



NIH Collaboratory

Health Care Systems Research Collaboratory

Health Care Systems Research Collaboratory:

Synchronizing Operations, Ethics and Regulatory

Oversight or Reducing Death and Disability Caused

by Knowledge Deficits (Ignorance)

A Virtual Home for Knowledge about Pragmatic Clinical Trials
using Health Systems: nihcollaboratory.org

Rethinking Clinical Trials



Why be Obsessed with Ethics and Regulatory Issues?

- We only know a small fraction of what we need to know to provide clinical care and to inform health decisions with high quality evidence
- The Collaboratory is demonstrating that the technical and cultural issues can be surmounted
- The PCORI NCRN is a once in a lifetime investment that could increase reliable evidence by a log order or more
- The major limiting factor is the cumbersome approach to regulations and protection of research participants (in my opinion)
- **Therefore, it is critical for us to find a way to respect the needs of research participants in a way that stimulates the efficient development of life saving and disability sparing evidence**



Personal Perspective (Bias)

- I am a clinician investigator who believes that many people are hurt every day by well-intentioned decisions based on inadequate evidence
- My hope is that we can improve participant involvement in learning activities while dramatically increasing efficiency, reducing cost and thereby reducing death and disability because of better evidence developed in a learning health system
- Many of these questions are not unique to CRTs, but CRTs add a special dimension to the considerations in most cases
- **I am neither an ethicist or a regulator—and these naïve questions have been vetted by neither ethicists nor regulators!**

Which Treatment is Best for Whom? High-Quality Evidence is Scarce < 15% of guideline recommendations supported by high quality evidence



 ORIGINAL CONTRIBUTION

Scientific Evidence Underlying the ACC/AHA Clinical Practice Guidelines

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CLINICAL PRACTICE GUIDELINES are systematically developed statements to assist practitioners with decisions about appropriate health care for spe-

Context The joint cardiovascular practice guidelines of the American College of Cardiology (ACC) and the American Heart Association (AHA) have become important documents for guiding cardiology practice and establishing benchmarks for quality of care.

Objective To describe the evolution of recommendations in ACC/AHA cardiovascular guidelines and the distribution of recommendations across classes of recommendations and levels of evidence.

Data Sources and Study Selection Data from all ACC/AHA practice guidelines issued from 1984 to September 2008 were abstracted by personnel in the ACC Science and Quality Division. Fifty-three guidelines on 22 topics, including a total of 7196 recommendations, were abstracted.

Tricoci P et al. JAMA 2009;301:831-41



CRT Regulatory and Ethics Meeting

- CRTs increasingly used
- Since CRTs randomize groups instead of individuals (iRCTs) fundamental differences may exist in
 - Design
 - Ethical considerations
 - Regulatory oversight
- Many issues that are unresolved in individual RCTs are also critical to efficient conduct of CRTs
- Excellent starting point from the “Ottawa Statement”



The Ottawa Statement on CRTs

- Canadian Institutes of Health Research funded project since 2007
- Three components
 - In-depth ethical analyses
 - Review of literature
 - Surveys of trialists and ethics review committee chairs
- Series of articles
 - Overview of ethics issues; who is the subject?; informed consent;
 - Clinical equipoise; benefits and harm assessment; gatekeepers; vulnerable populations
- Web site

Table 1. Summary of recommendations.

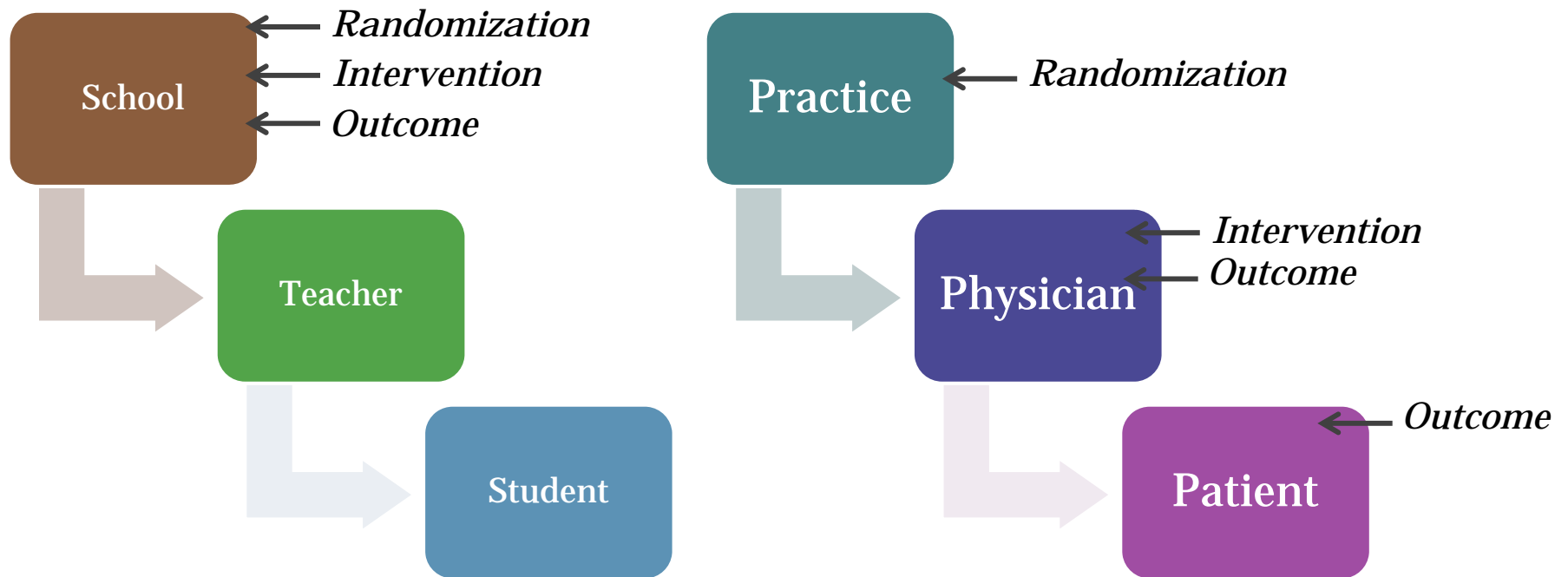
Ethical Issue	Recommendation Number	Recommendation
Justifying the cluster randomized design	1	Researchers should provide a clear rationale for the use of the cluster randomized design and adopt statistical methods appropriate for this design.
REC review	2	Researchers must submit a CRT involving human research participants for approval by a REC before commencing.
Identifying research participants	3	Researchers should clearly identify the research participants in CRTs. A research participant can be identified as an individual whose interests may be affected as a result of study interventions or data collection procedures, that is, an individual (1) who is the intended recipient of an experimental (or control) intervention; or (2) who is the direct target of an experimental (or control) manipulation of his/her environment; or (3) with whom an investigator interacts for the purpose of collecting data about that individual; or (4) about whom an investigator obtains identifiable private information for the purpose of collecting data about that individual. Unless one or more of these criteria is met, an individual is not a research participant.
Obtaining informed consent	4	Researchers must obtain informed consent from human research participants in a CRT, unless a waiver of consent is granted by a REC under specific circumstances.
	5	When participants' informed consent is required, but recruitment of participants is not possible before randomization of clusters, researchers must seek participants' consent for trial enrollment as soon as possible after cluster randomization—that is, as soon as the potential participant has been identified, but before the participant has undergone any study interventions or data collection procedures.
	6	A REC may approve a waiver or alteration of consent requirements when (1) the research is not feasible without a waiver or alteration of consent, and (2) the study interventions and data collection procedures pose no more than minimal risk.
	7	Researchers must obtain informed consent from professionals or other service providers who are research participants unless conditions for a waiver or alteration of consent are met.
Gatekeepers	8	Gatekeepers should not provide proxy consent on behalf of individuals in their cluster.
	9	When a CRT may substantially affect cluster or organizational interests, and a gatekeeper possesses the legitimate authority to make decisions on the cluster or organization's behalf, the researcher should obtain the gatekeeper's permission to enroll the cluster or organization in the trial. Such permission does not replace the need for the informed consent of research participants.
	10	When CRT interventions may substantially affect cluster interests, researchers should seek to protect cluster interests through cluster consultation to inform study design, conduct, and reporting. Where relevant, gatekeepers can often facilitate such a consultation.
Assessing benefits and harms	11	The researcher must ensure that the study intervention is adequately justified. The benefits and harms of the study intervention must be consistent with competent practice in the field of study relevant to the CRT.
	12	Researchers must adequately justify the choice of the control condition. When the control arm is usual practice or no treatment, individuals in the control arm must not be deprived of effective care or programs to which they would have access, were there no trial.
	13	Researchers must ensure that data collection procedures are adequately justified. The risks of data collection procedures must (1) be minimized consistent with sound design and (2) stand in reasonable relation to the knowledge to be gained.
Protecting vulnerable participants	14	Clusters may contain vulnerable participants. In these circumstances, researchers and RECs must consider whether additional protections are needed.
	15	When individual informed consent is required and there are individuals who may be less able to choose participation freely because of their position in a cluster or organizational hierarchy, RECs should pay special attention to recruitment, privacy, and consent procedures for those participants.

doi:10.1371/journal.pmed.1001346.t001

Weijer C, Grimshaw JM, Eccles MP, McRae AD, et al. (2012) The Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials. *PLoS Med* 9(11): e1001346. doi:10.1371/journal.pmed.1001346

<http://www.plosmedicine.org/article/info:doi/10.1371/journal.pmed.1001346>

Cluster-Randomized Trials





Minimal Risk Issues

- Minimal risk is a critical criterion for determination that consent can be waived or altered
- What are the relevant considerations in determining minimal risk in a CRT?
 - Should minimal risk be judged relative to healthy people or people with the disease/problem under study?
 - Is the critical issue incremental risk due to the study itself or total risk of study and non-study interventions?
 - Does randomization itself cause more than minimal risk?
Protocolization of study treatment?
 - In a cluster, is minimal risk determination an assessment of the average or does the study need to be minimal risk for every person in it?



Quality Improvement, Research and the Border Conditions

- In a learning health system, CRTs are often used to assess health services
- How can we deal with the border condition between quality improvement from research?
 - Can an algorithm be developed?
 - What is the appropriate governance model when a project is both research and quality improvement?
 - Is it reasonable to make this distinction in the future?
- What systems of governance and accountability can
 - Reduce “IRB avoidance” by using inferior methods in QI to avoid being labeled as “research”?
 - Encourage creation of generalizable knowledge from high quality QI



FDA Regulated Products

- When a trial falls under the purview of FDA there is not an option to waive or alter consent
- Are there different ethical considerations for CRTs evaluating a newly approved medicine or device versus a mature marketed product?
- Is there a need to consider a revision or reinterpretation of FDA regulations about informed consent to enable waiver or modification of consent for CRTs of products already in use?
 - Should the Common Rule differences with FDA regulations be resolved?
 - Could “clinical investigation” be re-interpreted for drug trials?



Indirect Participants

- CRTs may involve indirect participants (when the doctor is the target of intervention) or “collateral participants” (as in visitors to a hospital using different infection prevention strategies)
- Is it reasonable to define a research participant as “an individual whose interests may be affected”?
 - Is there a reason to deviate from the common rule?
 - Should “rights and welfare” also be considered?
- Should a distinction be made between testing of an educational or system intervention versus evaluation of product (drug or device)?
 - Different guidances from Ottawa statement and SACHRP



Vulnerable Populations

- When randomization occurs at the cluster level, vulnerable populations may be embedded in the population
- Are there special regulatory considerations needed for CRTs in which vulnerable populations are within the cluster?
 - Subpart B (Pregnant Women and Fetuses)
 - Subpart C (Prisoners)
 - Subpart D (Children)
- What practical approaches can be taken to deal with embedded vulnerable populations?



Dealing with Disparate Cultural Values

- In individual RCTs presumably an individual with different cultural values can decide to not participate if cultural values dictate such a decision. In CRTs, this may not be possible.
- How should we Incorporate local cultural values into approval and oversight functions when CRTs involve multiple and/or distant sites?



Risk-Benefit and Equipoise

- In iRCTs the IRB considers overall benefit risk and consent deals with the equation for individuals.
- How should an IRB determine risk-benefit in a CRT?
 - For direct participants (patients and/or providers)
 - For indirect participants
 - Considering risk benefit for individuals versus clusters
- How should an IRB or DMC apply equipoise in considering initial approval and monitoring of a trials
- When are Data Monitoring Committees needed in CRTs?



Gatekeepers

- In cluster RCTs, individual consent is often difficult or must occur after randomization. What is the role and authority of gatekeepers?
 - Can a gatekeeper ever serve as a proxy for consent?
 - How should possible conflict of interest/conflict of obligation of gatekeepers be considered?
 - Are health system administrators/leaders free of conflict when they serve as gatekeepers?
 - PCORI NCRN will give a new opportunity to assess whether priorities of patients and health systems for research priorities are positively related



The Research/Practice Divide

- In iRCTs the individual researcher approaches the individual participant for consent. That person's health care provider ("doctor") weighs in on the appropriateness of the individual's participation. In CRT's this is possible in some cases, but difficult or impossible in others.
- A fiduciary duty is a legal duty to act solely in another party's interest
- What role does the fiduciary relationship between the provider and the patient play?
 - Is the "fiduciary relationship" a useful construct?
 - If it is a useful construct should consent be required when it is impacted?
 - Therapeutic misconception refers to an inaccurate belief that an experimental therapy has a benefit; is belief in "usual care" a therapeutic misconception?



Alternative Approaches to Consent

- What is adequate information when consent cannot be obtained?
 - Passive notification
 - Routine disclosure
 - Post-randomization consent
 - Consent in the interventional arm only



Privacy Issues

- In many CRTs EMR's are harvested to measure key outcomes. Even with notification many patients are unlikely to conceptualize how their records are being used.
- Should there be any differences in privacy rules when CRT participants are enrolled with notification or modified consent?



Dealing with Autonomy of Individuals

- Choosing not to participate is a time-honored value in iRCTs, but may be difficult or seem impossible in CRTs
- What should be expected in CRTs to allow/enable individual participants to opt-out of CRTs?



Central IRB?

- Local IRBs may lack expertise in dealing with CRT issues.
- How do we deal with educating local IRBs about CRTs when there may not be local expertise?
- Should authority and oversight for CRTs be given to a central IRB with local IRB input (ex IRBshare)?



Study Design

- Some have expressed concerns that investigators may choose a CRT to avoid usual consent.
- Do different ethical and regulatory issues arise as a function of design?
 - Cluster-cluster
 - Professional-cluster
 - Individual-cluster



Summary

- For CRTs and iRCTs the system is inefficient and the financial costs are high
- More importantly, patients are suffering and bad health decisions are being made because of inefficiency in an era where data are abundant, but our human systems lead to ignorance instead of knowledge