Ward and Wilson Thursday Morning Presentation March 2015

Author: Pat Ward and Diane Wilson

Published Date: 03/09/2015
Clinical Trial Registration

Promises, Pitfalls, and Perils

Pat Ward and Diane Lehman Wilson
Office of Regulatory Affairs
University of Michigan Medical School
Memory Lane
Evolution of Clinical Trial Registration Requirements

- 1997: FDAMA calls for public registry
- 2000: ClinicalTrials.gov launched
- 2005: ICMJE requires registration of trials
- 2007: FDAAA expands ClinicalTrials.gov requirements
- 2008: ClinicalTrials.gov adds adverse event module
- 2009: ClinicalTrials.gov results modules added
- 2010: Proposed Rulemaking due …
- 2010-13: NIH shifts registrations to PIs
- 2011: ICD rule goes into effect
- 2012: BMJ article
- 2014: CMS rule
- November 2014: Proposed Rulemaking Published

Adapted and expanded from: [http://clinicaltrials.gov/ct2/about-site/history](http://clinicaltrials.gov/ct2/about-site/history)
Evolution of Clinical Trial Registration Requirements

1997
FDAMA calls for public registry

2000
ClinicalTrials.gov launched

2005
ICMJE requires registration of trials

2007
FDAAA expands ClinicalTrials.gov requirements

2008
ClinicalTrials.gov results modules added

2009
ClinicalTrials.gov adds adverse event module

2010
Proposed Rulemaking

2010-13
NIH shifts registrations to PIs

2011
ICD rule goes into effect

2012
BMJ article

2014
CMS rule

November 2014
Proposed Rulemaking Published

Adapted and expanded from: http://clinicaltrials.gov/ct2/about-site/history
International Committee Medical Journal Editors (ICMJE)

Require

- For prospective, interventional, comparative studies that evaluate health outcome
- Register before first enrollment

Purpose

- Mitigate publication/reporting bias
- Minimize unnecessary duplication of research
- Provide information about research and available trials to public and patients
- Provide information about similar research to IRBs
Just one more thing…
Required Registration of Clinical Trials

In the coming weeks and months, publishers of selected medical journals will begin to require prospective public registration of certain clinical trials as a prerequisite for publication.

**Which Journals?**

International Committee of Medical Journal Editors (ICMJE) member journals:

- JAMA
- New England Journal of Medicine
- The New Zealand Medical Journal
- Norwegian Medical Journal
- CMAJ
- The Lancet
- Annals of Internal Medicine
- Croatian Medical Journal
- Nederlands Tijdschrift voor Geneeskunde (Dutch Journal of Medicine)
- Journal of the Danish Medical Association
- The Medical Journal of Australia

**Which Studies?**

Any research project that prospectively assigns human subjects to intervention and comparison groups in order to study the cause-and-effect relationship between a medical intervention and a health outcome.

Studies designed for other purposes (retrospective records review, pharmacokinetics, major toxicity, other phase 1 trials, etc.) are exempt from this requirement.

**Which Registry?**

At present, the most prominent public trial registry that meets all ICMJE criteria is ClinicalTrials.gov, sponsored by the United States National Library of Medicine.

**By When?**

July 1, 2005 – After this date, register before beginning subject enrollment.
Evolution of Clinical Trial Registration Requirements

- 1997: FDAMA calls for public registry
- 2000: ClinicalTrials.gov launched
- 2005: ICMJE requires registration of trials
- 2007: FDAAA expands ClinicalTrials.gov requirements
- 2008: ClinicalTrials.gov adds adverse event module
- 2009: ClinicalTrials.gov requires registration of trials
- 2010: Proposed Rulemaking
- 2011: ICD rule goes into effect
- 2014: CMS rule
- 2012: BMJ article
- 2009: ClinicalTrials.gov adds adverse event module
- 2008: ClinicalTrials.gov results modules added
- 2007: FDAAA expands ClinicalTrials.gov requirements
- 2010: Proposed Rulemaking
- 2011: ICD rule goes into effect
- 2014: CMS rule
- November 2014: Proposed Rulemaking Published

Adapted and expanded from: http://clinicaltrials.gov/ct2/about-site/history
Food and Drug Administration Amendments Act (FDAAA)

- Expanded scope of trials that must be registered
- Required information that was previously optional
- Added additional registration data elements
- Required eventual inclusion of adverse event and results reporting
- Provided for penalties for noncompliance

Congress imposed short deadline

- Enacted in September; first deadline in December
Outrage, Panic, and Despair
Whhyy…?

Let’s back-up and review the drivers…

- Publicize trial opportunities to prospective subjects
- Transparency to stakeholders
- Promote data sharing
- Concern about redundant research
- Concern about negative drug and device trial results
  - Suspect Pharma burying
  - Academic publication bias
Whhyy…?

What’s the worst that could happen?

- Cost
  - Just 1 FTE per institution = tens of millions $ nationally

- Perhaps more importantly…

...Bottleneck!
Central CT Registration Administrator?

“By the way, while you were off sick yesterday we located the bottleneck.”
Federal Law Expands Clinical Trial Registration Requirement

The information below provides an overview of the steps researchers must take to register their clinical trials on ClinicalTrials.gov.

The links below jump to detailed information.

- Introduction
- Which Laws?
- Which Journals?
- Which Studies?
- Which Registry?
- By When?
- By Whom?
- How?
- IRBMED Approval?
- What Happens to Unregistered Trials?
- Automation?
- What About Submitting Information About Trial Results?
- Additional Information

Introduction

Recent years and months have seen progressively expanded requirements to provide the public with information about clinical trials available and conducted, including the results of those trials. These requirements have come from federal laws and regulations, as well as editors of prominent medical journals. Clinical trial sponsors, and in some cases research investigators, must be aware of and comply with their obligations under these requirements.

Which Laws?

The Food and Drug Administration Modernization Act (FDAMA) of 1997 resulted in the establishment of ClinicalTrials.gov and mandated registration of FDA-regulated efficacy drug trials for serious or life-threatening diseases and conditions.
Time Marches on...
Evolution of Clinical Trial Disclosure Requirements

- 1997: FDAMA calls for public registry
- 2000: ClinicalTrials.gov launched
- 2005: ICMJE requires registration of trials
- 2007: FDAAA expands ClinicalTrials.gov requirements
- 2008: ClinicalTrials.gov adds adverse event module
- 2009: ICD rule goes into effect
- 2010: Proposed Rulemaking
- 2010-13: NIH shifts registrations to PIs
- 2011: Proposed Rulemaking Published
- 2012: BMJ article
- 2014: CMS rule

Adapted and expanded from: [http://clinicaltrials.gov/ct2/about-site/history](http://clinicaltrials.gov/ct2/about-site/history)
Evolution of Clinical Trial Disclosure Requirements

1997
- FDAMA calls for public registry

2000
- ClinicalTrials.gov launched

2007
- FDAAA expands ClinicalTrials.gov requirements

2005
- ICMJE requires registration of trials

2008
- ClinicalTrials.gov results modules added

2009
- ClinicalTrials.gov adds adverse event module

2010
- Proposed Rulemaking due ...

2010-13
- NIH shifts registrations to PIs

2011
- ICD rule goes into effect

2012
- BMJ article

2014
- CMS rule

November 2014
- Proposed Rulemaking Published

Adapted and expanded from: http://clinicaltrials.gov/ct2/about-site/history
Evolution of Clinical Trial Disclosure Requirements

- **2000**: ClinicalTrials.gov launched
- **2007**: FDAAA expands ClinicalTrials.gov requirements
- **2009**: ClinicalTrials.gov adds adverse event module
- **2011**: ICD rule goes into effect
- **2014**: CMS rule
- **November 2014**: Proposed Rulemaking Published

- **1997**: FDAMA calls for public registry
- **2005**: ICMJE requires registration of trials
- **2008**: ClinicalTrials.gov results modules added
- **2010**: Proposed Rulemaking due ...
- **2010-13**: NIH shifts registrations to PIs
- **2012**: BMJ article

Adapted and expanded from: [http://clinicaltrials.gov/ct2/about-site/history](http://clinicaltrials.gov/ct2/about-site/history)
Evolution of Clinical Trial Disclosure Requirements

- **1997**
  - FDAMA calls for public registry

- **2000**
  - ClinicalTrials.gov launched

- **2007**
  - FDAAA expands ClinicalTrials.gov requirements

- **2008**
  - ICMJE requires registration of trials
  - ClinicalTrials.gov adds adverse event module

- **2009**
  - ClinicalTrials.gov results modules added

- **2010**
  - Proposed Rulemaking due …

- **2011**
  - ICD rule goes into effect

- **2012**
  - BMJ article

- **2013**
  - NIH shifts registrations to PIs

- **2014**
  - CMS rule

- **November 2014**
  - Proposed Rulemaking Published

Adapted and expanded from: [http://clinicaltrials.gov/ct2/about-site/history](http://clinicaltrials.gov/ct2/about-site/history)
Before I know it…

- FDAAA deadlines start kicking in
  - Results (2008)
  - Adverse events (2009)
But wait, there’s more…

- FDAAA deadlines start kicking in
  - Results (2008)
  - Adverse events (2009)
- Informed consent document regulation (2011-2012)
But wait, there’s more…

- FDAAA deadlines start kicking in
  - Results (2008)
  - Adverse events (2009)
- Informed consent document regulation (2011-2012)
- Transition of NIH-held registration to University PIs (starting 2011)
But wait, there’s more…

- FDAAA deadlines start kicking in
  - Results (2008)
  - Adverse events (2009)
- Informed consent document regulation (2011-2012)
- Transition of NIH-held registration to University PIs (starting 2011)

Time to call for reinforcements!
2011

Diane Lehman Wilson

- Legal: JD
- Public Policy: MPP
- Teaching: MA
- Enthusiastic
- Looking for challenge
- (not me)

Perfect!
Pass the baton or hot potato.
My Admonishment…

Please don’t make this problem any bigger than it has to be.

But it was getting bigger!

Luckily, Diane didn’t listen to me!
First Steps

- **2011 Network with colleagues**
  - Thank you, CTSA Regulatory Key Function Committee, Clinical trials registration subcommittee
  - Sarah White at Partners leads monthly calls

- **2012 Assess our own compliance**
  - Call in more help - Hire a temp for six months
  - Adapt our Informed Consent Language
  - Attend Train-the-Trainer 2-day “camp”
    - Thank you, National Library of Medicine

When will the NPRM come out?
Next steps

2013

- Develop Internal training
- Modify IRB forms
  - to integrate ClinicalTrials.gov registration number (NCT)
  - to facilitate compliance checking

JUST IN TIME...

To respond to new Medicare (CMS) billing requirement
Evolution of Clinical Trial Disclosure Requirements

- 1997: FDAMA calls for public registry
- 2000: ClinicalTrials.gov launched
- 2005: ICMJE requires registration of trials
- 2007: FDAAA expands ClinicalTrials.gov requirements
- 2008: ClinicalTrials.gov results modules added
- 2009: ClinicalTrials.gov adds adverse event module
- 2010: Proposed Rulemaking due ...
- 2011: ICD rule goes into effect
- 2012: BMJ article
- 2014-13: NIH shifts registrations to PIs
- November 2014: Proposed Rulemaking Published

Adapted and expanded from: [http://clinicaltrials.gov/ct2/about-site/history](http://clinicaltrials.gov/ct2/about-site/history)
Evolution of Clinical Trial Disclosure Requirements

1997
FDAMA calls for public registry

2000
ClinicalTrials.gov launched

2005
ICMJE requires registration of trials

2007
FDAAA expands ClinicalTrials.gov requirements

2008
ClinicalTrials.gov results modules added

2009
ClinicalTrials.gov adds adverse event module

2010
Proposed Rulemaking due …

2010-13
NIH shifts registrations to PIs

2011
ICD rule goes into effect

2012
BMJ article

2014
CMS rule

November 2014
NPRM Published

Adapted and expanded from: http://clinicaltrials.gov/ct2/about-site/history
Now What?

- **NPRM**
  - Elements
  - Specific Questions
  - Statutory Options (under FDAAA)
  - Items of Concern

- **NIH Policy**
  - Elements
  - Rationale
  - Concerns
NPRM Elements

- Provides Definitions
- Simplifies “Applicable Clinical Trial” determination
- Adds and refines database elements
- Adds new deadlines
NPRM Requests for Input

- Require actual protocols to be uploaded?
  - Improve quality? OR…
  - Discourage learning, safe risk-taking?
  - Drown in revisions?

- Require Technical and Lay Summaries?
  - Lay summaries helpful to public, BUT…
  - Risks:
    - Exceeding “prior publication” limits
    - Who will do the work?
    - Who will vet the summaries for accuracy, impartiality?
FDAAA Statutory Options

NPRM may:

Expand results reporting requirement to all Applicable Clinical Trials
- Many more trials will require results reporting
- Comments show that the public supports this widely
- Results still only required for drug and device trials

Expand Time frame to report results from 12 to 18 months
- Little cost to public
- Great benefit for Academic Medical Centers because researchers wear so many hats
NPRM Specific Concerns

TIME FRAMES:

- 15 and 30 day windows are confusing
  - Harmonize all urgent time frames to 30 days

- Improve efficiency by coinciding with IRB reporting
  - Use 1-year updates as allowed by FDAAA

- Results reporting extensions
  - Allow for academic activities similar to those proposed for Pharma commercial interests
NPRM Specific Concerns

Adverse Events

- Very challenging to upload; though getting better
- What’s included? Gaps between definition and practice
- “All cause mortality” helpful or not?
- Comparables in charts may not BE comparable
NPRM Specific Concerns

University research is different from corporate R&D

- Researcher autonomy
- Competing priorities
- Limited resources

Investigator-Initiated research is hard enough!

- Proposed expanded access links should come from manufacturer
- PIs need closure!
- Need greater simplicity for when PI leaves
NIH Proposed Policy

NIH following the modified “golden rule”
We give the gold, so we set the rules!
No cost-benefit analysis legally required, so…

All NIH clinical trials must register and report results

The catch…
- New clinical trials definition (October 2014 – 1 month before policy)
  - Includes behavioral interventions
    - This goes way beyond intention of FDAAA
2012 BMJ article asserted < 50% publication rates, but…

It looked at data for trials ending between 2005 and 2008, before the NIH “encouragement” was well publicized, before the ClinicalTrials.gov modules were even complete, and saw improvement trending over those years!

**Publication of Clinical Trial Results**

Less than 50% of NIH-funded clinical trials are published within 30 months of completion

Newer Data Sharing Drivers

In addition to NIH “encouragement”
Other NIH requirements (GDS and others)
Public Access policy (2013 enforcement)
ICMJE policy “encouragement” (2014)
Does the solution fit the “problem”?

MORE TAILORED OPTIONS

- Wait 3 years till the plane is “built”
  - continue “encouragement”
  - recheck publication data

- Require results reporting at three years or five years if no publication has occurred

- Give small pilot trials a “pass”
Weigh the Opportunity Costs

How should researchers spend 40+ hours?

- Conducting innovative research
- Publishing research
- Evaluation of research on NIH committees and via peer review
- Treating patients
- Educating and mentoring
- Laboring to enter complex results into formulaic charts
Promises, Pitfalls, and Perils

- **Promises**
  - Engaged and informed public
  - Transparency
  - Unbiased reporting
  - Data-sharing
  - Minimize duplicative research

- **Pitfalls**
  - Unfunded mandate
  - Discourage and distract from research

- **Perils**
  - Questionable quality without peer review
  - Misinterpretation without context
  - Misinformed public
Let’s finish building the plane before adding more passengers.