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**Ethical and Regulatory Issues for
Embedded Pragmatic Trials Involving People Living With Dementia**

Short running title: Ethical and Regulatory Issues

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Abstract

Embedded pragmatic clinical trials (ePCTs) present an opportunity to improve care for people living with dementia (PLWD) and their care partners but entail a particular constellation of ethical and regulatory challenges. These challenges begin with subject identification.

Interventions may be delivered in ways that make it difficult to identify *who* is a human subject and therefore who will need ethical and regulatory protections. The need for informed consent, a core human subjects protection, must also be considered but can be in tension with the goals of pragmatic approach. Thus, it is essential to consider whether the ePCT can be designed so that a waiver or alteration of informed consent is justifiable. If informed consent is needed, there is the question of how it is obtained, as investigators must acknowledge the vulnerability of PLWD—due in part to diminished capacity and to increased dependence on others. Further, investigators should recognize that many sites where ePCTs are conducted will be unfamiliar with research regulations and ethics. In this report, the Regulation and Ethics Core of the National Institute on Aging (NIA) Imbedded Pragmatic Alzheimer’s disease (AD) and AD-related dementias (AD/ADRD) Clinical Trials (IMPACT) Collaboratory discusses key ethical and regulatory challenges for ePCTs in PLWD. A central message is that investigators should anticipate and address these challenges early in the design of their ePCTs, as a means of not only ensuring compliance but also advancing the science.

Key words: dementia, ethics, informed consent, human subjects research

Alzheimer’s disease (AD) and AD-related dementias (AD/ADRD) affect over 5 million individuals in the United States, and more than 16 million informal care partners.¹ People living with dementia (PLWD) commonly experience fragmented, poor quality, and high-cost care that often fails to address their needs and those of their care partners. Presently, there is a paucity of evidence to support the adoption of effective interventions and services into health care systems (HCS) that improve the care of PLWD and their care partners.

The National Institute on Aging (NIA) Imbedded Pragmatic AD/ADRD Clinical Trials (IMPACT) Collaboratory aims to remedy this evidentiary gap by building the nation’s capacity to conduct embedded pragmatic clinical trials (ePCTs) to benefit PLWD and their care partners in the HCS that serve them. The Regulation and Ethics Core supports this mission through promulgation of guidance, best practices, and training materials for the research community. In doing this, we are building on considerable work done by others, including the National Institutes of Health HCS Research Collaboratory, and crucially extending it to PLWD.^{2,3} Additionally, our Core provides consultation for IMPACT Collaboratory pilot-grant applicants and recipients as well as with new and early-stage investigators who receive IMPACT Collaboratory career development awards.

Central to our Core’s guidance, training, and consultation activities is the fact that ePCTs in PLWD entail a particular constellation of ethical and regulatory challenges. These challenges begin with subject identification. Interventions may be delivered in ways that make it difficult to identify *who* is a human subject and therefore who needs ethical and regulatory protections. Because ePCT seek to evaluate interventions in actual clinical practice, research-related

informed consent, a core human subjects protection, can sometimes conflict with study goals. In such cases it is essential to consider whether the ePCT qualifies for a waiver of informed consent. If it does not and informed consent is required, investigators must then design a consent process that acknowledges the vulnerability of PLWD—due in part to diminished capacity and to increased dependence on others. Further, investigators should recognize that many study sites will be unfamiliar with research regulations and ethics frameworks. By highlighting these considerations, the Regulation and Ethics Core aims to illuminate how the features of an ePCT interdigitate with human subjects protections.

In this report, we discuss key aforementioned ethical and regulatory challenges in ePCTs for AD/ABRD populations. Our overarching message is that investigators should anticipate and address them early in the design of their ePCTs. This will ensure that ePCTs for PLWD reflect ethical reasoning and also comply with relevant regulations. Moreover, attention to regulatory and ethical issues from the outset can advance the pragmatic nature of a study and make the research more efficient.

Blurring the research/care distinction

A sharp conceptual distinction between research and care has been central to the development of research ethics and regulations.^{4,5} Yet, ePCTs are specifically designed to produce generalizable knowledge from contexts that are as close as possible to the conditions of usual care—that is, they blur the research/care distinction. The well-recognized Pragmatic Explanatory Continuum Indicator Summary (PRECIS-2) and Readiness Assessment for Pragmatic Trials (RAPT) tools allow investigators and institutional review boards (IRBs) to grade how pragmatic research is.^{6,7}

Features of a trial, such as delivery of the intervention, are “very pragmatic” if they are “identical” to or as “flexible” as clinical care. An ePCT that meets these conditions promises evidence with substantial external validity and so notable value to a health care system.

Unfortunately, there is not yet consensus that existing research ethics frameworks and regulatory structures—particularly with respect to subject identification and informed consent—are sufficiently flexible to appropriately guide the design and conduct of ePCTs.⁸ Attention to this difficulty has recently increased, and ethical and regulatory aspects of pragmatic trial design continue to evolve.^{9,10}

Subject identification

It is critical, albeit not always straightforward, to identify who is and who is not a human subject in an ePCT. This is important so investigators extend appropriate protections to those who need them and avoid unnecessary ethical and regulatory burdens for those who do not.^{11,12}

Subject identification involves important regulatory considerations. The Federal Policy for the Protection of Human Subjects (Title 45 Part 46 of the Code of Federal Regulations, known as the “Common Rule”) defines a human subject as “a living individual about whom an investigator . . . conducting research: (i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or (ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens” (45 CFR §46.102).¹³ The Common Rule goes on to explain that *intervention* includes both physical procedures and manipulation of the subject’s environment performed for

research purposes, and *interaction* includes communication or interpersonal contact between the investigator and subject.

Interventions tested in ePCTs with PLWD are typically programmatic or environmental in nature and implemented at the level of the unit of care—such as an entire nursing home or entire adult day program. Random assignment to the intervention or control arm is also typically done at the unit of care or “cluster” level. Together, these design features may complicate the usually straightforward process of identifying human subjects. For example, imagine that a particular nursing home is randomized to receive a training intervention for the staff and that after the training, the investigators use data from the medical records to measure both staff behaviors and patient health outcomes. Who are the subjects? The patient and staff environments have been manipulated, and the investigators are gathering information. One interpretation is that the human subjects are not only the PLWD but also facility staff and possibly other residents who also coincidentally receive the intervention.^{14,15} A closely related question, raised below, is whether facility staff in this example are “engaged in research.”

Waivers and alterations of informed consent

Written informed consent from human subjects is generally a regulatory and ethical requirement of research.^{16,17} Yet, the collection of informed consent can frustrate the pragmatic nature of a trial. A sound argument allows that a waiver or alteration of informed consent can, under certain conditions, be ethically acceptable,¹⁹ and the Common Rule details conditions that, if met, allow a waiver or alteration.

In ePCTs that involve PLWD, a waiver or alteration of consent presents an ethical dilemma.¹⁸ Individual level consent is typically obtained by research staff, or in some circumstances by clinical providers, with both approaches potentially undermining the pragmatic nature of a trial. If the ePCT design and consent are truly not compatible, the investigator—and ultimately the IRB—must determine if a waiver or alteration of informed consent is permissible. Researchers conducting ePCTs with PLWD have the added responsibility of considering PLWDs' vulnerability when assessing permissibility, as vulnerability is generally thought to merit more rather than fewer protections. Attention to, and understanding of, the conditions that must be met for a waiver or alteration of informed consent from the earliest phases of trial design can facilitate adjusting the design so that a waiver or alteration of consent is possible.

Figure 1 suggests steps to help determine the need for informed consent. The first step in assessing the need for written informed consent is to determine which aspects of the overall study design are research components. For example, if the intervention tested in the ePCT is itself considered a part of routine clinical practice and is delivered by usual care providers, it is likely not research. In contrast, the use of protected health information gathered from medical records to ascertain trial outcomes likely is research.

The next step to consider is whether some or all of the research components just identified may qualify for waivers or alterations of informed consent. The Common Rule lists five criteria that research proposing to waive or alter consent must conform to: (1) the research involves no more than minimal risk to subjects; (2) the research could not practicably be carried out without a waiver or alteration; (3) the research could not practicably be done with de-identified private

information; (4) subjects' rights and welfare will not be adversely affected; and (5) whenever appropriate, the researchers will provide subjects or their legally authorized representative with information after participation (45 CFR §46.116). All five criteria must be met to waive or alter consent (see Figure 1).

Minimal risk

The Common Rule tasks IRBs with reviewing and assessing risks and benefits that may result from research (45 CFR §46.111). “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” (45 CFR §46.102). There has been considerable debate about how to apply this definition in ePCTs.²⁰

It is unclear what the proper comparator is for making a minimal risk assessment. *Whose* daily life? For PLWD the concept of “minimal risk” is particularly fraught. Should the risk assessment account for the high morbidity of AD/ADRD and the poor quality of much existing care? If yes, PLWD could be exposed to significant risks that, paradoxically, would not exceed “minimal risk.” A more sensible baseline is to compare the research risks to risks encountered in the daily lives of persons with comparable impairment who live in a safe, high-quality care setting. This “real and ideal world standard” grounds the minimal risk standard in the lives of PLWD with an expectation that they receive appropriate care.

Practicability

How to determine whether research could not practicably be carried out without a waiver or alteration of informed consent is unsettled. Waiver or alteration may be appropriate if requiring consent would compromise the scientific validity of a trial. For instance, waiver or alteration may be appropriate if subjects declining to participate would likely result in a less representative study population, introduce bias, and so frustrate the pragmatic goal of a trial. Practicability should not be determined by considerations of the cost, convenience, or speed of obtaining informed consent.²¹

Respecting subjects' rights and welfare

A concern in all human subjects research is the potential of a dignitary harm when a subject is a mere means to an end.²² Dignitary harms ought to worry us even more when the subjects are PLWD. They progressively surrender privacy and self-control to others. In a private setting, such as one's own home, the terms of this surrender are personal matters, negotiated between the person with dementia and his care partners. This negotiation becomes more challenging in spaces, like nursing homes or adult day programs, where the private and the public are necessarily fused. Introducing research into spaces where the public and private are so intimately connected may carry dignitary risks to PLWD that need careful consideration.²³ For example, PLWD who live in a nursing home have a reasonable expectation of privacy in their bedrooms—even if their bedrooms are also sites of substantial amounts of care delivery. Thus, there may be heightened risk of dignitary harm from waiving or altering consent if a research intervention will change the individual's bedroom environment.

Engagement with PLWD and their care partners will often be essential to a determination that subjects' rights and welfare will not be adversely affected by a waiver or alteration of informed consent. Patient or care partner engagement in research design (and oversight), though potentially difficult, can provide important insights and help ensure that patients' values and interests are respected.²⁴

Notification

When appropriate, researchers should provide subjects with information about their research participation, including their results. This is an opportunity for messaging, communications, and community engagement that builds trust in and identification with the research. This can occur through mechanisms such as notices posted in common areas of a long term care facility or newsletters.

Obtaining informed consent

All five of the Common Rule criteria outlined above must be met to waive or alter consent. If an ePCT (or any portion thereof) is not eligible for a waiver or alteration, the Common Rule details how investigators should seek informed consent from those identified as human subjects (45 CFR §46.116).

When research is conducted with PLWD, the consent process must account for subjects' broad spectrum of cognitive impairments. It cannot be assumed that everyone diagnosed with dementia lacks capacity to consent to the ePCT. Capacity is a task-specific ability to appreciate

the situation and its consequences, understand relevant information, reason about options, and communicate a choice.²⁵

Because it is essential that investigators seek consent from PLWD if possible, they must have a plan for assessing prospective subjects' capacity to consent to the ePCT.²⁵ Assessment methods should list out the key facts a person need to understand and use a conversation-based approach to assess understanding. Cognitive tests like the Mini Mental Status Exam (MMSE) are useful to predict the likelihood a person will have capacity but cannot substitute for an assessment of understanding.²⁶ As an aside, capacity testing—particularly in longitudinal studies where consent is ongoing and capacity testing is iterative—may offer insights into declining cognition that can be upsetting to PLWD. This potential harm should be factored into the risk/benefit assessment of the trial.

PLWD who lack capacity will often have a legally authorized representative (LAR).[16] The most common approach to obtaining consent for research when the PLWD lacks capacity is to seek surrogate consent from the LAR. Some state and local regulations distinguish the ability of an LAR to consent to clinical care from the ability of an LAR to consent to research participation on behalf of the PLWD. Therefore, researchers should understand the regulations governing surrogate consent at their study sites.

Surrogate consent does not preclude the participation of the PLWD in research-related decision-making. Foregoing a conversation with a PWLD seems a dignitary harm. Two important ways to demonstrate respect for PLWD are to seek their assent and respect their dissent.^{27,28} Thus, the

recommended approach to obtaining consent for research participation when the PLWD lacks decision-making capacity combines surrogate consent with subject assent or (lack of) dissent.

Given the vulnerability of PLWD, other people and institutions often control researchers' access to PLWD. These “gatekeepers” could include informal caregivers as well as staff and leadership in a long-term care setting.²⁹ These individuals are charged with protecting their rights and welfare. While it will often be necessary to secure their permission to conduct an ePCT, this permission is not a substitute for subject informed consent or assent.¹²

Additional issues

Conflicts of Interest: In situations when investigators have a financial interest in the intervention—for example, it has been developed with a commercial intent—their primary interest in producing generalizable knowledge is at risk of being biased by their secondary, financial interest.³⁰ Such conflicts of interest may bias judgments about ePCT design and interpretation of results. Conflict management often requires the investigator-owner to step away and instead serve as a consultant.

Unique Institutional Settings: The Common Rule applies to all research funded by the U.S. Department of Health and Human Services (HHS), regardless of where that research occurs. Any institution “engaged in research”—generally, when its employees are obtaining data for research purposes or consent of human subjects—is required to have an approved Federalwide Assurance (FWA) committing to compliance with the requirements in the Common Rule on file with the Office for Human Research Protections (OHRP) in HHS (45 CFR § 46.103). It is also

important to determine which individuals within the institution are “engaged in research,” as they must be listed as study team members and receive adequate training in human subjects research.

Often, ePCTs in PLWD are conducted in institutions such as nursing homes or adult day programs that do not typically participate in research and therefore lack familiarity with relevant ethics frameworks and research regulations. Investigators must be attuned to the possibility that, depending on the study design, the institutions may be considered “engaged in research.”

Investigators should consider whether the study can be altered to avoid this; if it cannot, investigators should be willing to assist facilities in obtaining needed FWAs, human subjects training, and IRB oversight.

Protected Health Information: Researchers conducting ePCTs will often seek to use administrative data such as electronic health records and insurance claims routinely collected by study sites or other health care providers to recruit their cohorts, characterize their subjects, and measure outcomes. These data are considered protected health information and subject to the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. The data owners (i.e., covered entities such as nursing homes) may be aware of HIPAA requirements surrounding the use of the data for clinical care and billing purposes, but less familiar with the requirements surrounding the release of the data for research purposes. Researchers must understand HIPAA authorization requirements for identifiable health information.

Beneficiary Inducement: Medicare and Medicaid serve nearly all PLWD. The federal Anti-Kickback Statute prohibits inducements to beneficiaries of these federal healthcare programs,

and many states have similar prohibitions. These prohibitions are intended to prevent overutilization of medical services, which inappropriately increases federal and state healthcare program costs, potentially harms beneficiaries, and improperly influences patients' treatment decisions. Advisory Opinions from the HHS Office of the Inspector General suggest that these prohibitions potentially apply to a range of clinical research designs and recruitment strategies.³¹ If an ePCT intervention is designed in a way that offers subjects something of value in return for participation, it may implicate these beneficiary inducement prohibitions.

Conclusion

The IMPACT Collaboratory's Regulation and Ethics Core will work to clarify and advance understanding of the issues discussed herein (see Table 1). As our Core gains additional insights into the particular ethical and regulatory challenges that arise when conducting ePCTs with PLWD—such as through our pilot-grant consultations—our list of research priorities will continue to grow and evolve. Our findings will inform the guidelines, best practices, and training materials we develop and disseminate. Understanding and addressing ethical and regulatory challenges early in the design of an ePCT is not just a means of ensuring compliance but also a means of advancing the science.

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Table 1. IMPACT Collaboratory Regulation and Ethics Core Research Agenda

Topic	Description	Challenge	Our Plan
Research/care distinction	Existing regulatory and ethical frameworks are grounded in a distinction between medical research and medical care.	ePCTs are specifically designed to blur or erase the research/care distinction, making existing frameworks less suitable or inapplicable.	Develop new regulatory and ethical frameworks that are tailored to guide the practice of ePCTs for PLWD.
Subject identification	Appropriate human subject protections require clear criteria for identifying who are the research subjects in a study and how they should be recruited.	ePCTs for PLWD will often employ designs that include multiple stakeholder groups as subjects (e.g., nurses or care partners may be subjects in addition to the PLWD) or that fundamentally change the recruitment structure (e.g., cluster randomization).	Develop guidance to help investigators clearly identify which stakeholders are research subjects and how these groups should be recruited.

<p>Informed consent</p>	<p>Collecting written, informed consent is the primary mechanism of demonstrating respect for all research subjects.</p>	<p>Decision-making capacity of PLWD may be impaired; traditional informed consent can make the study population less representative, potentially frustrating the aims of ePCTs.</p>	<p>Clarify how the regulatory and ethical conditions for adopting waivers or modification of informed consent should be applied to ePCTs with PLWD.</p>
<p>Conflict of interest</p>	<p>Minimizing risk and ensuring research integrity demands strict, comprehensive conflict of interest policies.</p>	<p>Investigators may often have investments in the innovative products that they believe will benefit PLWD.</p>	<p>Develop policies to help manage conflicts of interest, without stifling scientific incentives.</p>
<p>Regulatory compliance for new research settings</p>	<p>Multiple laws and complex regulatory frameworks exist to protect the rights and</p>	<p>ePCTs for PLWD may involve care settings (e.g., nursing homes) that are not accustomed to research and lack</p>	<p>Develop guidance, training, and checklist materials to help study sites that are new to</p>

	welfare of research subjects (e.g., FWA, HIPAA, AKS).	dedicated staff/experts to navigate the regulatory environment.	research understand the relevant regulations.
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Figure 1. Logical flowchart for satisfying ethical and regulatory criteria for waivers or alterations of informed consent. These criteria are stipulated in the U.S. Code of Federal Regulations (45 CFR 46 §116(e)). Abbreviations: CFR = Code of Federal Regulations, LAR = legally authorized representative. * §116(d) of 45 CFR 46 describes the requirements for “broad consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens” as an alternative to the traditional informed consent requirements.

