The Role and Importance of Clinical Trial Registries & Results Databases

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April 2016

Outline

Background

Current Policies

About ClinicalTrials.gov

Registering Clinical Trials at ClinicalTrials.gov

Points to Consider

Reporting Results to ClinicalTrials.gov

Points to Consider

Individual Participant-Level Data (IPD)

Final Thoughts

Background

Why is disclosure important?

Evidence Based Medicine (EBM)

Clinical and policy decisions should be informed by evidence regarding the benefits, risks and other burdens associated with all possible alternatives.

Clinical trials are a key component of the body of scientific evidence that must be used to make decisions.

Most decision makers depend on summary data from journal articles

What's All The Fuss About?

Suppression of research results impedes scientific process

Suppression of clinical trial data is particularly problematic:

Trials depend on human volunteers

Trial results inform our medical decisions

Three Key Problems

Not all trials are published

Publications do not always include all prespecified outcome measures

Unacknowledged changes are made to the trial protocol that would affect the interpretation of the findings

e.g., changes to prespecified outcome measures

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.

Internal Corporate Email

“They swallowed our story, hook, line and sinker…”

ClinicalTrials.gov and
Levels of “Transparency”

Trial Reporting System (TRS)

Prospective Registration

Documents existence and enables tracking of trials

Assists potential participants in finding trials

Provides a “denominator” to assess research enterprise

Date stamped protocol details

Supports assessing fidelity of reporting to pre-specified research plan

Summary Results Reporting

Provides a minimum set of results data for each trial

Structured data enables accurate search and retrieval

Contribute to evidence-based medicine

Individual Participant Data (IPD) Sharing

Audit trail for summary results reporting

Enables re-analysis of trial data

Enables combining of trial data with other data

Definitions

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 information about study results available in a structured, publicly accessible web-based results database”

Registration

208,114 registered studies (trials & observational)

About 500 new studies registered each week

Study locations in all 50 states and > 190 countries

1/3 of trials are registered “late” (> 3 mo. after start)

300,000+ studies accessible in World Health Organization (WHO) Search Portal

Includes ClinicalTrials.gov and 15 other registries

Total number of trials in U.S. and worldwide not known

Registries likely to be most comprehensive for trials that are subject to legal reporting requirements

Summary Results Reporting

20,000 registered studies with results

About 100 studies with results submitted each week

FDAAA 801 requires “applicable clinical trials” of approved or cleared drugs and devices to have results submitted within 1 year of primary completion date

About 42% of results posted on ClinicalTrials.gov are not subject to FDAAA 801

Public interest in overall rates of results reporting

Stages in Disclosure Parallel the Research Life Cycle

Current Policies

US and International

Selected Int'l Policies & Laws

ICMJE requires registration of all clinical trials

European Union requires registration and results reporting of certain 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

WHO considers registration a "scientific, ethical and moral responsibility" & ethical imperative to report results

And many others …

Key Disclosure Policies for US investigators

ICMJE – Journal Editors Policy (2004)

Prospective registration of all clinical trials as a precondition for publication of the study results

Effective Date: September 13, 2005

FDA Amendments Act, Section 801 (2007)

Enacted on September 27, 2007

Expanded Trial Registration Requirements (FDAMA)

Added New Results Reporting Requirement

Added Enforcement Provisions: e.g.,

Civil monetary penalties (up to $10,000/day)

Withholding of NIH grant funds

Current Status: Proposed Rule issued for public comment (Deadline: March 23, 2015)

Rate of New Registrations

After FDAMA (2000):
25 – 30 registrations per week

After ICMJE (2005):
200 – 250 per week

After FDAAA (2007):
300 – 350 per week

After NPRM (2014):
~500 per week

ClinicalTrials.gov Reporting Policies

Status of Regulations and Policies

Public comment period ended March 23, 2015

HHS is currently reviewing and addressing submitted comments

Publish Final Rule for FDAAA

NIH will also publish final policy for trial reporting

Studies Estimating Rates of FDAAA Results Reporting

STAT News – December 13, 2015

Assessed whether institutions reported results and whether they were reported “on time”

Analysis included trials of unapproved drugs or devices (if a certification was not on file)

“The worst offenders included four of the top 10 recipients of federal medical research funding from the National Institutes of Health: Stanford, the University of Pennsylvania, the University of Pittsburgh, and the University of California, San Diego.”

Need for Org. Infrastructure to Support Results Reporting

Examples of Other Relevant Policies

Veterans Affairs funded clinical trials

PCORI funded studies

Trials conducted under the CMS “coverage with evidence development”

Impact of Reporting Policies
on US AMCs

Most AMCs have over 50% of their trials under a reporting policy (median: 58.6%)

AMCs need to modify their incentive structure, and need to provide support for their investigators

Policies hold the AMC accountable, not just the investigator

About ClinicalTrials.gov

http://ClinicalTrials.gov/

Registration at ClinicalTrials.gov

Scope of Registry

ClinicalTrials.gov permits the registration of any biomedical or health-related research studies in humans that meet the following two requirements:

Conformance with any applicable human subject protections or ethics review regulations (or equivalent) (e.g., institutional review board (IRB) approval) AND

Conformance with any applicable regulations of the national (or regional) health authority (or equivalent)

ClinicalTrials.gov Statistics
(as of 2/25/2016)

ClinicalTrials.gov Statistics

Content of ClinicalTrials.gov Records

One record per trial

Registration record

Submitted at trial initiation

Summarizes information from trial protocol

Condition

Interventions

Design, etc

Includes recruitment information (e.g., eligibility, locations)

Results record

Submitted after trial completion

Summarizes trial results

Participant flow

Baseline characteristics

Outcome measures (including statistical analyses)

Adverse events

Public Archive for Records

Changes can and should be made to records

Estimated dates become “actual” dates

Estimated enrollment becomes “actual”

Other protocol changes

Overall recruitment status changes

Results may be added or changed

All changes are publicly “tracked”

Registry: Minimal Dataset
(Needed to Describe a Study)

Descriptive information

e.g., phase, study design, outcomes

Recruitment information

e.g., eligibility criteria, recruitment status

Location and contact information

e.g., sponsor name, facility, and contact

Administrative data

e.g., organization’s protocol ID, secondary IDs

Registration:
Points to Consider

“Interventional” vs. “Observational”

Interventional Study (“Clinical Trial)

Participants assigned to receive one or more or no interventions based on a protocol

Observational Study

Participants identified as belonging to study groups, not assigned by researcher

Note: Many Diagnostic studies are interventional

What is a Single Clinical Trial?

Single core protocol, regardless of the number of sites

Collected data are intended to be combined and analyzed in aggregate

Systems to prevent “duplicate registration”

Follow-on studies?

Considered a single trial if defined in one protocol and includes same participants

May be a separate trial if re-consent required and/or involves participants not in the “initial” study

Importance of the Protocol

Research plan that includes

Prespecified hypotheses

Prespecified methods, including explicitly defined variables of interest

The validity of any statistical analyses or conclusions is based on adherence to those prespecified methods.

Registration provides a summary of the protocol

Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT, 2013)

Keeping Information Up to Date

All data must be current

Some data elements expected to change

e.g., recruitment status, anticipated start and completion dates

Others only change if the protocol has been amended

e.g., modification of a primary outcome measure

All changes tracked in the Archive

Results Reporting to ClinicalTrials.gov

The Results Database

FDAAA enacted in September 2007

Results Database launched in Sept 2008

Design based on statutory language and informed by CONSORT and other relevant standards

Requires reporting of “minimum data set” that was specified in the trial protocol

Tabular format for data with minimal narrative

EMA has developed a database based on our model

4 Scientific Modules

Participant Flow

Baseline Characteristics

Outcome Measures

Adverse Events

Key Concepts

The Basic Results Database requires the reporting of what was done; it does not require a change in study design or study procedures;

The intended audience is “readers of the medical literature.” It is not intended to inform the lay public. However, the tables need to be informative with minimal narrative text.

Results Review Focus

Concept: Tables should convey the design, conduct and analysis of the data

Logical table structure

Measure Title/Description and Units of Measure consistent

Complete scale information

Construct and domain

Best/worst values

“Units on a scale” if no other units

Review Criteria Overview

Complete and meaningful entries

[“Zarin scale” without further detail; “IOP” without explanation]

Logic and internal consistency

[number of participants must be consistent across modules; time to event must be measured in a unit of time]

Apparent validity

[624 years cannot be the mean age]

Examples of Incoherent Entries

823.32 mean hours sleep/day

“time to survival”

36 eyeballs in study of 14 people

“mean time to seizure” = 18 people

“first occurrence of all cause mortality (adjudicated)”

Results Reporting:
Points to Consider

Data Preparation

Summarizing results is similar in complexity to preparation of results for journal publication

Must understand the study design and analytic plan

Must have basic understanding of principles of clinical trial conduct and analysis

Must have access to necessary data:

Participant flow; Baseline characteristics

Outcome measures; Adverse events

Relation to Publication

Both seek to report accurate and informative data

ClinicalTrials.gov Results Reporting

Does not reject submissions

Permits disclosure of all outcome measures

Tabular data only

Peer-reviewed Journal Publication

Selects quality research of interest to readers

Editors may limit the focus of the report

Narrative for providing context and conclusions

Reporting Specific Outcome Measures

On the Horizon:
Individual Participant-Level Data (IPD)

Figure. Information loss as clinical trials data progress from raw uncoded data to summary data

Recent Developments in IPD

Institute of Medicine (IOM). Sharing clinical trial data: Maximizing benefits, minimizing risk. Washington, DC: National Academies Pr; 2015.

Sharing Clinical Trial Data: A Proposal From the International Committee of Medical Journal Editors (ICMJE). Ann Intern Med. 2016.

At time of registration, specify plan for data sharing

Share IPD supporting publication within 6 months

Effective 1 year from date policy finalized (only for clinical trials beginning to enroll participants)

Current: “Informational Chaos”
Diffuse, hard-to-access information about a single study

Potential Role for ClinicalTrials.gov

Provide framework and access to key trial information

Registration

Results

Links

Documents

Provide context for available information

List of all trials for given topic

Documentation of what information is available for each trial

Help to avoid “disclosure biases” of all sorts

ClinicalTrials.gov:
Informational Scaffold

New IPD Data Elements in ClinicalTrials.gov (Dec. 2015)

At Time of Registration

Plan to Share Data?: Whether there is a plan to make individual participant data (IPD) available.

Description: Brief description of what will be shared, when, and how data may be obtained (if known).

After Study Completion

Available Study Data/Documents: Study data sets and documents that are being shared.

Type: Select from pick-list (data set, protocol, etc.)

URL: Web address of repository for accessing data

Identifier: Unique identifier assigned by repository

Comments: Additional information about accessing data

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Linking ClinicalTrials.gov Records and Sources of Trial IPD

Linking Sources of Trial IPD to ClinicalTrials.gov Records

Zarin DA, Tse T. PLoS Med 2016.

Identifies types of IPD

Describes IPD in context of TRS

Illustrates, using a case study, the role of each component of the TRS

Final Thoughts

ClinicalTrials.gov reflects the “CRE”

Its utility as a scientific tool depends on its accuracy and completeness.

Your diligence in submitting accurate and timely reports will reflect on you and the “CRE”

Select Publications
Available at: http://www.clinicaltrials.gov/ct2/resources/pubs

Additional Information