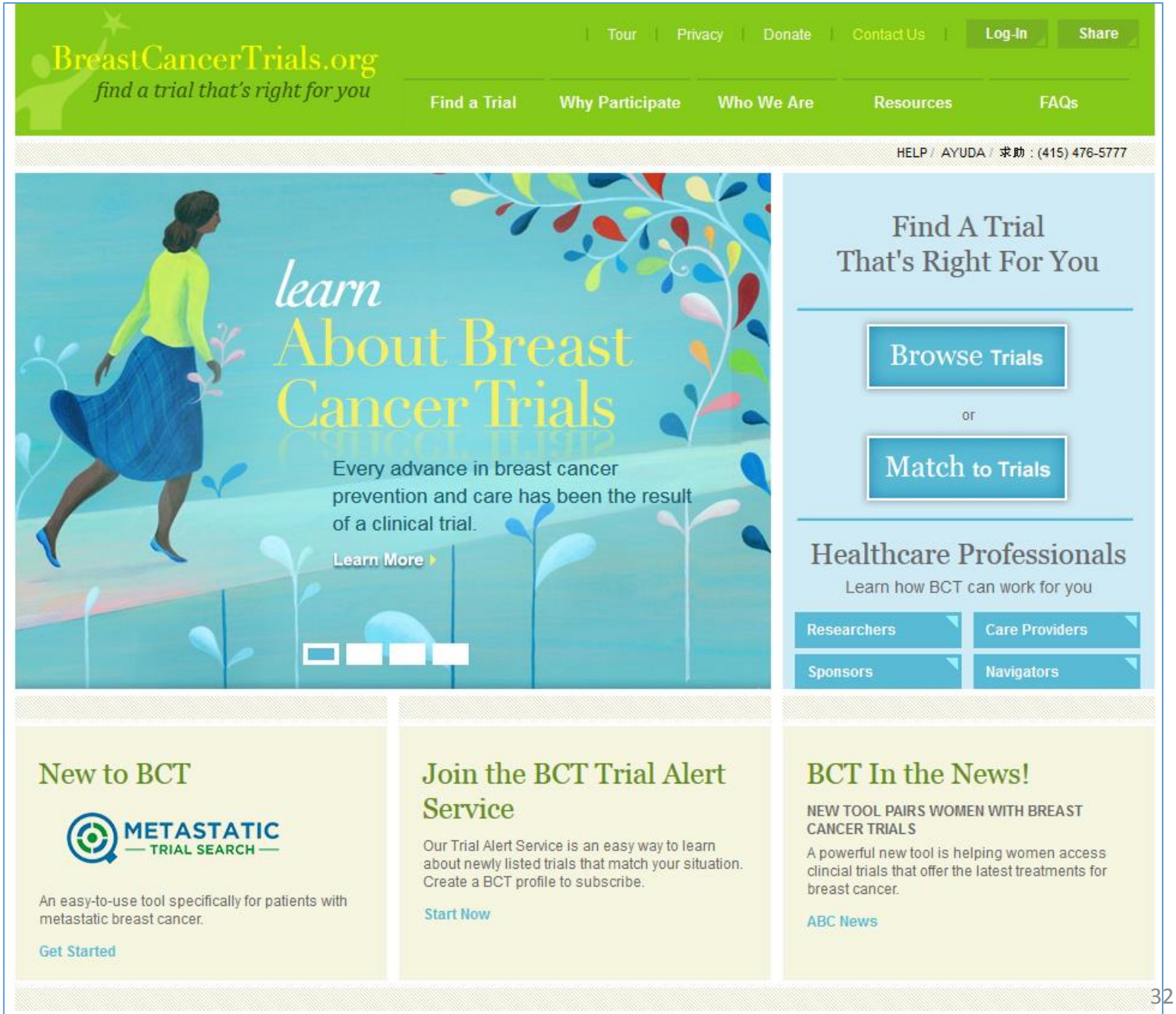
- Finding a trial in which to participate
- Finding an expanded access drug
- Finding a center of research for a given condition/intervention

ClinicalTrials.gov

ClinicalTrials.gov Apps






BreastCancerTrials.org
find a trial that's right for you
Tour
Privacy
Donate
Contact Us
Log-In
Share
Find a Trial
Why Participate
Who We Are
Resources
FAQs
HELP / AYUDA / 求助 : (415) 476-5777
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
METASTATIC TRIAL SEARCH
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 clincial 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;

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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

ClinicalTrials.gov

OPEN ACCESS Freely available online

PLOS | MEDICINE

Timing and Completeness of Trial Results Posted at ClinicalTrials.gov and Published in Journals

Carolina Riveros[1,2,3], Agnes Dechartres[1,2,3]*, Elodie Perrodeau[1,3], Romana Haneef[1,3], Isabelle Boutron[1,2,3,4], Philippe Ravaud[1,2,3,4,5]

1 INSERM U738, Paris, France, **2** Université Paris Descartes—Sorbonne Paris Cité, Paris, France, **3** Centre d'Épidémiologie Clinique, Hôpital Hôtel-Dieu, Assistance Publique-Hôpitaux de Paris, Paris, France, **4** French Cochrane Centre, Paris, France, **5** Mailman School of Public Health, Columbia University, New York, New York, United States of America

Abstract

Background: The US Food and Drug Administration Amendments Act requires results from clinical trials of Food and Drug Administration–approved drugs to be posted at ClinicalTrials.gov within 1 y after trial completion. We compared the timing and completeness of results of drug trials posted at ClinicalTrials.gov and published in journals.

Methods and Findings: We searched ClinicalTrials.gov on March 27, 2012, for randomized controlled trials of drugs with posted results. For a random sample of these trials, we searched PubMed for corresponding publications. Data were extracted independently from ClinicalTrials.gov and from the published articles for trials with results both posted and pub... We assessed the time to first public posting or publishing of results and compared the completeness of results pos... ele... (e.g... diff... 600...

"**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…

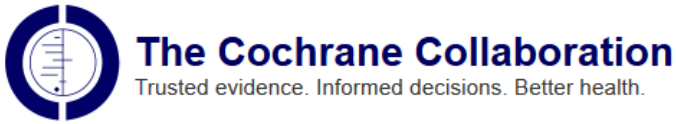
- Search engine allows one to identify all trials that meet certain criteria
  - Search results are listed by relevance
- Must understand nuances of database
- May be best to call for help
- Alternative site to find ClinicalTrials.gov data; CTTI:
  - http://www.ctti-clinicaltrials.org/what-we-do/analysis-dissemination/state-clinical-trials

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]



ClinicalTrials.gov

ORIGINAL CONTRIBUTION

Characteristics of Clinical Trials Registered in ClinicalTrials.gov, 2007-2010

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Judith M. Kramer, MD, MS
Rachel E. Sherman, MD, MPH
Laura H. Aberle, BSPH
Asba Tasneem, PhD

Context Recent reports highlight gaps between guidelines-based treatment recommendations and evidence from clinical trials that supports those recommendations. Strengthened reporting requirements for studies registered with ClinicalTrials.gov enable a comprehensive evaluation of the national trials portfolio.

Objective To examine fundamental characteristics of interventional clinical trials registered in the ClinicalTrials.gov database.

Methods A data set comprising 96 346 clinical studies from ClinicalTrials.gov was

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.

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Journal Editors (ICMJE) announced a policy, which took effect in 2005, of requiring registration of clinical trials as a prerequisite for publication.[6,7] The Food and Drug Administration Amendment Act (FDAAA)[8] expanded the mandate of

randomization and blinding were less frequently reported in earlier-phase, oncology, and device trials.

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.

JAMA. 2012;307(17):1838-1847 www.jama.com

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Available online at www.jpain.org and www.sciencedirect.com

Use of ClinicalTrials.gov to Estimate Condition-Specific Nocebo Effects and Other Factors Affecting Outcomes of Analgesic Trials

M. Soledad Cepeda, Victor Lobanov, and Jesse A. Berlin
Janssen Pharmaceutical Research & Development, LLC, Titusville, New Jersey.

Abstract: ClinicalTrials.gov is a registry and results database of federally and privately supported clinical trials conducted worldwide. We sought to answer: what are the characteristics of pain trials; how frequently are these trials stopped and why; what is the magnitude of attrition due to lack of

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..."

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. We learned that recruitment challenges account for the largest proportion of noncompleted trials, attrition rates differed across pain conditions, and migraine studies had the lowest withdrawal rate.*

Key words: ClinicalTrials.gov, pain, trial design, placebo response, withdrawal rate, nocebo effect.

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

ClinicalTrials.gov

Faubel S et al. *Clin J Am Soc Nephrol*. 2012 May;7(5):861-7.

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

30 Studies found for:

"tau protein" | Interventional Studies | Alzheimer Disease

Also searched for **Disorders**. See Search Details

List | By Topic | On Map | Search Details

Show Filters | Download | Subscribe to RSS

Showing: 1-30 of **30** studies 50 studies per page | Show/Hide Columns

Row	Saved	Status	Study Title	Conditions	Interventions
1	☐	Not yet recruiting	Evaluation of **Tau Protein** in the Brain of Participants With **Alzheimer's Disease** Compared to Healthy Participants	• **Alzheimer Disease**	• Drug: [18F]MNI-1020
2	☐	Recruiting	Phase 0 Evaluation of [18F]MNI-958 as a Potential PET Radioligand for Imaging **Tau Protein** in the Brain	• **Alzheimer Disease** • Healthy Volunteers • Progressive Supranuclear Palsy	• Drug: [18F]MNI-958 • Drug: [18F]Florbetapir • Drug: DaTscan
3	☐	Recruiting	Evaluation of [18F]MNI-952 as a Potential PET Radioligand for Imaging **Tau Protein** in the Brain	• Progressive Supranuclear Palsy • **Alzheimer Disease** • Healthy Volunteers	• Drug: [18F]MNI-952 • Drug: [18F]Florbetapir
4	☐	Completed	18-months Safety Follow-up Study of AADvac1, an Active Tau Vaccine for **Alzheimer's Disease**	• **Alzheimer's Disease**	• Drug: AADvac1

ClinicalTrials.gov

11 Studies found for:

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

List | By Topic | On Map | Search Details

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Showing: 1-11 of **11** studies 50 studies per page

Show/Hide Columns

Filters

Apply Clear

Status

Studies:

- [ ] Not yet recruiting
- [ ] Recruiting
- [ ] Enrolling by invitation
- [ ] Active, not recruiting
- [ ] Suspended
- [x] Terminated
- [x] Completed
- [x] Withdrawn
- [ ] Unknown status†

Expanded Access:

Row	Saved	Status	Study Title	Conditions	Interventions
1	☐	Completed	18-months Safety Follow-up Study of AADvac1, an Active Tau Vaccine for **Alzheimer's Disease**	• **Alzheimer's Disease**	• Drug: AADvac1
2	☐	Completed	Evaluation of [18F]MNI-815 as a Potential PET Radioligand for Imaging **Tau Protein** in the Brain of Patients With Tauopathies	• **Alzheimer's Disease** (AD) • Progressive Supranuclear Palsy (PSP) • Cortical Basal Syndrome (CBS) • (and 1 more...)	• Drug: [18F]MNI-815 (MNI-815)
3	☐	Completed	Safety Study of AADvac1, a Tau Peptide-KLH-Conjugate Active Vaccine to Treat **Alzheimer's Disease**	• **Alzheimer Disease**	• Biological: AADvac1 • Other: Placebo

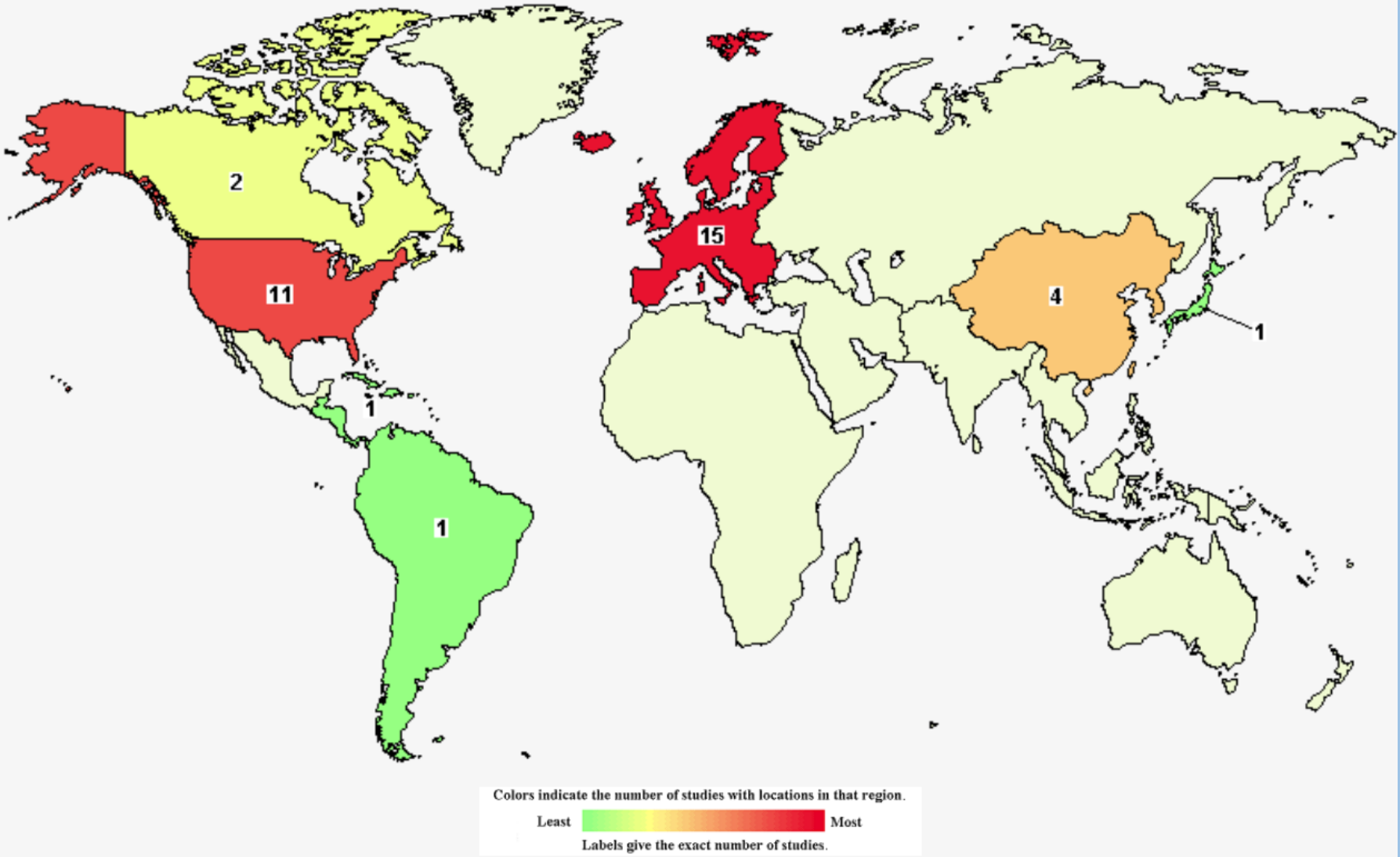
30 Studies found for:

"tau protein" | Interventional Studies | "Alzheimer Disease"

List | By Topic | On Map | Search Details

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).



Source:https://ClinicalTrials.gov

30 Studies found for:

"tau protein" | Interventional Studies | "Alzheimer Disease"

List | By Topic | On Map | Search Details

Sponsor/Collaborators related to search results

See All Studies by Topic

Conditions

- Alphabetical
- By Category

Rare Diseases

- Alphabetical

Drug Interventions

- Alphabetical
- By Category

Showing: 1-43 of **43** Sponsor/Collaborators 100 per page

Find in Table:

Sponsor/Collaborators	Studies
Molecular NeuroImaging	4
Assistance Publique - Hôpitaux de Paris	3
Axon Neuroscience SE	3
University Hospital, Tours	3
University Hospital, Grenoble	2
Asan Foundation	1
Asan Medical Center	1
Avid Radiopharmaceuticals	1
Biopolis S.L.	1

Contact Us

register@clinicaltrials.gov

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL REPORT

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.[1] 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.

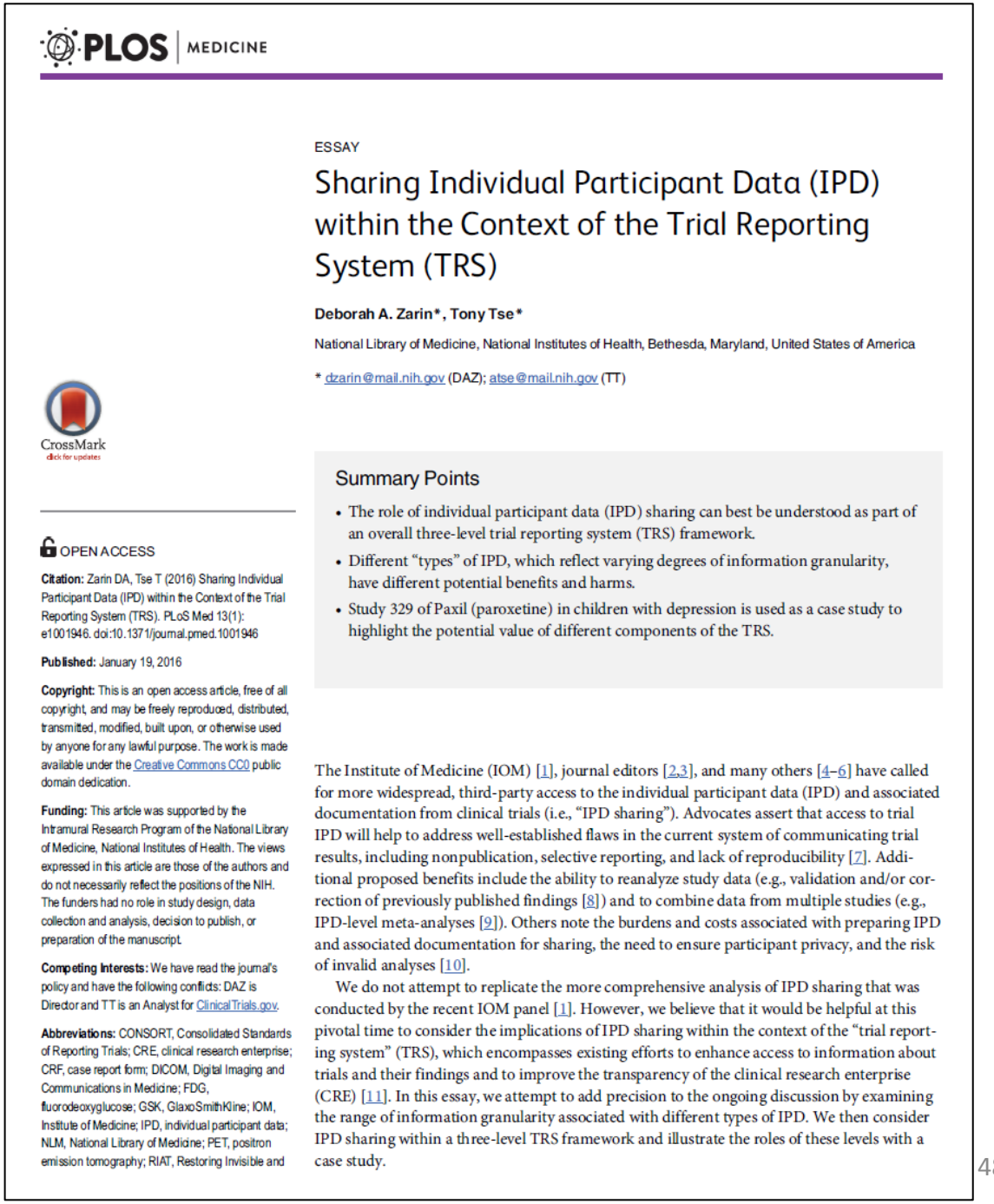
KEY GOALS OF TRIAL REGISTRATION IN THE TRIAL REPORTING SYSTEM

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.

EVOLUTION OF THE GLOBAL TRIAL REPORTING SYSTEM

After the announcement of the International Committee of Medical Journal Editors (ICMJE) trial registration policy[2] in September 2004, a series of related laws and policies were implemented in the United States[3] and internationally[4] 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,[5] 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,[6-8] 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.[9] In response, the National Institutes of Health (NIH) launched the ClinicalTrials.gov results database in September 2008.[10] In September 2016,

Zarin DA, Tse T, Williams RJ, Rajakannan T. Update on trial registration 11 years after the ICMJE Policy was established. *N Engl J Med.* 2017 Jan 26;376(4):383-391.



PLOS | MEDICINE

ESSAY

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

Deborah A. Zarin*, Tony Tse*

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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.

OPEN ACCESS

Citation: Zarin DA, Tse T (2016) Sharing Individual Participant Data (IPD) within the Context of the Trial Reporting System (TRS). PLoS Med 13(1): e1001946. doi:10.1371/journal.pmed.1001946

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Competing Interests: We have read the journal's policy and have the following conflicts: DAZ is Director and TT is an Analyst for ClinicalTrials.gov.

Abbreviations: CONSORT, Consolidated Standards of Reporting Trials; CRE, clinical research enterprise; CRF, case report form; DICOM, Digital Imaging and Communications in Medicine; FDG, fluorodeoxyglucose; GSK, GlaxoSmithKline; IOM, Institute of Medicine; IPD, individual participant data; NLM, National Library of Medicine; PET, positron emission tomography; RIAT, Restoring Invisible and

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 [7]. Additional proposed benefits include the ability to reanalyze study data (e.g., validation and/or correction of previously published findings [8]) and to combine data from multiple studies (e.g., IPD-level meta-analyses [9]). 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 [10].

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) [11]. 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.

Zarin DA, Tse T. Sharing individual participant data (IPD) within the context of the trial reporting system (TRS). *PLoS Med.* 2016 Jan 19;13(1):e1001946.

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

The ClinicalTrials.gov Results Database — Update and Key Issues

Deborah A. Zarin, M.D., Tony Tse, Ph.D., Rebecca J. Williams, Pharm.D., M.P.H., Robert M. Califf, M.D., and Nicholas C. Ide, M.S.

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N Engl J Med 2011;364:852-60.

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.

Zarin DA, Tse T, Williams RJ, Califf RM, Ide NC. The ClinicalTrials.gov results database—update and key issues. *N Engl J Med*. 2011;364(9):852-60.