Rethinking Clinical Trials™: A Living Textbook of Pragmatic Clinical Trials

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Responding to Change

- Rapidly changing clinical research landscape
  - New technologies and advent of era of “Big Data”
  - New methodologies (cluster trials; adaptive designs)
  - Large regional/national networks (and “networks of networks”)
- Imperative to build a true learning healthcare system
- Re-examination of ethical & regulatory structures surrounding research

Is there a map to help navigate this new landscape?
What Is the Living Textbook?

From the Introduction:

Our goal in creating Rethinking Clinical Trials is to provide a living document to guide the many different people with an interest in practical (or “pragmatic”) clinical trials and health systems research.
Overarching Goals

• Create flexible, updatable reference with high-quality, curated content
• Provide complete suite of information on how to understand, design, conduct, analyze & disseminate pragmatic clinical trials (PCTs)
• Build a community of engagement around PCT issues
Initial Vision

• Grew out of vision articulated in Collaboratory Coordinating Center grant application
• Early concept inspired by collaborative web references such as Wikipedia and Wikidoc
• Initial discussions centered on harnessing collaborative strengths and flexibility of wikis while ensuring valid, trusted & useful content
Refinements

• “Open” web resources such as Wikidoc leverage advantages of crowdsourcing, but require massive distributed volunteer effort to ensure reliability of information
• Living Textbook concept had to be harmonized with Collaboratory Knowledge Repository, which contains carefully curated and tagged content
Living Textbook: Structure & Organization

- Chapter-like “topics” written by Collaboratory subject matter experts in close collaboration with writers/editors at Coordinating Center
  - Drafting process is flexible, iterative
- Descriptive text designed for multiple audiences
  - Experienced clinical trialists/staff
  - Relatively new researchers/staff
  - Patient advocates
  - Patients interested in participating in research
- Scholarly citations combined with links to other web resources
Highlighting Key Information

• Particularly valuable links and references are highlighted in special pullout boxes in page margins
• Emphasis on facilitating access to high-quality resources for conducting & understanding PCTs
• Examples include:
  • Key CFR references
  • FDA guidances for industry
  • Group Health PRISM toolkit
  • IOM reports & publications
• Will include increasing number of resources and products from developed by Collaboratory & partners

Rethinking Clinical Trials
Current Major Topics

- Introduction
- Basics of Clinical Research
- Learning Health Systems
- Principles of Study Design
- Data Analysis
- Electronic Health Records
- Patient-Reported Outcomes
- Provider-Health System Interactions
- Regulatory Issues
- Research Ethics
- Stakeholder Engagement
- Dissemination of Research Findings & Lessons Learned
Informed Consent in Pragmatic Clinical Trials

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Informed consent describes a process for enabling individuals to make voluntary decisions about participating in research with an understanding of the purpose, procedures, risks, and benefits of the investigation, as well as alternatives to participating. As described below, the basis for informed consent—including the requirement to obtain consent, situations in which that requirement might be modified or waived, and the content of the information provided—is grounded both in ethical principles and government regulations.

Ethical Foundations of Informed Consent

U.S. federal regulations for the protection of human research participants are founded upon a 1979 report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Known as the Belmont Report, this landmark document defines three fundamental ethical principles for research involving human participants:

- Respect for Persons – that competent individuals should be treated as autonomous (self-determining) agents, and that persons with diminished autonomy are entitled to protection;
- Beneficence – that persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being; and
- Justice – that the benefits and burdens of research be distributed fairly.

Based on these principles, the Belmont Report identifies three key parts to informed consent:

Information
Links to persistent, high-quality resources

Data suggest that the public is generally supportive of such research; for example, in a large survey (n=4020) that explored the prospect of a national cohort study investigating genes, environment, and lifestyle, 84% of respondents supported the idea and 98% said they would participate [31]. Similar results have been found in other studies of attitudes toward the research use of specimens originally collected under a variety of circumstances [32-37].

Even so, biosampling and genomic research raise questions about when consent must be obtained and present challenges in communicating complicated information.

When is Informed Consent Required?

With limited exceptions, informed consent is required for research that involves human subjects. Federal regulations define a "human subject" as a living individual about whom an investigator obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information (45 CFR 46.102(f)). Collecting biospecimens constitutes an "intervention or interaction with the individual"; thus, consent must be obtained when biospecimens are collected for research use.

When research involves only the study of biospecimens and data that were collected for purposes other than the currently proposed project, the second component of the regulatory definition—"identifiable private information"—becomes pivotal. Samples used in genomic research are often coded, meaning that direct patient identifiers are removed and replaced with a code that is linked to identifying information through a code.

In 2008, CHESP issued a guidance stating that when coded materials were not collected for the currently proposed project and the investigators involved in the research cannot readily ascertain the identities of the individuals, the research could be determined not to involve human subjects and thus would not require informed consent. Investigators involved in the research would be unable to readily ascertain individuals' identities when, for example, the key linking the code to identifying information is destroyed before the research begins, or when the key holder is prohibited from releasing it to the investigators (such as through an agreement with the researchers, a repository's IRB-approved written policies and procedures, or other legal requirements).

Thus, much genomic research using banked specimens and data takes place without the specific consent of the individuals from whom they were obtained. In general, this approach is not consistent with studies of public attitudes and preferences, which suggest the following:

People want to be asked. People typically want to be asked whether their biospecimens can be used for research. For example, in a survey (n=751) about a proposed biobank at a major academic medical center, 67% of respondents preferred an opt-in approach over opt-out or no consent at all [38]. Similar results have been found in other studies asking about biospecimens collected for research and about biospecimens originally collected for clinical purposes [39, 40, 41].

Many accept broad consent for future research use. Beyond being asked for initial consent, people often do not want significant control over how their biospecimens are used. In the survey noted above, broad consent was preferred over categorical and study-specific consent models. Again, similar results have been found in other studies with regard to both research and clinical biospecimens [36, 37, 40-43].

Context matters. Different kinds of biospecimens can be procured for different purposes from people in different situations within different geographical, social, and historical contexts. For example, a one-time general consent may be inappropriate when the research involves a defined community that is vulnerable to group harm or stigmatization [44].

Informed Consent Disclosures

Despite the lack of a "one-size-fits-all" approach, it is safe to assume that when consent is required for biospecimen research, prospective participants want concise, understandable information—"to spend as much time as necessary, but not more, obtaining information and making a decision about taking part in research" [45].

In addition to the elements of information required by federal regulations, best practice guidelines recommend that additional elements be communicated to prospective participants in genomic and biosampling research, such as explanations of large-scale data sharing (e.g., dbGaP); the possibility of recontact (to obtain updated information, to collect a new biospecimen, or for recruitment into additional research); confidentiality, privacy, and confidentiality; and the potential for financial compensation.

Resources for Informed Consent in Genomic Research

Best practice guidelines and recommendations:

- NCI (2011): Best Practices for Biospecimen Resources (PDF)

Review articles and resources:

- NHGRI's Informed Consent for Genomics Research

Model templates and related materials:

- Beck et al. Simplified consent form for biobanking
- Cancer Human Biobank (CAHUB): Consent template and supplement
- NHGRI: Consent form examples and model language
- NCI's Cooperative Group Banks Consent template, IRB information sheet, and patient brochure
- P3G: Model consent form and information pamphlet
Federal Rules Regarding Conflict of Interest

The first half of the regulations regarding COI in research funded by the U.S. Public Health Service was issued in 1999. These regulations were comprehensively rewritten and released in 2011 as 42 CPR Part 50, Subpart F, with a parallel set of rules for contractors (42 CPR Part 94). Together, these regulations provide clear rules regarding declarations of COI and place responsibility on institutions for identifying and managing conflicts of interest. However, they offer relatively little guidance on how an institution should actually manage cases of COI. The rules do not address the issue of institutional COI, which occurs when the institution where the research is conducted (such as a university or hospital) or the senior officials supervising the research have a financial stake in the outcome. The regulations also exempt the payment of royalties processed through an institution from federal rules governing COI, although the potential for increased royalties may in fact create an enormous incentive for bias.

There are two key definitions in 42 CPR 50 Subpart F that guide how institutions manage COI. The first is the definition of Significant Financial Interest; the second is the definition of a Financial Conflict of Interest.

A few points regarding these regulations should be emphasized:

- The list of what counts as a "significant financial interest" is comprehensive, with the minimal level for "significant" set at $5,000 per year (although some institutions require reporting of any payments at all, regardless of amount).
- Spouses and dependent children are included in the determinations of whether a significant financial interest is present.
- "Institutional responsibilities" on the part of individuals are comprehensive and include research, teaching, clinical work, and administrative tasks. Anyone with outside financial interests that overlap with their institutional responsibilities must be evaluated.
- Section 2 of the regulations requires that most sponsored travel be reported, and includes required reporting of sponsored travel for spouses and dependent children.
- Section 3 defines types of financial interests that are exempt, such as royalties paid through the institution.

42 CFR 50 Subpart F applies to all faculty and staff who receive funding from the Public Health Service, which includes the National Institutes for Health (NIH), the Centers for Disease Control and Prevention (CDC), the Agency for Healthcare Research and Quality (AHRQ), and the Biomedical Advanced Research and Development Authority (BARDA).

The definition for COI used in 42 CFR 50 Subpart F entails two institutional responsibilities. First, the institution should evaluate whether the individual has both a significant financial interest and a role in the research that could affect the design, conduct, or reporting of research. If those two conditions are both fulfilled, the next step is to evaluate whether the financial interest could "directly and significantly" affect the research. Institutions vary substantially as to what they consider direct and significant, and the regulations provide very little guidance beyond the definition.

Managing Personal Conflict of Interest in Translational Research

Management of COI is an imperfect art and is typically inconsistent across institutions. Federal regulations define issues likely to affect research, but are much less likely to suggest means for managing conflicts. The most common COI management strategy requires public disclosure of outside interests, usually in publications, presentations, grant applications, and informed consent documents. Disclosure is, however, a mixed blessing, because many people take industry relationships to be an endorsement as well as a potential source of bias. In addition, COI is often presented in ways—such as simply listing outside interests without disclosing the actual amounts—that translate into an important and complex issue.

Some institutions restrict the role a conflicted individual can play in the conduct of research. Typical restrictions include limitations on serving as a principal investigator (PI) [2], restrictions on obtaining informed consent, a requirement for external oversight, or limitations on study authorship and/or participation in data analysis. However, the dollar amount thresholds that trigger different types of management vary across institutions, providing little basis for identifying "standard" amounts.

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Federal Regulations Governing Conflicts of Interest in Research

- 42 CFR Part 50, Subpart F (PDF)
- 42 CFR Part 94

Guidance for Identifying & Managing COI

- Financial Conflict of Interest (PPT - 12.2 MB)
- Responsible Conduct Research: Conflicts of Interest
- AHRQ COI Initiatives
- NIH COI tutorial (PDF)
- FDA Guidance: Clinical Trial Data Monitoring
Secure dedicated discussion forum for Collaboratory members
Rapid Response

- During drafting of Informed Consent topic, SUPPORT study controversy became news
- We were able to include and update section on the fly
- Now includes discussion of and active links to viewpoints published in NEJM as well as video and transcripts from August 2013 OHRP hearings
Guiding Principles

• Emphasis on not reinventing the wheel
  • Wherever high-quality resources exist, we try to raise visibility and “boost signal” for users
• Close integration with curated and tagged resources available through Knowledge Repository is key to long-term usefulness
Governance Model

Collaboratory Website Content Governance

Note: Arrows represent operational communication between groups
* Facilitators will help resolve any issues by directing them through appropriate channels

A. Tasneem, 2013
Soft Rollout

• The Living Textbook was made publicly available in a “soft rollout” on November 1, 2013. Initial topics included:
  • Introduction
  • Informed Consent in PCTs
  • Conflicts of Interest in Translational Research
• Multiple additional topics in development:
  • Patient-Reported Outcomes (early January)
  • Learning Healthcare Systems (preliminary article; January)
  • Regulatory Issues (preliminary article; late January)
  • Phenotypes (February [tentative])
Usability Challenges

• Limited ability to customize appearance
• Current platform (SharePoint) good for security and version control, but less flexible for publishing
• Consistency issues across browsers
• Not optimized for mobile technologies
• Need more appealing interface for broadest range of users
Changing Platforms

• Planning move to more user-friendly & flexible platform
  • Will retain content-control attributes & integration with Knowledge Repository
• Exploring alternatives that allow more dynamic content presentation and integration with mobile technology
  • Enabling customized views of Living Textbook
Picking up the Pace

• Accelerate engagement with subject matter experts & obtain commitments for producing content
• Expand bandwidth at Coordinating Center as more contributors engage & volume of Collaboratory products increases
• Surge of interest and need anticipated as Patient-Centered Outcomes Research Institute (PCORI) fosters widespread interest and engagement with pragmatic clinical research
New Synergies

• PCORI’s national patient-centered clinical research network (PCORnet) comes online in December
• PCORnet’s “network of networks” will comprise a vastly expanded audience of potential Living Textbook readers and contributors
• As PCORnet projects get underway and begin to report results, we expect tremendous and rapid growth in knowledge and tools related to patient-centered research and comparative effectiveness studies
  • Living Textbook can contribute to visibility and accessibility of these resources for patients, providers, and public
Accelerating Output

- New topics currently in various stages and slated for rolling release in late 2013/early 2014
- Additional writing and editorial support:
  - Contract writer Karen Staman, MS, joined Living Textbook effort in Q4 2013 for 0.5 FTE
  - Two additional FTEs joining Collaboratory writing team in Q1 2014
- Additional design support
Scaling Up

• Developing mid- and long-range plans for faster, higher-volume content creation
  • Use of preliminary article “stubs” to facilitate access to resources
• Developing plans for ensuring rolling content curation, updating & revision as needed
• Coordination with other complementary groups
  • Clinical Trials Transformation Institute (CTTI)
  • Patient-Centered Outcomes Research Institute (PCORI)
What Does Success Look Like?

• A successful, mature Living Textbook, in our vision, is one that:
  • Includes dynamic, trustworthy content
  • Can be customized for multiple audiences and platforms
  • Keeps pace with changes in the clinical research landscape
  • Serves as a hub for bidirectional learning
    • Multiple communities (research, clinical care, patients, public) can learn about and participate in the learning healthcare system
Unique Opportunities

• Textbooks and even e-books are nothing new
• Living Textbook and Knowledge Repository provide a nexus at intersection of significant networked knowledge and expertise
• Go beyond a “look-up” reference resource:
  • Jump to other books/web-based resources
  • Locate experts/potential collaborators in a field
  • Learn about ongoing trials
  • Access to portals for participation
Engaging Across the Collaboratory and Beyond

• We need you!
  • Volunteers to help create & expand content
  • Feedback & discussion around topics
  • Channels for both public engagement and Collaboratory member access