Ethical & Regulatory Considerations and Posttrial Obligations

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Learning goals

- Learn about recurring and emerging ethical and regulatory issues in ePCTs
- Understand posttrial obligations related to dissemination, sustainment, and deimplementation
- Discuss ethical considerations for sharing aggregate results

Important things to know

Ethical analysis for ePCTs is (still) a work in progress

Federal and local policies and their operationalization regarding oversight of ePCTs are in flux

There is often confusion and misunderstanding about ePCTs on the part of patient-subjects, providers, IRBs, and DSMBs

ePCTs are motivated by ethical imperatives

They also raise interesting ethical and regulatory questions

Evolving understanding of ethical and regulatory issues

- Informed consent
- Data monitoring
- Defining minimal risk
- Distinction between research and quality improvement
- Vulnerable subjects
- IRB harmonization
- Data sharing
- Identifying direct and indirect subjects
- Gatekeepers
- FDA-regulated products
- Nature of ePCT interventions
- Privacy
- Management of collateral findings
- Posttrial obligations
- ….

Article

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Exploring the ethical and regulatory issues in pragmatic clinical trials

Robert M Califf[1,2,*] and Jeremy Sugarman[3,4]

Abstract

The need for high-quality evidence to support decision making about health and health care by patients, physicians, care providers, and policy-makers is well documented. However, serious shortcomings in evidence persist. Pragmatic clinical trials that use novel techniques including emerging information and communication technologies to explore important research questions rapidly and at a fraction of the cost incurred by more "traditional" research methods promise to help close this gap. Nevertheless, while pragmatic clinical trials can bridge clinical practice and research, they may also raise difficult ethical and regulatory challenges. In this article, the authors briefly survey the current state of evidence that is available to inform clinical care and other health-related decisions and discuss the potential for pragmatic clinical trials to improve this state of affairs. They then propose a new working definition for pragmatic research that centers upon fitness for informing decisions about health and health care. Finally, they introduce a project, jointly undertaken by the National Institutes of Health Health Care Systems Research Collaboratory and the National Patient-Centered Clinical Research Network (PCORnet), which addresses 11 key aspects of current systems for regulatory and ethical oversight of clinical research that pose challenges to conducting pragmatic clinical trials. In the series of articles commissioned on this topic published in this issue of *Clinical Trials*, each of these aspects is addressed in a dedicated article, with a special focus on the interplay between ethical and regulatory considerations and pragmatic clinical research aimed at informing "real-world" choices about health and health care.

Keyword

Clinical trials, cluster-randomized trial, ethics, evidence-based medicine, learning health-care system, patient-centered outcomes research, pragmatic clinical trial

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- ….

Informed Consent, Waivers & Alterations

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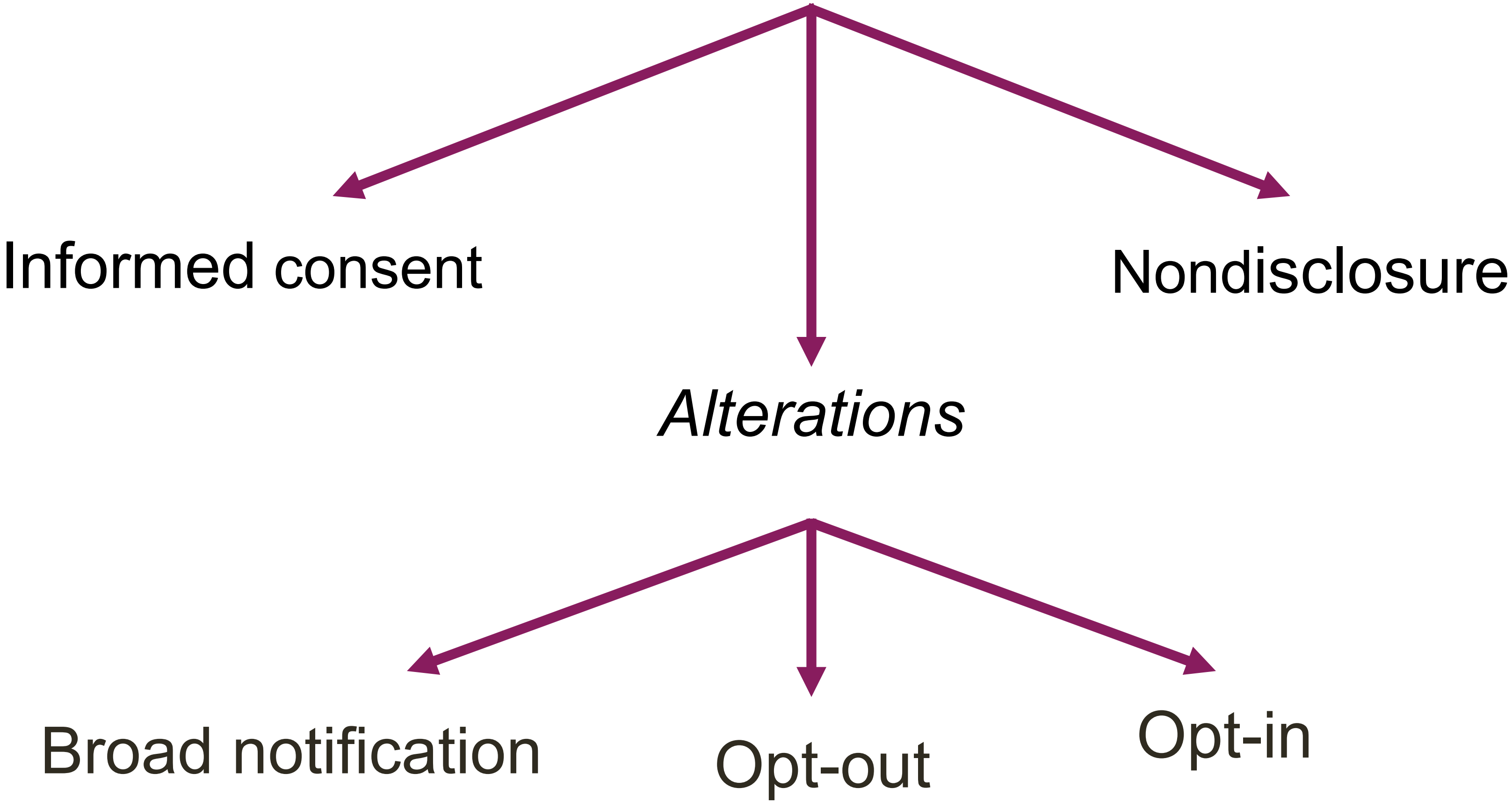
Approaches to notification and authorization



Informed consent

Alterations

Nondisclosure

Broad notification

Opt-out

Opt-in

Knowledge checkpoint

- True or false: The same regulatory criteria apply for both waivers and alterations of consent.

Knowledge checkpoint

- Which of the following is NOT an acceptable justification for waiving or altering informed consent?
  a. Research involves no more than minimal risk
  b. Research could not practicably be carried out without the waiver or alteration
  c. Refusals to participate could bias the study results
  d. Waiver or alteration will not adversely affect the rights and welfare of the subject

Criteria for waiver or alteration of consent

- Research involves no more than minimal risk
- Research could not practicably be carried out without the waiver or alteration
- If research involves using identifiable private information or identifiable biospecimens, it could not practicably be carried out without using such information or biospecimens in an identifiable format
- Waiver/alteration will not adversely affect rights and welfare of subject
- Where appropriate, subjects will be provided with additional information about their participation

Common Rule: 45 CFR 46.116(f)

Criteria for waiver/alteration of informed consent

- Research involves no more than minimal risk

> “Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.” (46.102)

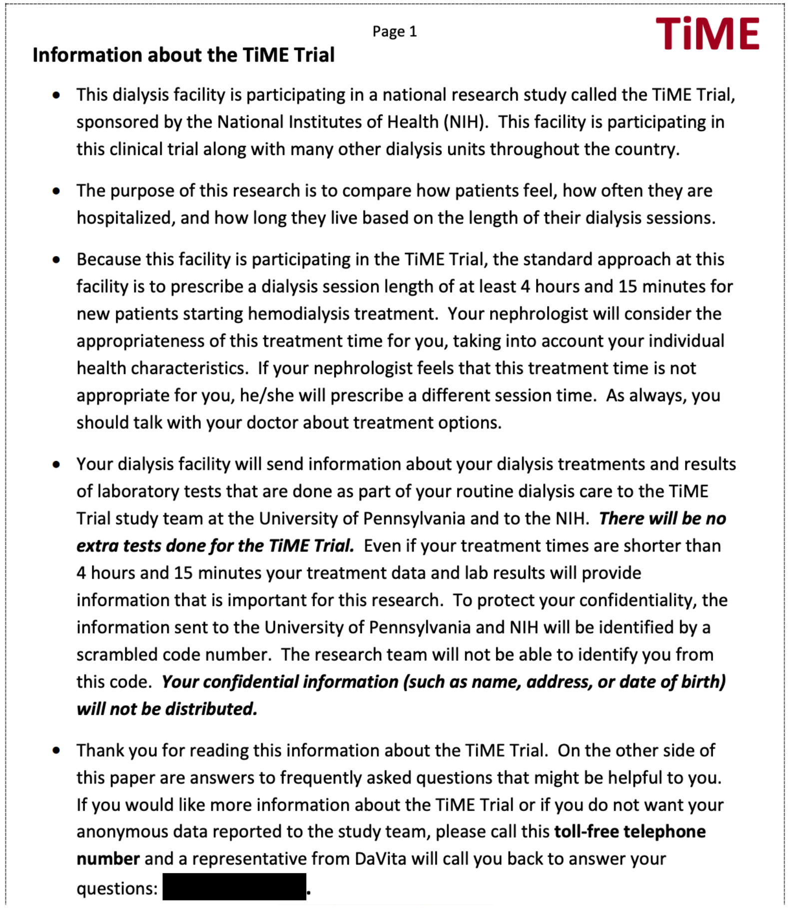
Distinguishing research risks

- “Minimal risk” refers only to the additional risk of the research (not the underlying risk of the disease)

Regulatory permissible ≠ ethically optimal

- Regulatory criteria for waivers and alterations identical…but they are ethically distinct
  - Aim for alterations to consent to be the “minimum necessary”
  - Consider options to demonstrate respect for persons, beyond consent processes

Examples: Information sheets or flyers

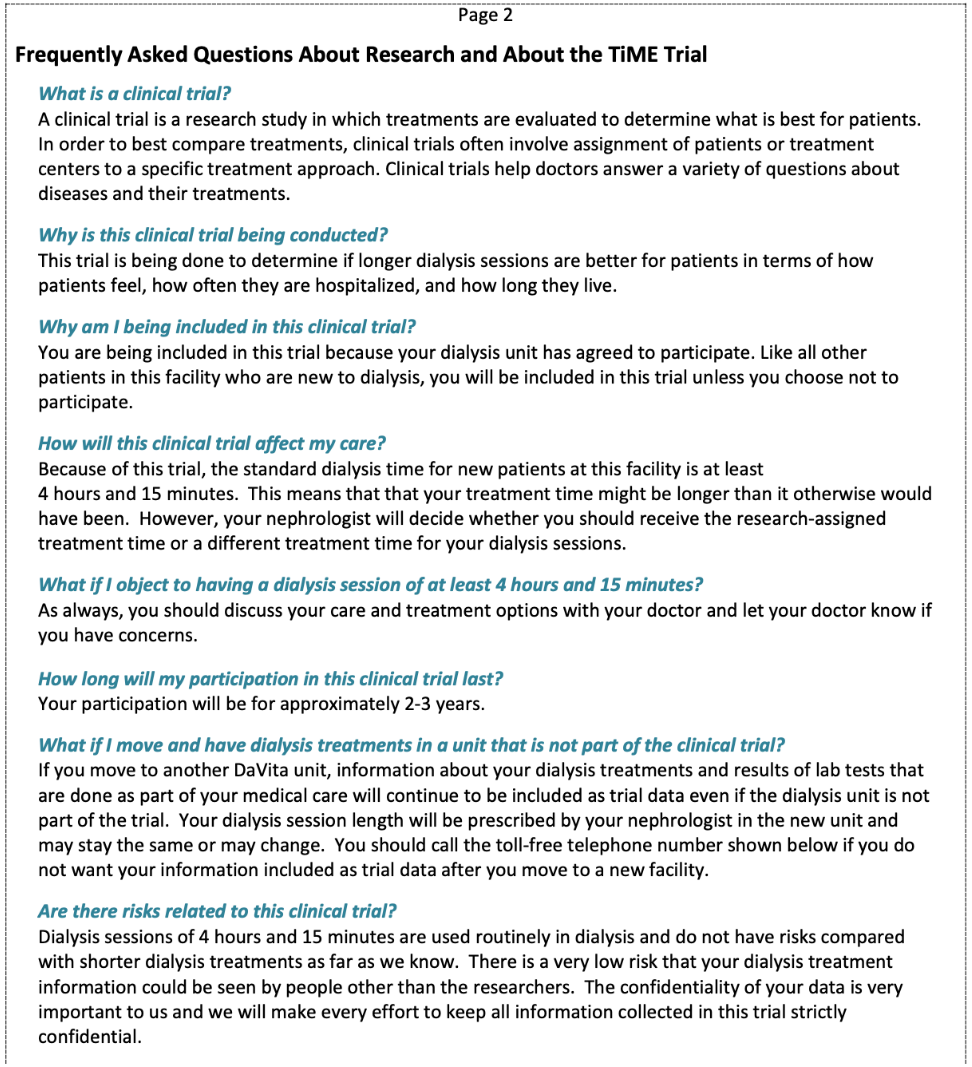


Page 1

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].



Page 2

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.

Knowledge checkpoint

- Why might a study team notify patients about a PCT, even if the study meets the regulatory criteria for a waiver of consent?

Data Sharing & PCTs

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Increasing expectation for sharing clinical trials data

Challenges for sharing PCT data

Often conducted with waivers or alterations of informed consent

Use of extant data (eg, EHR, claims)

If PCT uses a waiver or alteration of consent…

- Cannot assume sharing data is consistent with preferences of patient-subjects
- Cannot rely on informed consent to fulfill ethical obligation of respect

What does it mean to respect patient-subjects in the context of (not) sharing data from a PCT conducted under a waiver/alteration of informed consent?

Implications of embeddedness for PCT data sharing

- Data may be “about” those beyond patient-subjects
- Increased risk of privacy violations
- Increased risk of biased or misleading analyses
- Data may be controlled by a third party (eg, CMS)

Recommendations for PCT data sharing

- Consider interests of those beyond patient-subjects
- Proactively engage health system partners, other data partners & funders in decision-making about data sharing

Sharing Aggregate Results

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Ethical arguments for sharing aggregate results

- Respect and reciprocity
- Promoting participant trust and research(er) trustworthiness

Countervailing considerations

- Lesser risks/burdens of research → reduced obligations to share?
- Consequentialist-based considerations
- Logistical and practical barriers to sharing
- Privacy and confidentiality considerations

Recommendations for sharing aggregate results

- Sharing aggregate results should be the presumptive default
- Planning for aggregate results sharing should begin at the earliest phases of research and be incorporated into study protocols, funding applications, IRB applications, and, where appropriate, informed consent processes
- Healthcare system partners have a key role in decision-making about and implementation of sharing aggregate results
- PCTs conducted with a waiver of consent involve special considerations

Posttrial Obligations in PCTs

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Posttrial obligations in explanatory clinical trials

- Existing scholarship and research ethics guidelines are largely focused on posttrial access to study medications or interventions

Declaration of Helsinki

"Sponsors, researchers, and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial."

Council for International Organizations of Medical Sciences (CIOMS)

Researchers and sponsors should make plans for "providing continued access to study interventions that have demonstrated significant benefit."

Ethical arguments for posttrial obligations

- Avoid exploitation
- Respect and reciprocity
- Preventing harm
- Social value

Considerations for posttrial obligations in PCTs

- Lower-risk interventions, fewer (individual-level) burdens – but potentially obligations owed to those beyond individual participants?
- Interventions delivered by and within healthcare delivery systems—healthcare systems must be key partners in fulfilling post-trial obligations
- Ethical presumption that practice/operations should change in light of PCT results
- Existing guidance focuses on successful interventions, but should also address *de*implementation

Q&A

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