Continuing Challenges and Opportunities with ClinicalTrials.gov

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Eras of ClinicalTrials.gov: Public View

2000-2005	FDAMA only (regarding serious and life-threatening diseases)
2005	ICMJE policy announced
Late 2007	FDAAA enacted
2012	Informed Consent requirements for Applicable Clinical Trials
2014	Draft regulations and Draft NIH policy
2015	CMS rule
2016	Final Regulations 42 CFR 11 and NIH policy promulgated
2017 pre-June	Final Regulations 42 CFR 11 and NIH policy effective
2017 future	Uploading of full protocols required with results for trials ending after 1/17/2017

Before Results were required, results interpretive statements were allowed (2006 example)

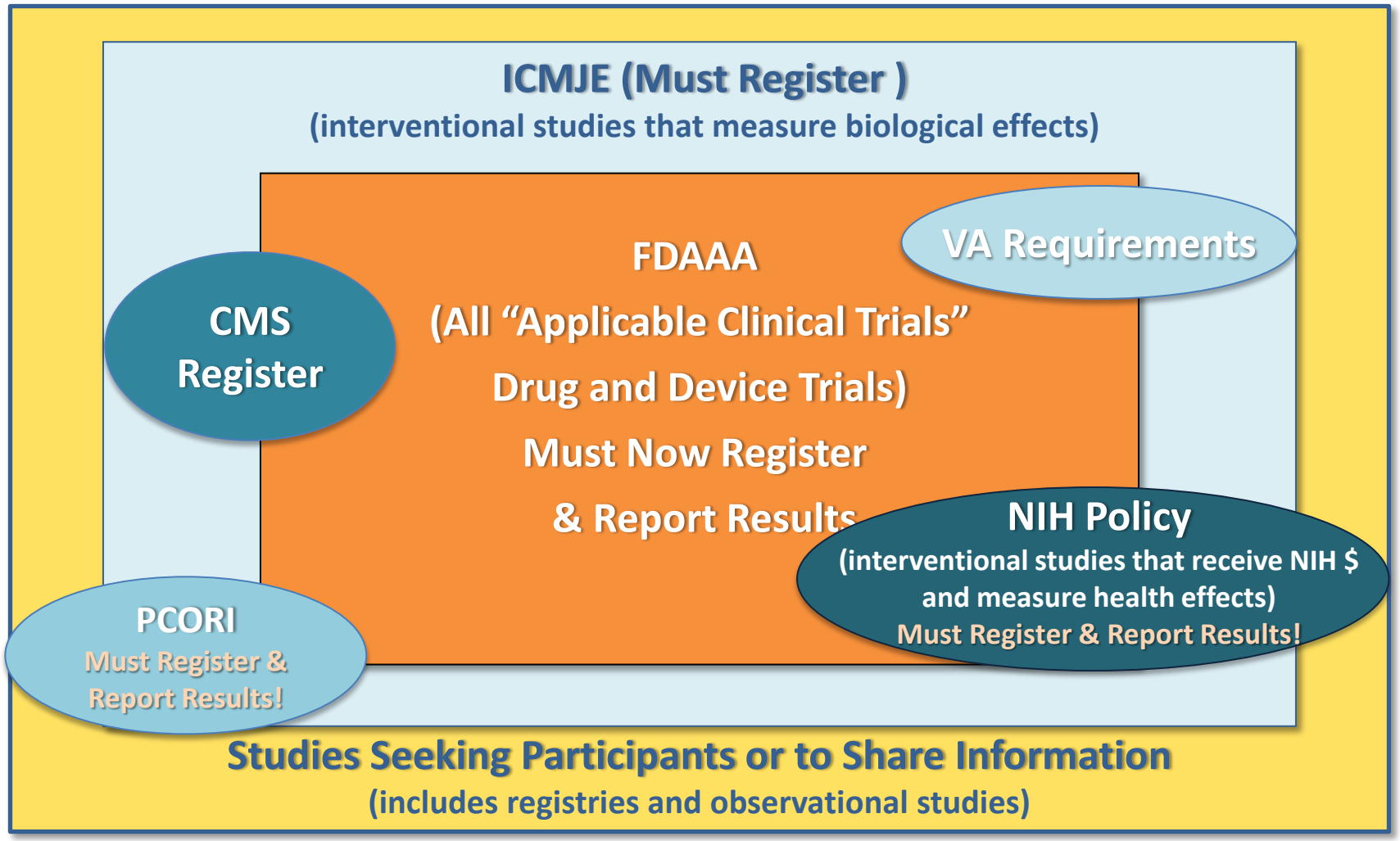
- ... We assessed whether people systematically misremember the "myths" (false information) as true, and to assess effects on perceptions of risk and behavioral intentions.
- In sum, people show a bias to think that incompletely remembered information is true, turning "myths" into "facts." Hence public information campaigns should emphasize information that is true. Repeating false information, even as a warning, can create the unintended consequence of belief in the information.

Statements like this indicating the interpretation of results would not be allowed now.

Eras of ClinicalTrials.gov Behind the Scenes – As it looks to a lay outsider

1997 - 2000	Building the system
2000 - 2005	“Shoestring era” - registry only (<3000 per year)
2006-2009	Massive expansion and build of results reporting modules: Participant Flow, Baseline Characteristics, Outcome Measures; Adverse Events (15,000 per year)
2008	Recording of PRS Review events
2012-2016	Continuous Quality Improvement; cycles of revision of greater ease of use; increasing administrative functionality
2016-2017	Additional retooling and restructuring of questions to match new regulatory requirements

Reasons to Register in Clinicaltrials.gov



Conceptual and practical challenges increase when a system isn't stable

- We know change is necessary;
- We know change is often helpful, but ..
- when it is nearly continuous, there is a push-pull between appreciation and frustration, even while people are trying very hard to do the right thing.

ClinicalTrials.gov has been asked at least three times to change what it is supposed to be:

- Is it a registry?
- Is it a searchable database of results?
- Is it a repository for protocols/ informed consents?

Conceptual Challenges for Faculty - #1

Changing Standards:

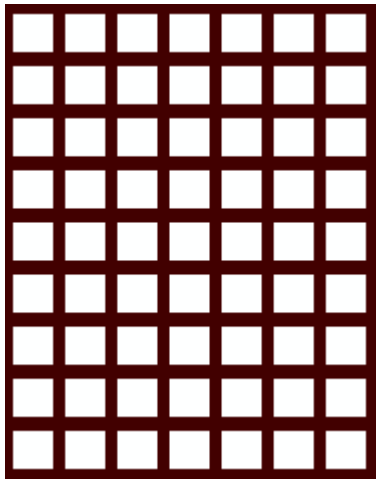
(example from an actual trial)

- Primary Outcome Measures: Exercise capacity [Time Frame: Single day testing] [Designated as safety issue: No]

- Secondary Outcome Measures: **Many** exercise parameters, including peak VO2, HR, BP, **others** [Time Frame: single day testing] [Designated as safety issue: No]

In 2008 this was allowable and published; In 2017 it will NOT pass through their QA

Conceptual Challenges for Faculty - #2



Multiple drivers with inconsistent needs:

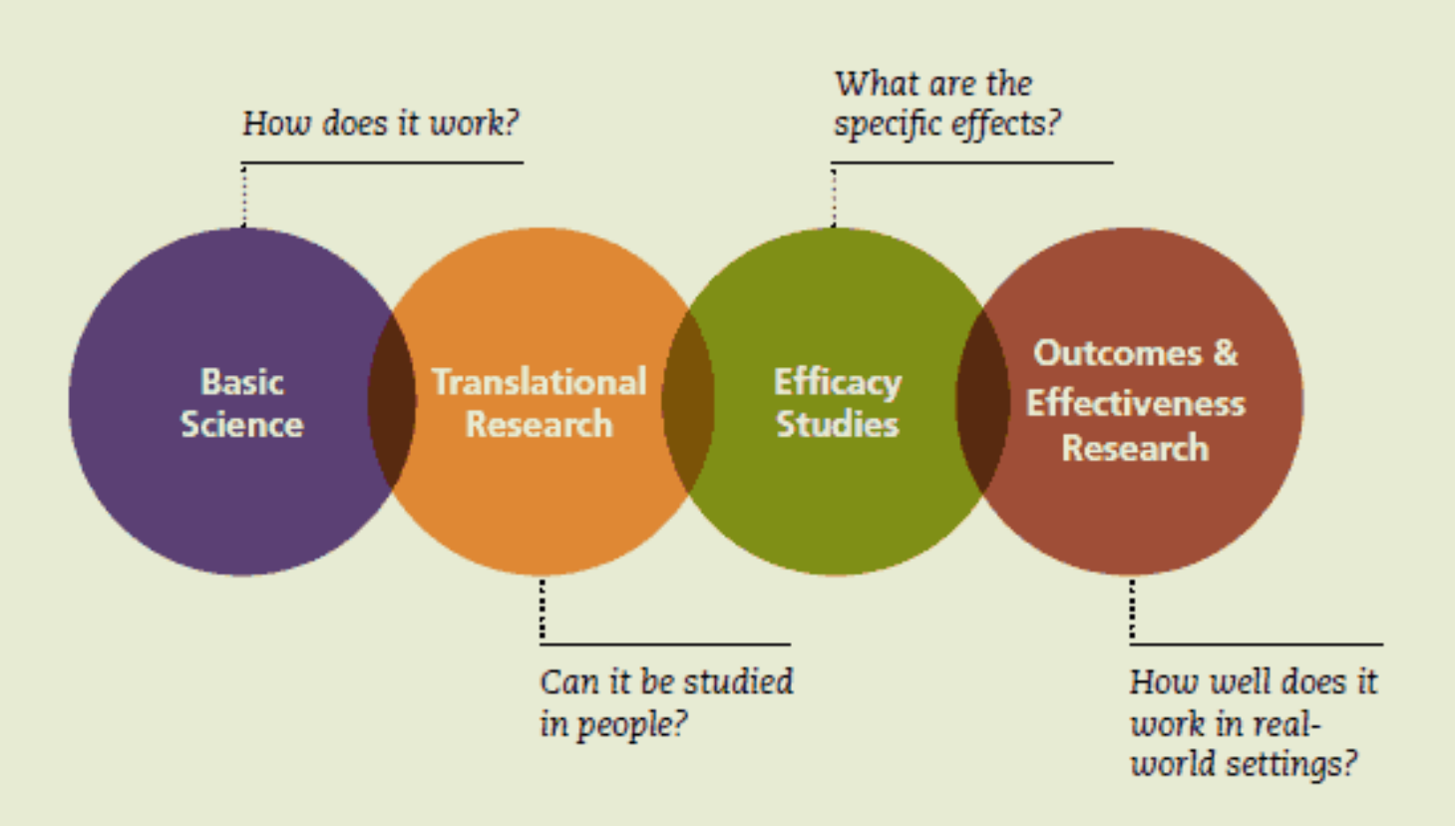
One approach: "Just do it" ….

BUT Principal Investigators still need to know how to answer the questions:

Studying one or more U.S. FDA-regulated drug or biologic products?

Definition: Indication that a clinical study is studying a drug product (including a biological product) subject to section 505 of the Federal Food, Drug, and Cosmetic Act or to section 351 of the Public Health Service Act. Select Yes/No.

Conceptual Challenge - #3:



Faculty view certain interventional studies as “basic science” when others may view them as clinical trials.

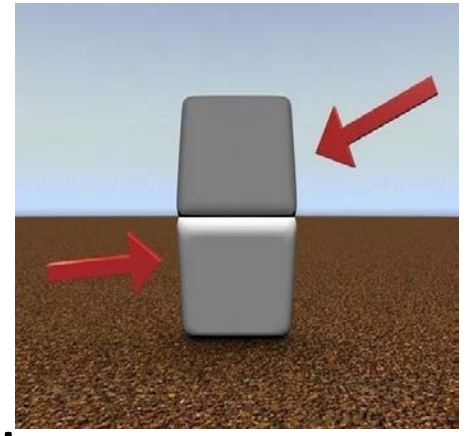
Source: https://nccih.nih.gov/about/plans/2011/introduction.htm

Conceptual Challenges for Faculty #4

NIH Definition and Regulatory Definition of Clinical Trial (42 CFR 11) **almost match**, but not quite:

- NIH: A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on **health-related biomedical or behavioral outcomes**.
- 42 CFR 11: a clinical investigation or study in which human subject(s) are prospectively assigned, according to a protocol, to one or more interventions (or no intervention) to evaluate the effect(s) of the intervention(s) on **biomedical or health-related outcomes**.

Conceptual Challenges for Faculty - #5



GRAY ZONES:

- If an intervention (e.g. a diagnostic device) is being tested, but not for its health or biomedical effects, is it an interventional trial under the regulation?
- If a device is being used solely to “look at” different groups of people, is that an “interventional trial” or is it an observational study?

Conceptual Challenges for Faculty - #6

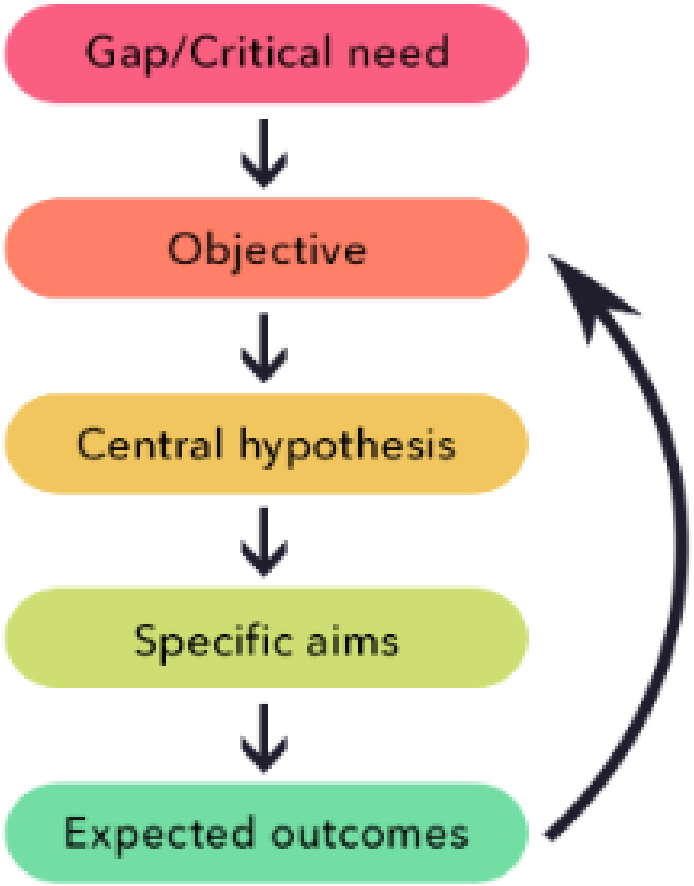
- Community Based Participatory Research may **not** have all outcome measures pre-established;
- Outcome measures may **need** to change and evolve to properly engage and cycle with the participants;
- Yet in a highly transparent, archived system, that can seem to be inconsistent

Conceptual Challenges for Faculty - #7

Mixed Methods and Qualitative Research:

- How are qualitative outcome measures to be shown?
- Will only those measures that are quantitative be required?
- Must qualitative data be coded into quantitative summaries?

Conceptual/Practical Challenges for Faculty



Reframing required for many different audiences

Grants with their Aims and Objectives: High level scientists

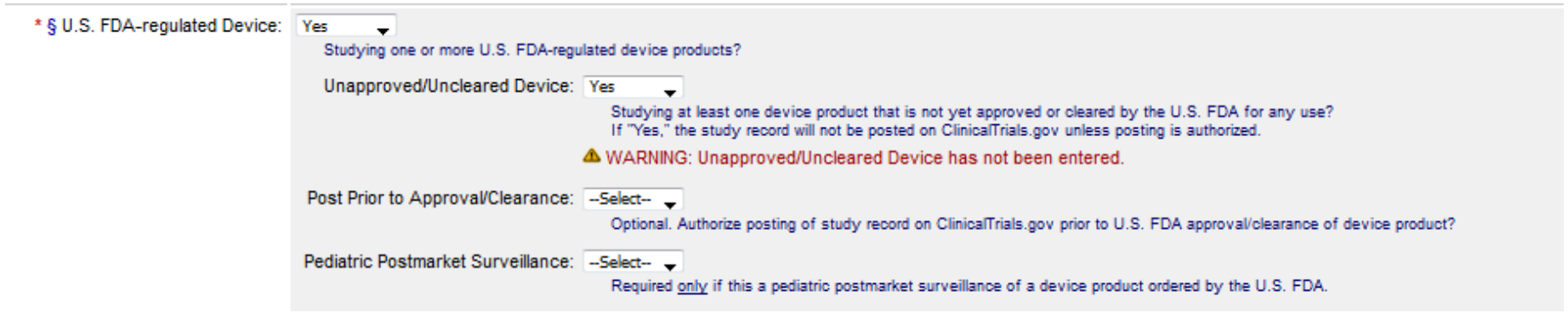
IRB Applications' Objectives and Protocols: Scientists – but NOW they will also face the public

Informed Consents: 8th grade reading level

ClinicalTrials.gov: Brief Summary: Lay public
Detailed Description: Scientists?
Results: Someone with "some college and not afraid of science"

Source: https://science.nichd.nih.gov/confluence/pages/viewpage.action?pageId=88771536

Practical Challenge for Faculty with Inventions



To protect patents, the law allows for unapproved devices' records to NOT face the public, BUT if a Responsible Party chooses to NOT have the study record posted, it will defeat the purpose of registering to protect the right to publish: See ICMJE policy FAQs: http://icmje.org/about-icmje/faqs/clinical-trials-registration/

So, according to ICMJE one must either choose not to delay posting OR register it in another acceptable registry!

Future and Ongoing Practical Challenges

- How will Protocol Uploads work for version control and for redaction?
- How will Informed Consent Uploads work?

- Attempts at “merger” with Clinical Trials Management Systems have huge financial costs
  - and risks with them – e.g. differing definitions of “completed”
  - One major company’s CTMS representatives didn’t know this spring that new regulations and questions had come out!

Institutional Challenge #1

Does academic leadership recognize the work involved?
Now they do! (hiring nationwide)

60 hours work per trial

65134 Federal Register / Vol. 81, No. 183 / Wednesday, September 21, 2016 / Rules and Regulations

Institutional Challenge #2

WHO is the Responsible Party?

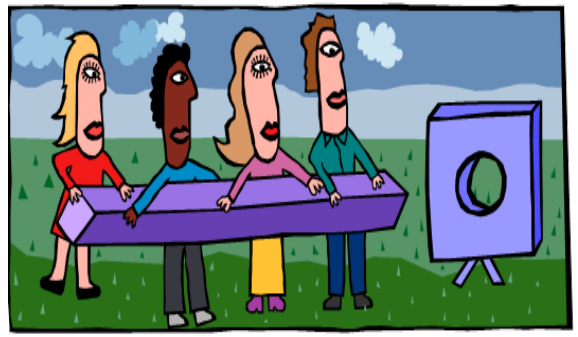
- For IND/IDE trials it MUST be the Sponsor-Investigator
- Otherwise, institution or Principal Investigator

Institution can build up expertise in ClinicalTrials.gov system, but only PI knows the trial/data issues

Finding the sweet spot is not always easy

Systemic Challenges

- Trials with unusual features, like adaptive trial design, are even harder to enter than Pharma “cookie cutter” trials.

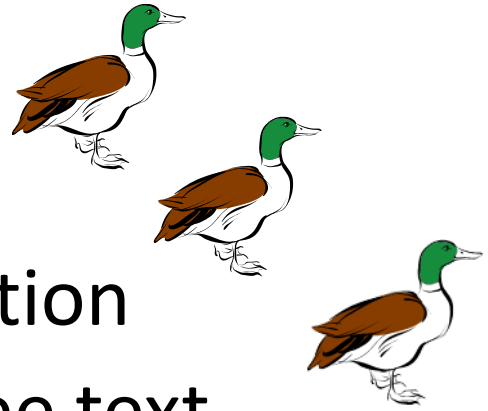


- Minimal free text; only tables
- No graphs; area under a curve is shown numerically, not graphically
- No illustrations: Brain excitation mapping? Wounds? Tumors?

Systemic Challenges

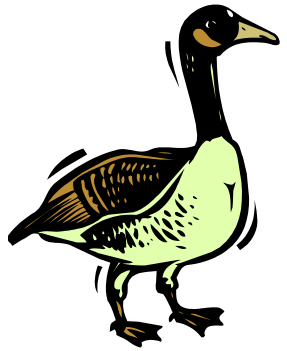
In ClinicalTrials.gov,

- Results take serious time like publication
- Results go public like publication
- Results may advance science like publication



But… Results, not having peer review or free text CANNOT

  - provide context and nuance like publication
  - share qualitative findings easily
  - assume anything about the audience



Systemic Challenges

How do we continue to incentivize researchers?

If pilot trials need to post within 1 year, will others scoop their work before they can get their larger studies approved and underway?

How do we share responsibly?

- Is 250 characters of Limitations and Caveats enough when a trial is only a small pilot, without scientific power?

We are trying…

But can we keep on talking?