NIA IMPACT COLLABORATORY
TRANSFORMING DEMENTIA CARE

Grand Rounds

ePCTs and Health System Obligations

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Housekeeping

- All participants will be muted upon entry
- Enter **all questions** in the Zoom **Q&A/chat box** and send to Everyone
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IMPACT Grand Rounds
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Central Argument:

Partnerships with health care institutions are not only important for ensuring the successful conduct of embedded pragmatic clinical trials (ePCTs), they also create moral obligations for those institutions.

Example ePCTs

Preoxygenation Strategies to Prevent Hypoxemia During Tracheal Intubation	Individually randomized study conducted at 24 EDs and ICUs of critically ill adults undergoing tracheal intubation comparing: • Noninvasive ventilation • Oxygen mask Outcome: hypoxemia during intubation

Example ePCTs

Comparing Recombinant to Standard-Dose Influenza Vaccines in Adults Under 65	Cluster-randomized study comparing two influenza vaccines delivered to participants 18-64 as part of routine clinical care w/in a large health system: • high-dose recombinant influenza vaccine • standard-dose influenza vaccine Outcome: PCR-confirmed influenza

Example ePCTs

Comparing Two Nighttime Staffing Strategies in a Tertiary Care Intensive Care Unit	Cluster-randomized study comparing two methods of nighttime staffing: • in-hospital intensivists *and* medical residents, or • in-hospital medical residents only. Outcomes: ICU length of stay, in-hospital mortality, rates of ICU admission

Example ePCTs—Shared Characteristics

- Compare current clinical practices (not new therapies)
- Embedded into “real world” health care settings
- Use extant clinical/operational data

Why a Framework for Institutions?

Three Overlapping Justifications

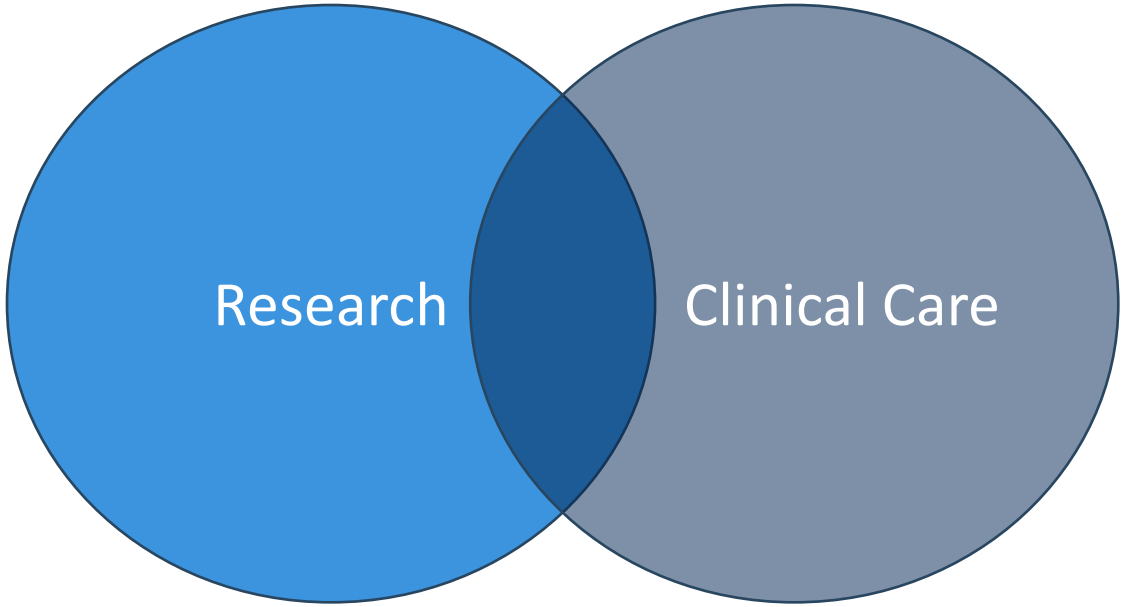
1. Institutional role as gatekeepers for ePCTs.
2. Insufficiency of prior bioethical accounts to address ethical issues arising in ePCTs.
3. Prior empirical scholarship on ePCTs.

1: Gatekeeper Role

- Institutions shape investigators' access to critical resources needed to conduct ePCTs.
- Granting of access brings with it corresponding duties.
- Institutions are important parties when assessing what we owe to each other in the conduct of ePCTs.

2: Insufficiency of Dyadic Accounts of Moral Responsibility for ePCTs

Traditional bioethics accounts of dyadic (physician-patient and investigator-subject) relationships are ill-equipped to address many issues arising in ePCTs.



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Think Pragmatically: Investigators' Obligations to Patient-Subjects When Research is Embedded in Care

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ABSTRACT

Growing interest in embedded research approaches—where research is incorporated into clinical care—has spurred numerous studies to generate knowledge relevant to the real-world needs of patients and other stakeholders. However, it also has presented ethical challenges. An emerging challenge is how to understand the nature and extent of investigators' obligations to patient-subjects. Prior scholarship on investigator duties has generally been grounded upon the premise that research and clinical care are distinct activities, bearing distinct duties. Yet this premise—and its corresponding implications—are challenged when research and clinical care are deliberately integrated. After presenting three case studies from recent pragmatic clinical trials, we identify six differences between explanatory trials and embedded research that limit the application of existing scholarship for ascertaining investigator duties. We suggest that these limitations indicate a need to account for the implications of usual care and to move beyond a narrow focus on the investigator-subject dyad, one that better reflects the team- and institution-based nature of contemporary health systems.

KEYWORDS

Research ethics; professional ethics; health services research; human subjects research

3: Key theme of empirical work: institutions matter (morally)!

- Defining minimal risk
- Data sharing
- Management of collateral findings
- Sharing aggregate results
- Post-trial responsibilities
- Transparency/notification
- Equity & (under)representation

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

"*A key finding in our work is the* ***central role for institutions*** *in PCT-CF management*."

"…our data highlight the ***key role of the healthcare institutions*** *in PCT data sharing."*

"..who bears the duty to fulfill post-trial responsibilities in PCTs?…healthcare delivery systems have generally not been a focus of post-trial responsibilities. Yet, ***these systems are integral to the conduct of PCTs—and therefore play a central role in what happens when trials end****."*

*"Existing literature on sharing aggregate research results largely emphasizes the role of researchers, and, to a more limited extent, funders, insofar as they can support the associated costs. Yet…**the healthcare institutions in which PCTs are embedded are key stakeholders for PCTs**, and, correspondingly, should be directly involved in their conduct, including in decisions about whether and how to return aggregate results."*

Forthcoming Manuscript

Morain SR, Semler M, Casey J. A Framework of Institutional Obligations for Pragmatic Clinical Trials. *AJOB*. 2026.

Call for Open Peer Commentary: August*

Foundational Assumption:

Embedded PCTs are a morally good activity in which health care institutions should participate.

(And institutions therefore shouldn't avoid the following obligations by refusing to participate in ePCTs)

A Framework of Health System Obligations: Some (More) Preliminaries

1. Intended as moral guidelines – not absolute rules
2. Correspond (roughly) with the lifecycle of a research project
3. Obligations will often be held jointly with other stakeholders
4. May presuppose resources/systems/processes that do not yet exist in many health care institutions
5. Strength/scope of obligations may vary based upon specific features of a given PCT

Ten Obligations of Health Systems in PCTs

1. Assess and prioritize PCTs in comparison to other institutional priorities
2. Facilitate and support the identification & engagement of relevant research partners
3. Ensure treatments under evaluation are consistent with usual care practices within the institution or otherwise reflect high-quality clinical practice
4. Promote fair distribution of the benefits and burdens of embedded research
5. Collaborate in the identification of & planning for potential collateral findings and related signals of potential risk

Ten Obligations of Health Systems in PCTs

6. Minimize imposition of additional burdens on patients, clinicians, & broader health system operations
7. Ensure appropriate data protections for patient & employee data
8. Promote appropriate transparency about PCTs underway within the institution
9. Disseminate research findings within the institution
10. Implement, sustain, expand, or de-implement the evaluated interventions based on the findings of the PCT

1. Assess and prioritize PCTs in comparison to other institutional priorities

3. Ensure treatments under evaluation are consistent with usual care practices within the institution or otherwise reflect high-quality clinical practice

6. Minimize imposition of additional burdens on patients, clinicians, & broader health system operations

8. Promote appropriate transparency about PCTs underway within the institution

1: Assess & Prioritize PCTs

General Ethical Justifications:

- Research should have social value
- Ethical research requires the responsible use of scarce resources
- Studies that enroll patient-subjects but fail to complete expose individuals to unjustified risks & burdens

1: Assess & Prioritize PCTs

PCT Considerations

- ePCTs often present additional burdens on clinical & operational systems
- May require institution to forgo/delay QI activities or other practice changes
- Goal of ePCTs is to accelerate adoption of evidence into practice

- Traditional processes for institutional sign-off often insufficient to assess broader set of institutional-level resources required for conduct of ePCT AND downstream implications for (de)implementation.

1: Assess & Prioritize PCTs

2 Levels:

1. Impact of research on ongoing clinical/operational activities
2. Whether/how research outcomes should be incorporated into future clinical & operational systems

Framework for Prioritization

1. Should the study be conducted?	• Clinical or operational importance of the targeted disease • Ripeness or timeliness of the research question • Impact on health equity
2. Can the institution do the study?	• Operational feasibility • Resource burden of the trial
3. Is the institution prepared to act on the results?	• Institutional commitment to the appropriate dissemination & implementation • Resource impact of acting on trial results

Morain, Semler, Casey. A Framework for Health Systems to Assess & Prioritize Participation in Pragmatic Clinical Trials. *Learning Health Systems* 2025.

3: Ensure Evaluated Treatments are Consistent with Usual Care Within the Institution or Otherwise Reflect High-Quality Clinical Practice

<u>Ethical Considerations:</u>

- Selection of appropriate comparator arms implicate trial's risk-benefit ratio, scientific validity, & social value
- Participation in ePCTs may result in substantial changes to the care patients would otherwise receive

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Oxygen-Saturation Targets in Extremely Preterm Infants

Published May 16, 2013 | N Engl J Med 2013;368:1949-1950 | DOI: 10.1056/NEJMc1304827 | VOL. 368 NO. 20

In Support of SUPPORT — A View from the NIH

Kathy L. Hudson, Ph.D., Alan E. Guttmacher, M.D., and Francis S. Collins, M.D., Ph.D.

Each year in the United States, nearly 500,000 infants — 1 in every 8 — are born prematurely, before 37 weeks of gestation. Despite substantial advances in their care, premature infants face a daunting array of challenges; they are at high risk for death in infancy and face severe and lifelong health problems if they survive.[1] The National Institutes of Health (NIH) has a legal and moral responsibility to do research in partnership with scientists and families to optimize the care of these highly vulnerable infants. In recent weeks, a major public debate has arisen regarding a

CORRESPONDENCE

The OHRP and SUPPORT

Published June 20, 2013 | N Engl J Med 2013;368: e36 | DOI: 10.1056/NEJMc1307008 | VOL. 368 NO. 25

Even if we assume a trial is ethically appropriate to conduct, it may not be ethically appropriate to conduct at a given site.

- Comparison of surgical procedures
- Trial of antibiotic in setting in which rate of antimicrobial resistance to that antibiotic is high

Assessing the Appropriateness of Local Participation:

1. Clinical Training & Institutional Capacity
   - Do clinicians have (or could easily acquire) appropriate training?
   - Does appropriate infrastructure exist to support the intervention?

2. Appropriateness for a Given Patient Population
   - Are there patient characteristics that may influence the clinical or cultural appropriateness of a given intervention within the institution/site?

6: Minimize Imposition of Additional Burdens on Patients, Clinicians, & Health System Operations

Ethical Considerations:

- While ePCTs are generally designed to be less disruptive than explanatory trials, they can still interrupt the flow of clinical practice
- Minimizing impact of PCTs on patient care is respectful of patients & clinicians
- Ideally, ePCTs can *promote* clinician well-being, enabling to contribute to efforts that improve care quality & patient outcomes

6: Minimize Imposition of Additional Burdens on Patients, Clinicians, & Health System Operations

In collaboration with investigators…

- Calibrate data needs to minimize burdening members of the care team
- Identify – and mitigate – impacts of the research intervention on clinical workflows

8: Promote Appropriate Transparency about PCTs Underway within the Institution

Ethical Considerations:

- Transparency demonstrates respect for individuals, recognizing as persons who should be offered genuine explanations about practices that affect them, rather than merely as means to an end

- When transparency not provided via (research) informed consent, alternative mechanisms may be needed

Institutional Role in Transparency about PCTs:

1. Institutional role as gatekeeper
   - Transparency can promote trustworthiness that institution is acting appropriately

2. Institutions control many notification mechanisms

3. Transparency-promoting mechanisms often require involvement of & coordination with clinical & operational staff

Example: Study Information Sheets

TiME

Information about the TiME Trial

- This dialysis facility is participating in a national research study called the TiME Trial, sponsored by the National Institutes of Health (NIH). This facility is participating in this clinical trial along with many other dialysis units throughout the country.
- The purpose of this research is to compare how patients feel, how often they are hospitalized, and how long they live based on the length of their dialysis sessions.
- Because this facility is participating in the TiME Trial, the standard approach at this facility is to prescribe a dialysis session length of at least 4 hours and 15 minutes for new patients starting hemodialysis treatment. Your nephrologist will consider the appropriateness of this treatment time for you, taking into account your individual health characteristics. If your nephrologist feels that this treatment time is not appropriate for you, he/she will prescribe a different session time. As always, you should talk with your doctor about treatment options.
- Your dialysis facility will send information about your dialysis treatments and results of laboratory tests that are done as part of your routine dialysis care to the TiME Trial study team at the University of Pennsylvania and to the NIH. ***There will be no extra tests done for the TiME Trial.*** Even if your treatment times are shorter than 4 hours and 15 minutes your treatment data and lab results will provide information that is important for this research. To protect your confidentiality, the information sent to the University of Pennsylvania and NIH will be identified by a scrambled code number. The research team will not be able to identify you from this code. ***Your confidential information (such as name, address, or date of birth) will not be distributed.***
- Thank you for reading this information about the TiME Trial. On the other side of this paper are answers to frequently asked questions that might be helpful to you. If you would like more information about the TiME Trial or if you do not want your anonymous data reported to the study team, please call this **toll-free telephone number** and a representative from DaVita will call you back to answer your questions: [redacted].

Frequently Asked Questions About Research and About the TiME Trial

What is a clinical trial?
A clinical trial is a research study in which treatments are evaluated to determine what is best for patients. In order to best compare treatments, clinical trials often involve assignment of patients or treatment centers to a specific treatment approach. Clinical trials help doctors answer a variety of questions about diseases and their treatments.

Why is this clinical trial being conducted?
This trial is being done to determine if longer dialysis sessions are better for patients in terms of how patients feel, how often they are hospitalized, and how long they live.

Why am I being included in this clinical trial?
You are being included in this trial because your dialysis unit has agreed to participate. Like all other patients in this facility who are new to dialysis, you will be included in this trial unless you choose not to participate.

How will this clinical trial affect my care?
Because of this trial, the standard dialysis time for new patients at this facility is at least 4 hours and 15 minutes. This means that that your treatment time might be longer than it otherwise would have been. However, your nephrologist will decide whether you should receive the research-assigned treatment time or a different treatment time for your dialysis sessions.

What if I object to having a dialysis session of at least 4 hours and 15 minutes?
As always, you should discuss your care and treatment options with your doctor and let your doctor know if you have concerns.

How long will my participation in this clinical trial last?
Your participation will be for approximately 2-3 years.

What if I move and have dialysis treatments in a unit that is not part of the clinical trial?
If you move to another DaVita unit, information about your dialysis treatments and results of lab tests that are done as part of your medical care will continue to be included as trial data even if the dialysis unit is not part of the trial. Your dialysis session length will be prescribed by your nephrologist in the new unit and may stay the same or may change. You should call the toll-free telephone number shown below if you do not want your information included as trial data after you move to a new facility.

Are there risks related to this clinical trial?
Dialysis sessions of 4 hours and 15 minutes are used routinely in dialysis and do not have risks compared with shorter dialysis treatments as far as we know. There is a very low risk that your dialysis treatment information could be seen by people other than the researchers. The confidentiality of your data is very important to us and we will make every effort to keep all information collected in this trial strictly confidential.

- Transparency is ethically valuable, but may be outweighed by other considerations (e.g., scientific validity)

- Institutions have an obligation to—in collaboration with investigators—proactively assess whether (and if so, how & when) to share information about ePCTs

CLINICAL TRIALS

Clinical Trials
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DOI: 10.1177/17407745251377730
journals.sagepub.com/home/ctj
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Patient notification about pragmatic clinical trials conducted with a waiver of consent: A qualitative study

Stephanie R Morain[1,2], Abigail Brickler[3], Matthew W Semler[4,5] and Jonathan D Casey[4,5]

Summing Up…

- Health care institutions are not "just" critical partners to the successful conduct of ePCTs, they are also critical for ethical conduct
- Prospective consideration of the moral obligations of health care institutions can promote better decision-making
- Fulfilling obligations will generally require partnership with other stakeholders

Appendix

Features of PCTs Limit Application of Existing Scholarship for Ascertaining Investigator Duties

1. Embedded research often conducted with a waiver of consent
2. Embedded research may not involve direct communication between patient-subjects & investigators
3. Addressing individual-level findings in embedded research entails costs for institutions the research enterprise
4. Embedded research occurs in real-world settings, where gaps in care are common
5. Individual-level findings in embedded research may have implications for the well-being of non-subjects
6. Clarity on how to address individual-level findings in embedded research is often lacking

Research-Care Integration: The Challenge

Recall:
A key feature of PCTs is integrating research into everyday clinical care

Yet:
Traditional ethics oversight is predicated on the view that research & care are distinct activities

Research ≠ practice

“Medical care is characterized by a convergence of the doctor’s interests and the patient’s interests. The patient desires to regain or maintain health; the physician is dedicated to providing the medical help that the patient needs.

"By contrast, in clinical trials, the principal interests of the investigator and the participating patient may diverge. Patient-subjects typically seek therapeutic benefit from research participation…Investigators are primarily interested in answering scientific questions about groups of patients…"

--Miller & Rosenstein, NEJM

- Informed Consent
- Voluntary Participation
- Balance of benefits/burdens
- Reasonable risk-benefit ratio

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Questions?

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