# Ward and Wilson Thursday Morning Presentation March 2015

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Published Date: 03/09/2015

# Clinical Trial Registration

## Promises, Pitfalls, and Perils

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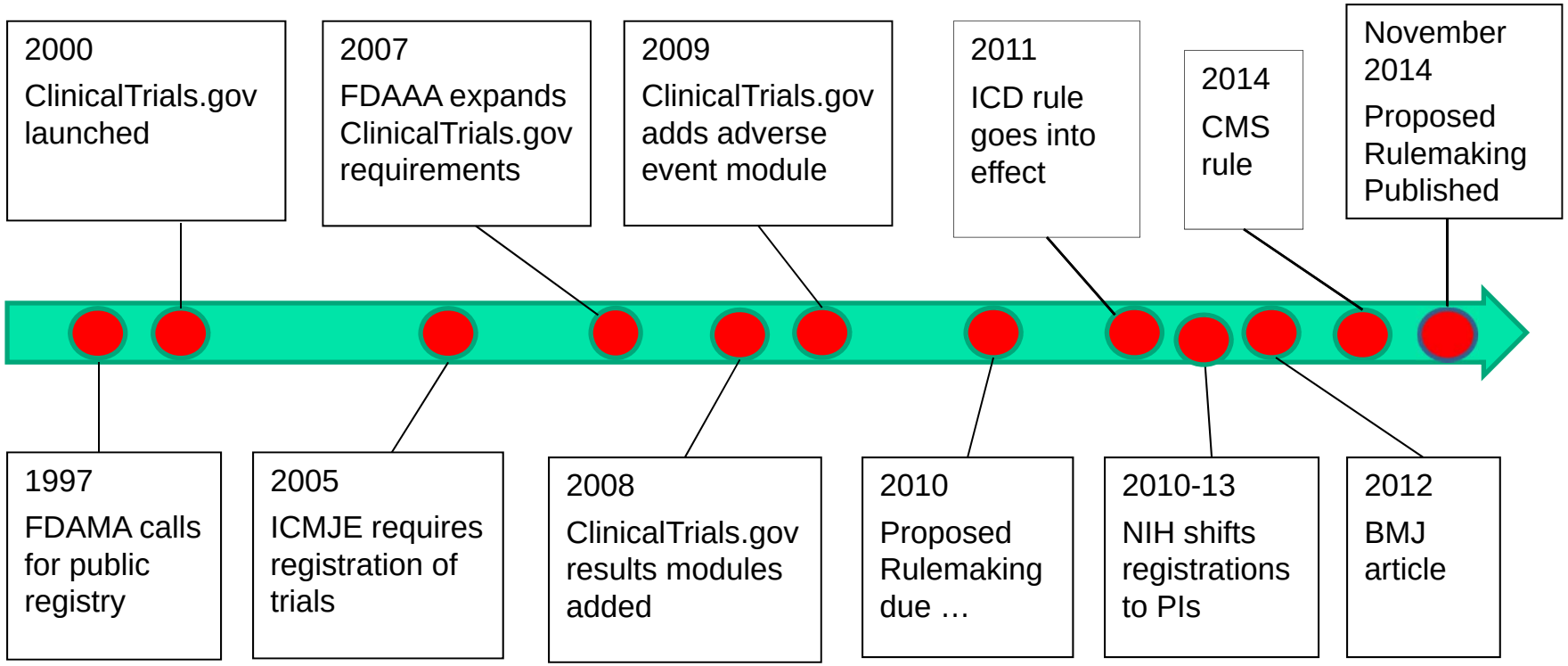
# Memory Lane

# Evolution of Clinical Trial Registration Requirements

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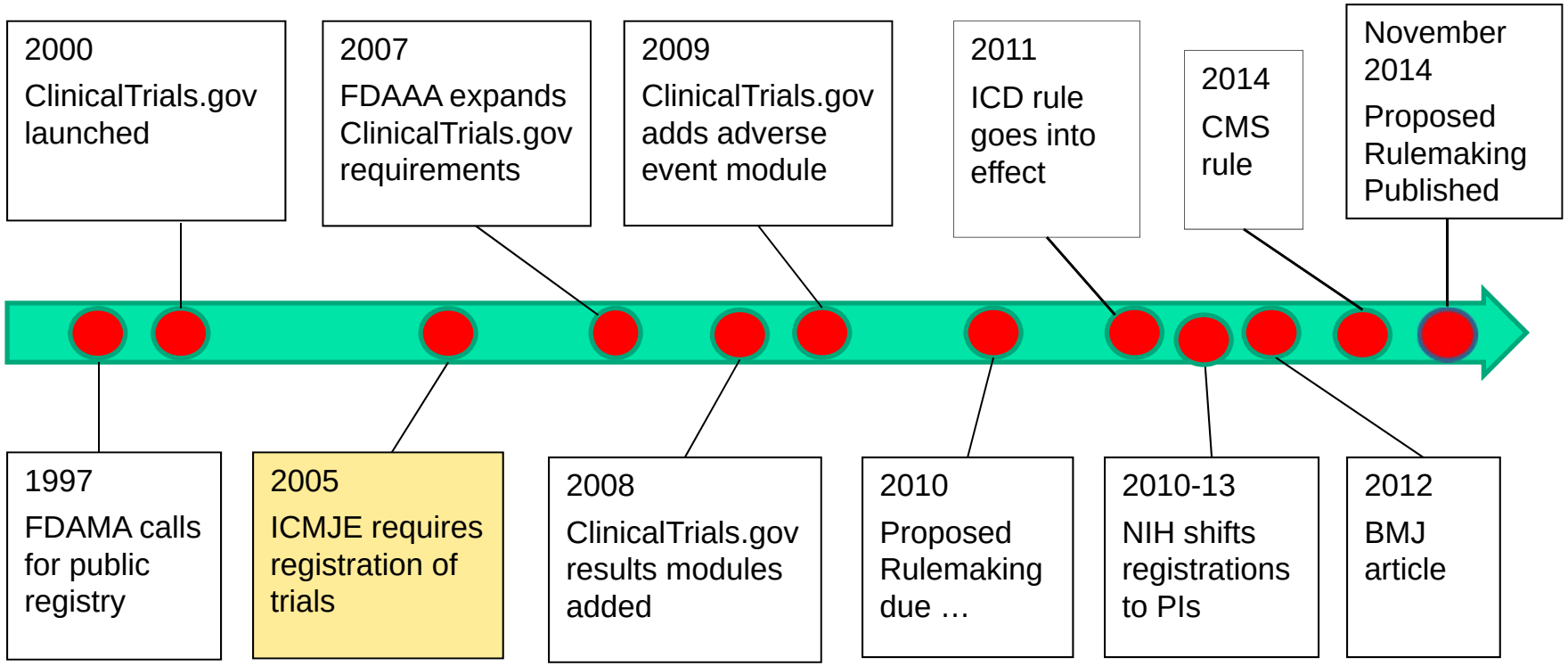


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# 2005

## 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…

# Minimalist Approach

## 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.

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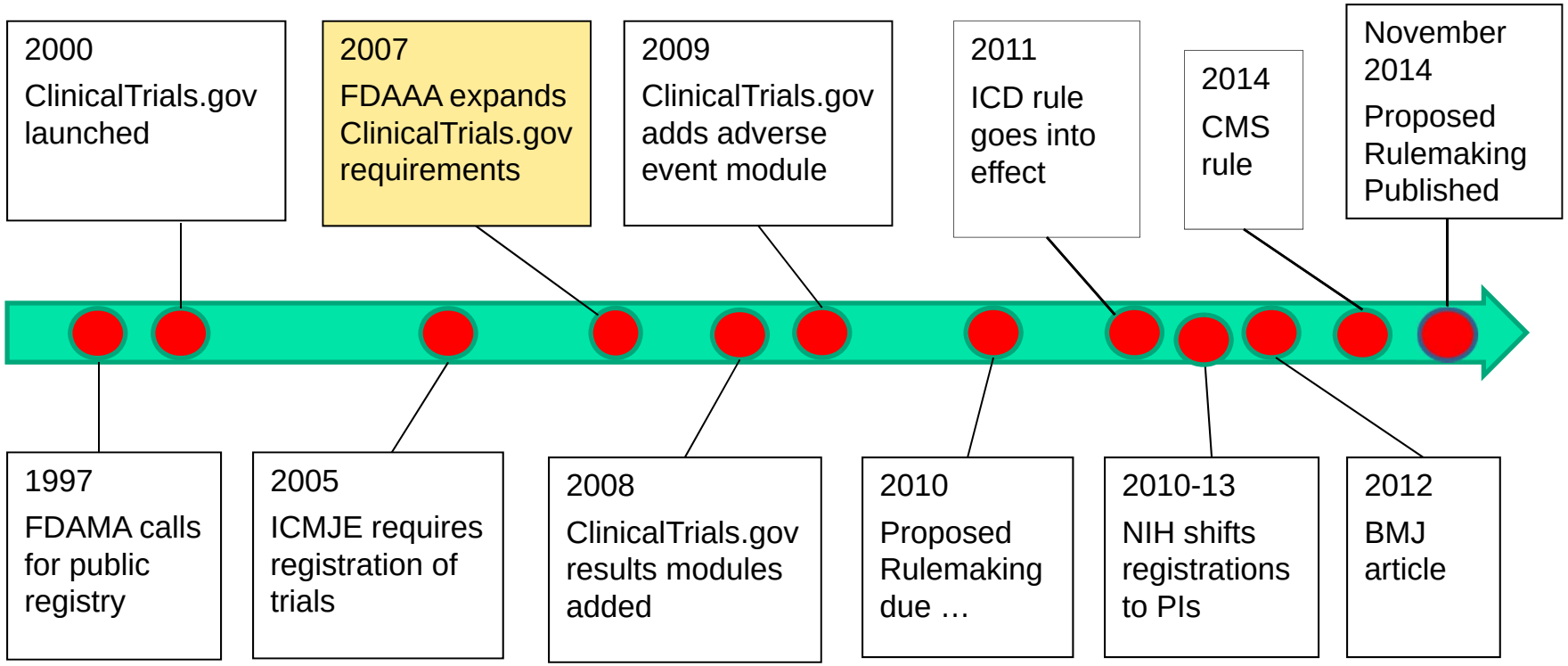


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# 2007

## 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

# Whhyyy…?

## 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

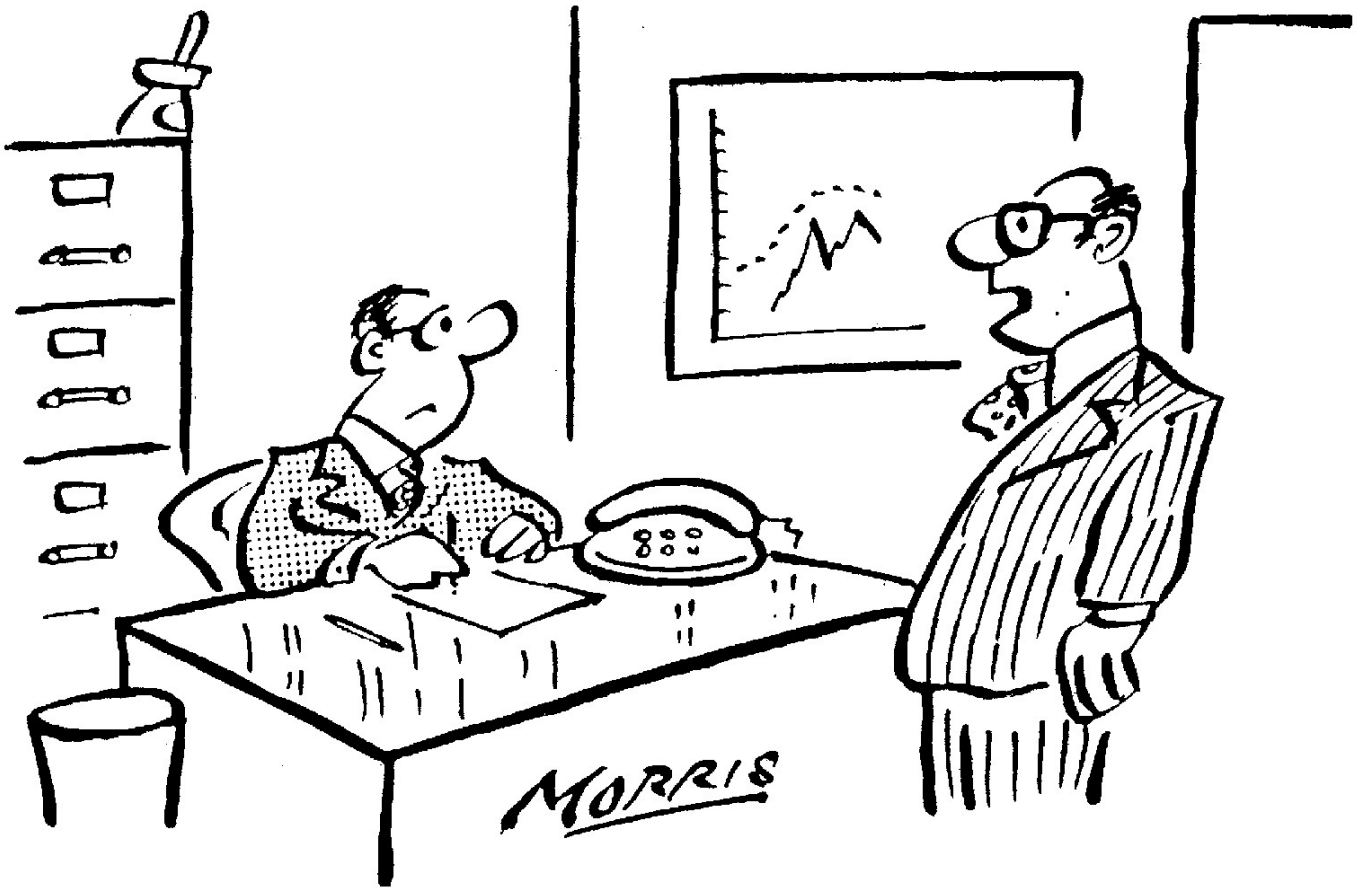
# Whhyyy…?

**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."

# Still Stubbornly Minimalist

## 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

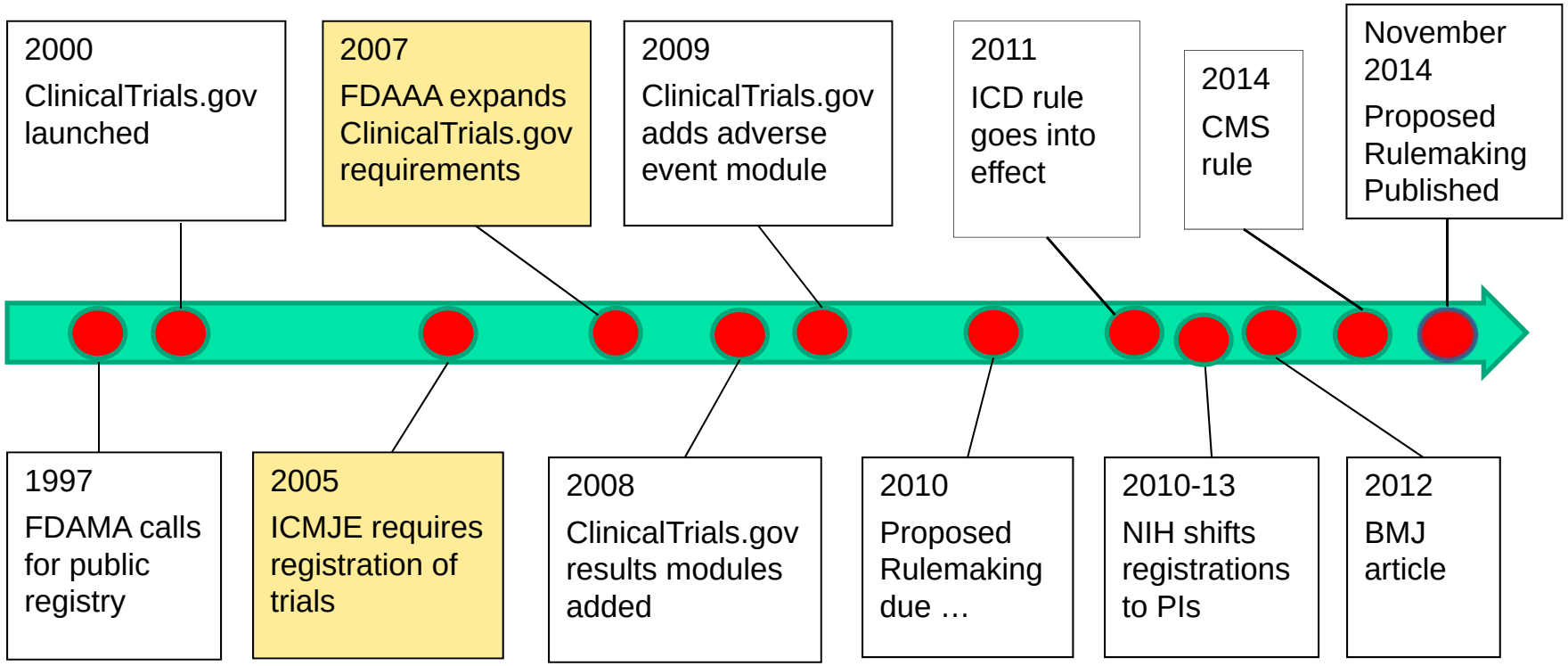
Recent years and months have seen progressively expanded requirements to provide the public with information about clinical trials available and conducted, including the results of those trials. These requirements have come from federal laws and regulations, as well as editors of prominent medical journals. 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

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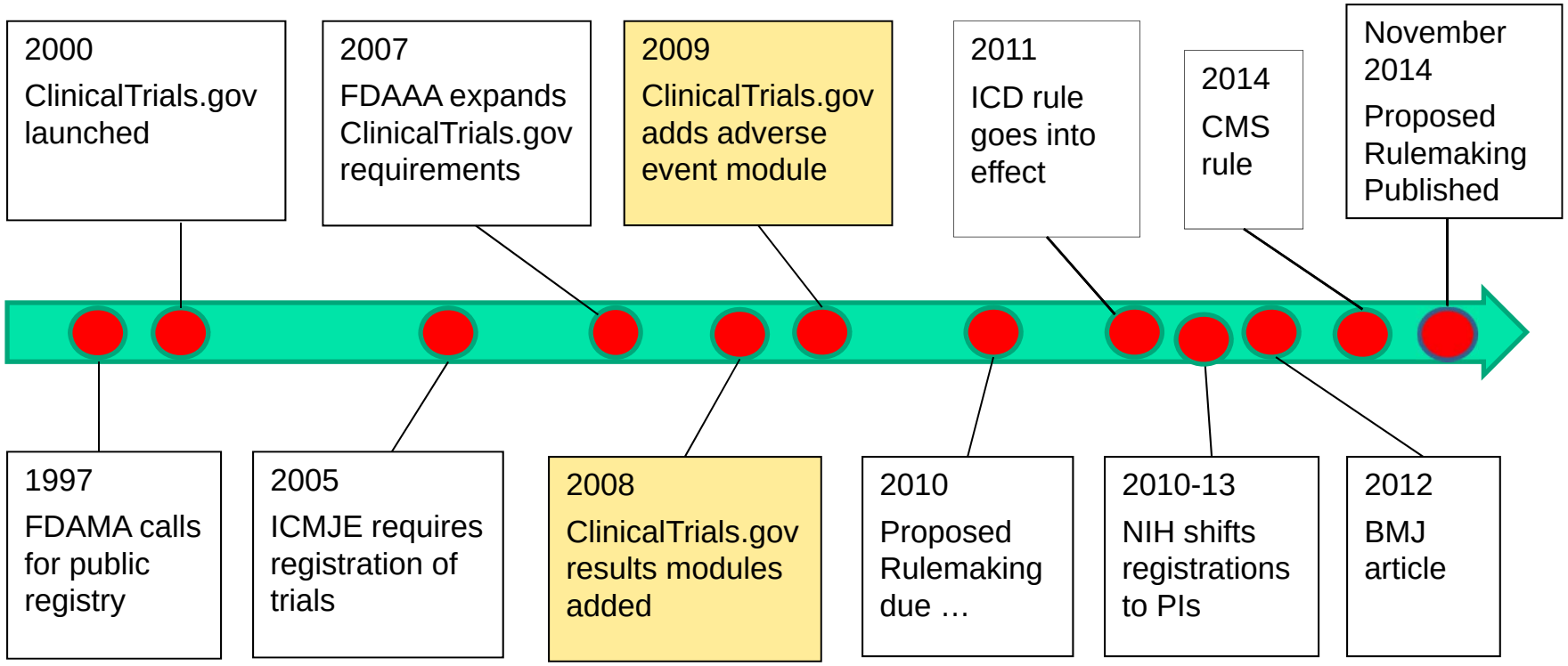


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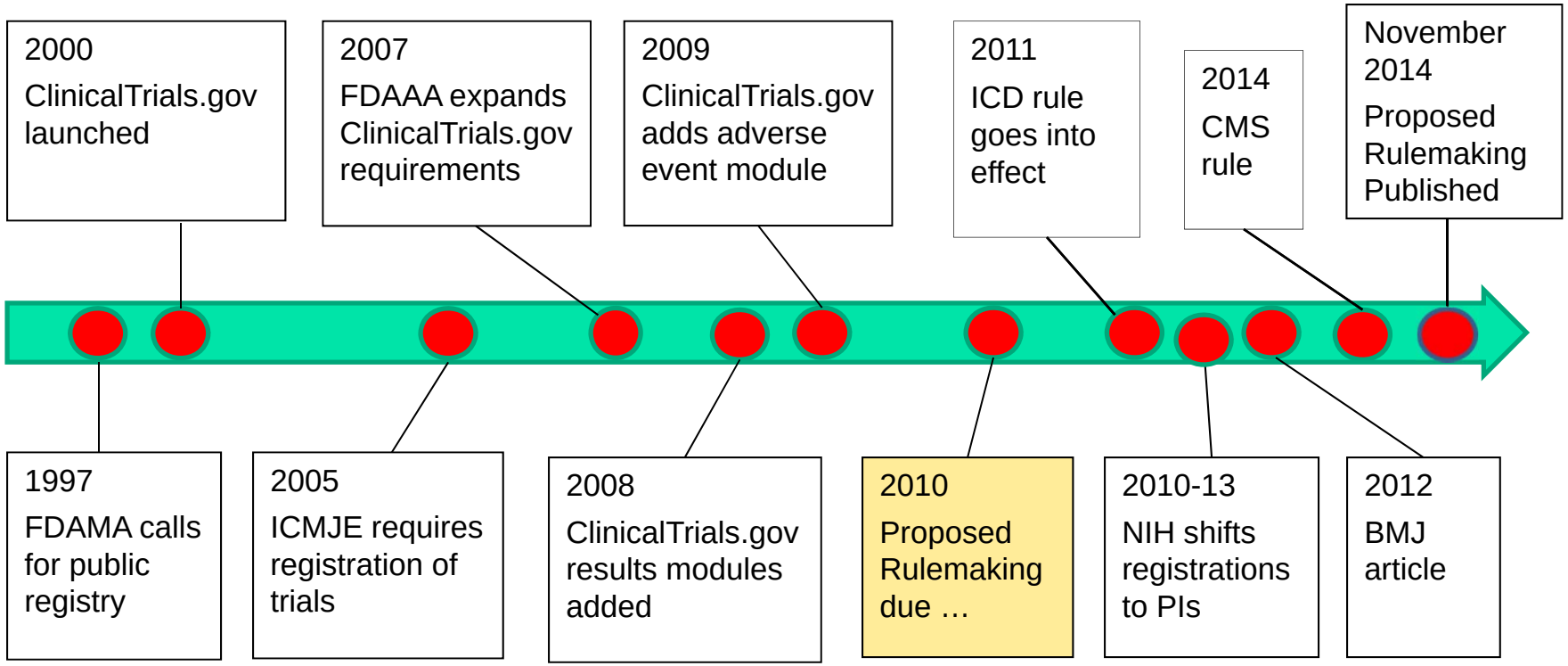


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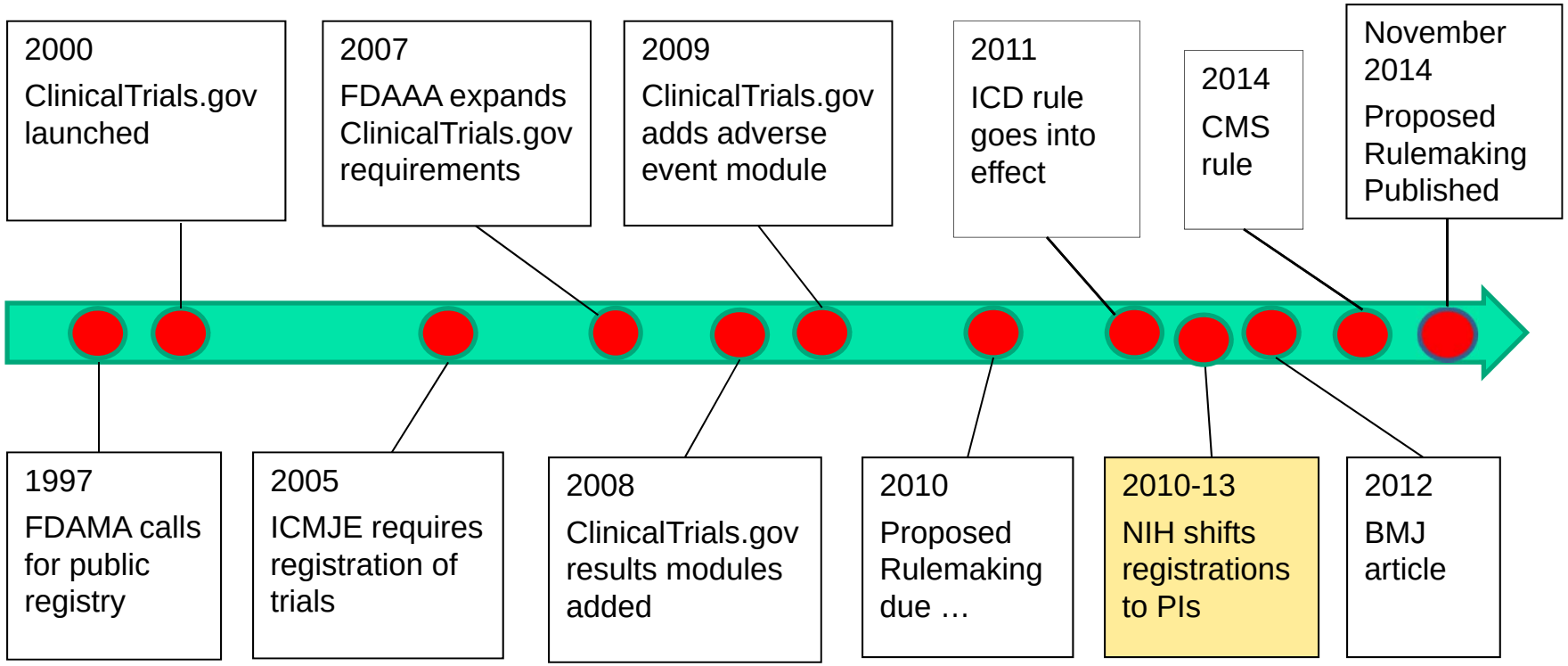


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# Before I know it…

- **FDAAA deadlines start kicking in**
  - Results (2008)
  - Adverse events (2009)

# But wait, there's more…

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- **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

# 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

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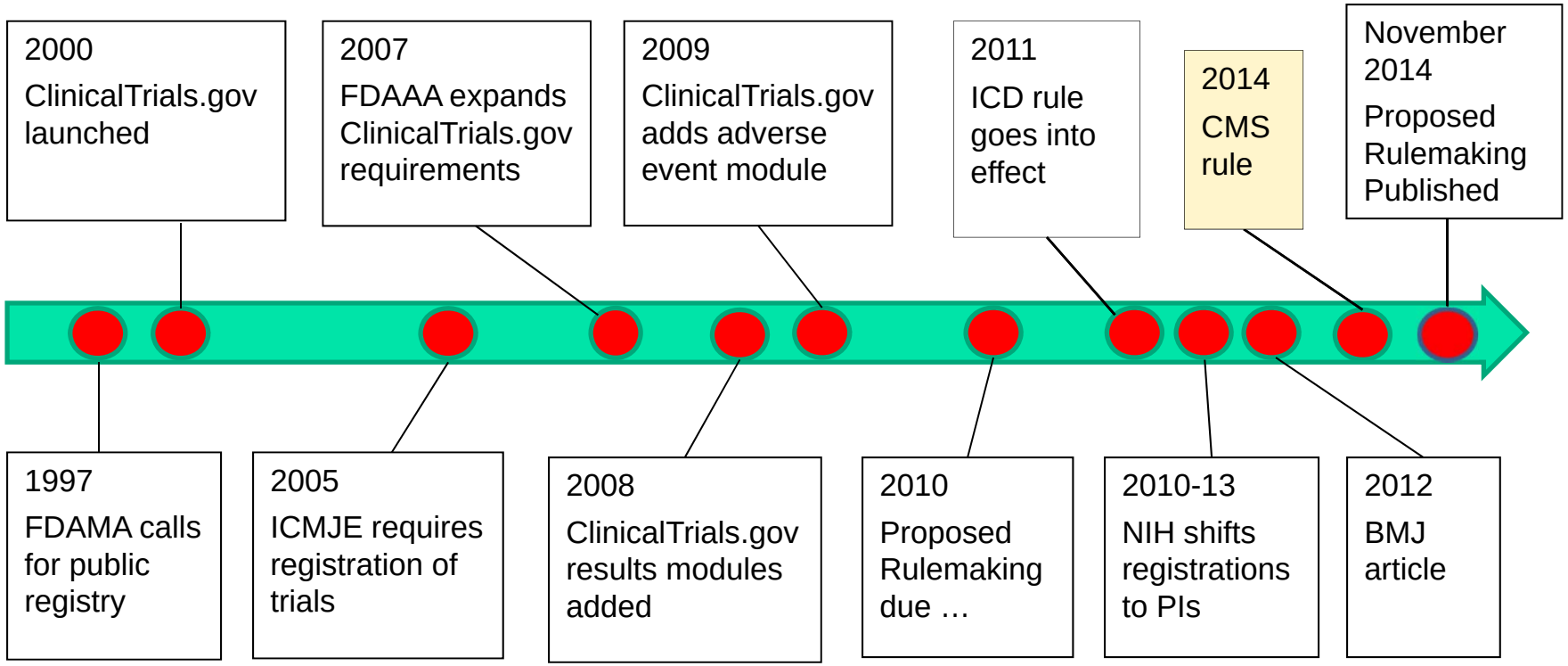


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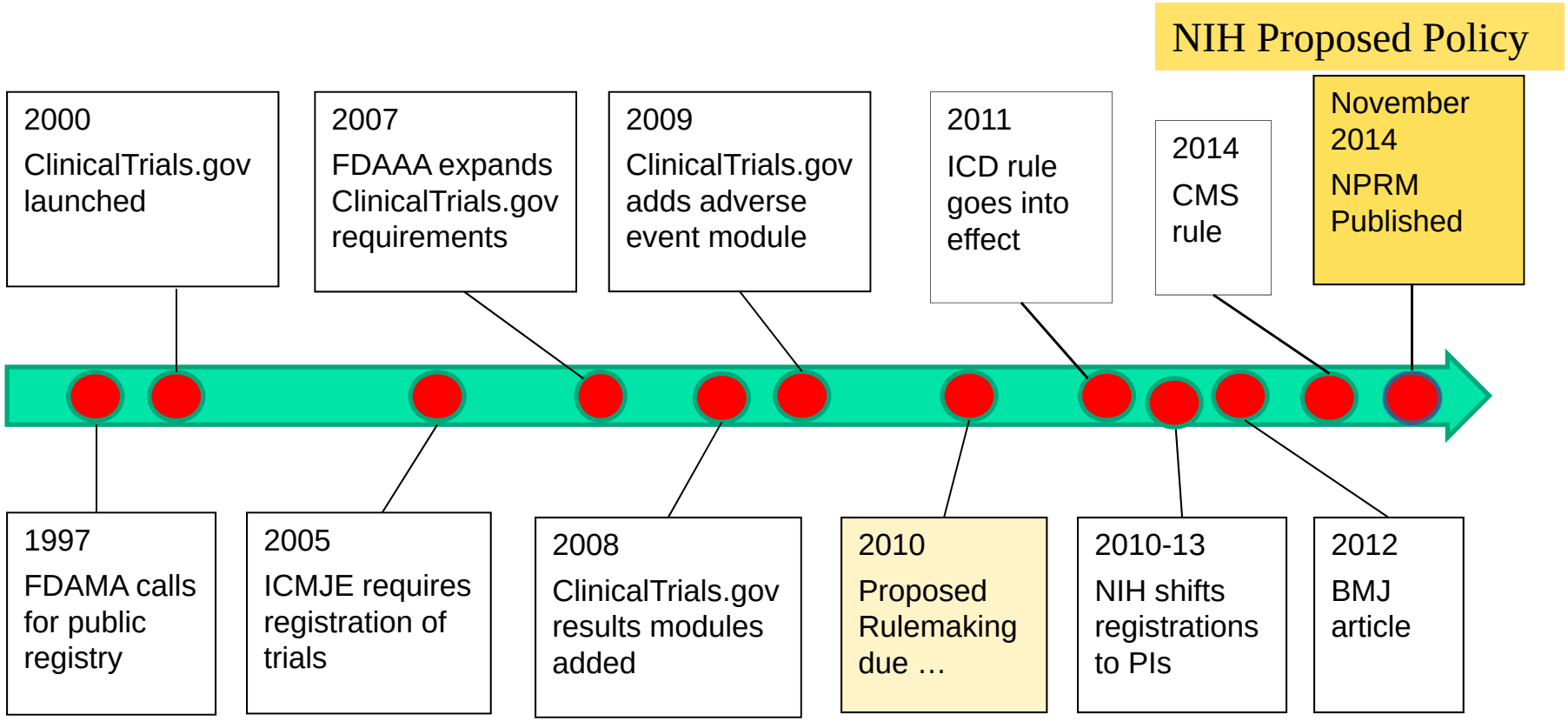


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# Now What?

- **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

# NIH Proposed Policy Rationale

**2012 BMJ article asserted < 50% publication rates, but…**

It looked at data for trials ending between 2005 and 2008,

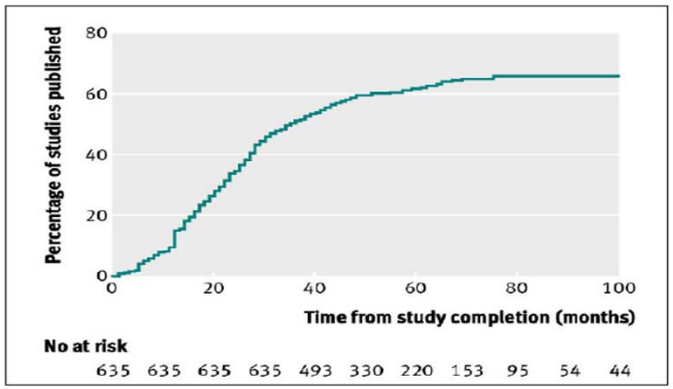
**before** the NIH "encouragement" was well publicized,

**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

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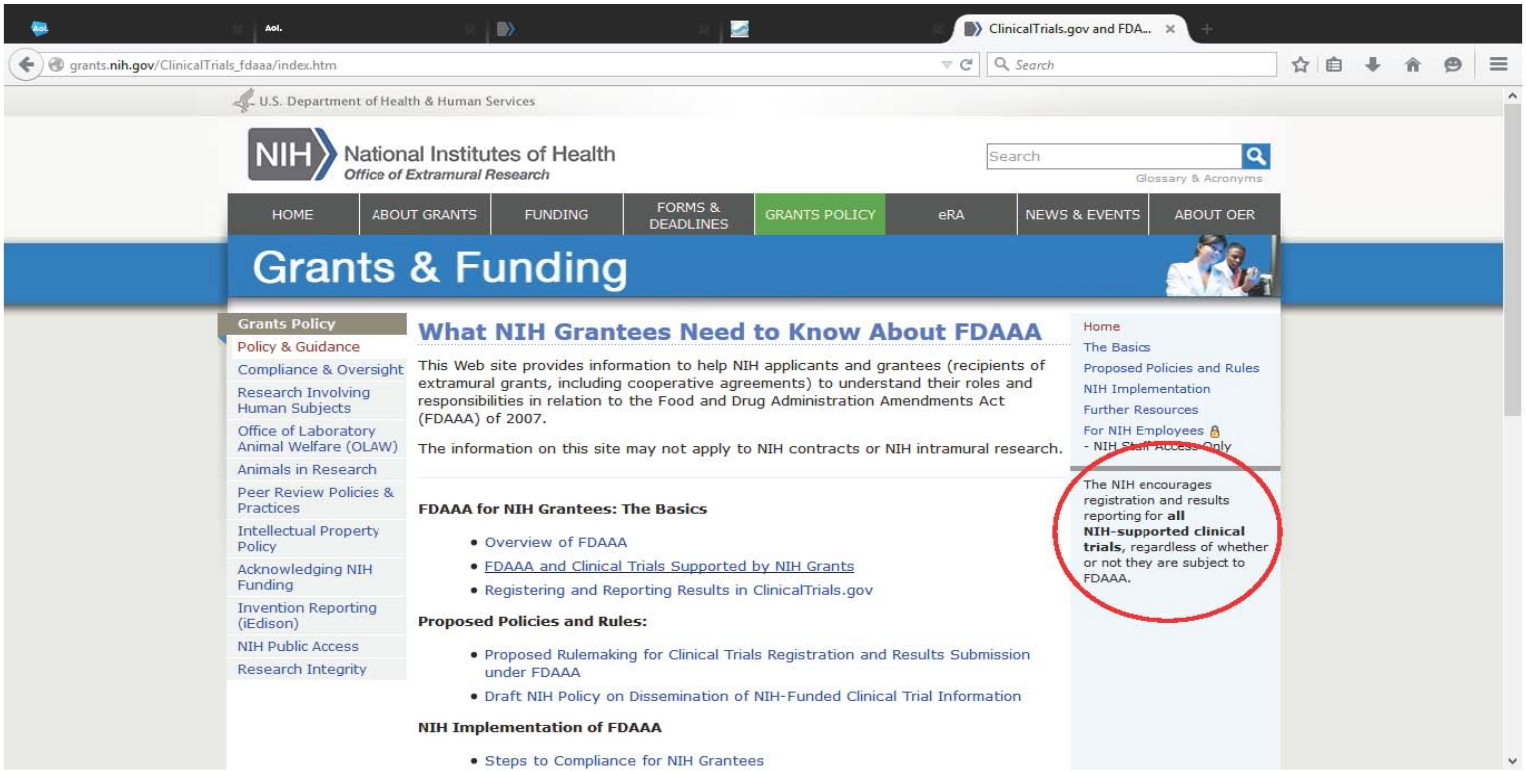
Source: *BMJ* 2012;344:d7292.

# Newer Data Sharing Drivers

**In addition to NIH "encouragement"**

- Other NIH requirements (GDS and others)
- Public Access policy (2013 enforcement)
- ICMJE policy "encouragement" (2014)
- IOM Report (2015)



# 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