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Achieving health equity in embedded pragmatic trials for PLWD and their family caregivers

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Abstract

Pragmatic clinical trials (ePCTs) advance research on Alzheimer’s disease and related dementias (AD/ADRD) in real world contexts; however, health equity issues have not yet been fully considered, assessed, or integrated into ePCT designs. Health disparities populations may not be well represented in ePCTs without special efforts to identify and successfully recruit sites of care that serve larger numbers of these populations. The National Institute on Aging (NIA) Imbedded Pragmatic Alzheimer’s disease (AD) and AD Related Dementias (AD/ADRD) Clinical Trials (IMPACT) Collaboratory’s Health Equity Team (HET) will contribute to the overall mission of the NIA IMPACT Collaboratory by developing and implementing strategies to address health equity in the conduct of ePCTs to ensure that the Collaboratory is a national resource for all Americans with dementia. As a first step toward meeting these goals, this paper reviews what is currently known about the inclusion of health disparities populations of people living with dementia (PLWD) and their caregivers in ePCTs, highlights unique challenges related to health equity in the conduct of ePCTs, and suggests priority areas in the design and implementation of ePCTs to increase the awareness and avoidance of pitfalls that may perpetuate and magnify healthcare disparities.

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Author Contributions

All authors contributed to the study concept and design, drafting, and reviewing of the manuscript.

Conflict of Interest

The authors have no conflicts to disclose.

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None.

Introduction

Minority ethnic groups have higher rates of dementia, yet worse health outcomes relative to white people living with dementia (PLWD).^{1,2} Nonetheless, minority ethnic and low socioeconomic groups and their caregivers remain underrepresented in traditional dementia efficacy clinical trials.^{2,3,4} Indeed, the efficacy, safety, and tolerability of treatments have not been sufficiently assessed for health disparities populations writ large—racial and ethnic minorities, low socioeconomic status groups, underserved rural residents, and sexual and gender minority groups⁵—creating critical knowledge gaps at a time when our aging population is becoming increasingly diverse. These gaps threaten the generalizability and applicability of future dementia treatments to the wide array of PLWD from underrepresented communities and disadvantaged populations experiencing health disparities.^{4,6}

The sparse evidence applicable to health disparity populations derived from Alzheimer's disease (AD) and AD Related Dementias (AD/ADRD) efficacy trials extends to pragmatic clinical trial designs embedded in health care systems (ePCTs, HCS). While the aim of ePCTs is to improve the evidence base by conducting clinical research in real-world settings, there is virtually no prior work examining a range of health equity issues that may impact ePCTs in AD/ADRD research. ePCTs have unique design features that introduce additional novel challenges with respect to health equity. For example, HCS and other sites of care that commonly serve PLWD—such as nursing homes—are commonly segregated along racial and ethnic dimensions. Thus, minority ethnic groups and other health disparity populations may be underrepresented or worse, excluded, from ePCTs without special efforts to identify and successfully recruit HCS and other community sites that serve these populations.

The reproduction of existing disparities may be another significant challenge when moving from efficacy to effectiveness trials. ePCTs are, by definition, embedded in existing systems of care. To the extent that healthcare disparities in access and quality of care exist within these systems, there is a significant risk of reproducing or exacerbating these inequities as ePCTs are implemented as part of “routine care” in HCS. ePCTs also operate under the general assumption that sufficient evidence for the efficacy of the interventions has been established when in fact evidence may be lacking or not well established for minority ethnic and other health disparities populations.^{4,7,8} In addition, the accurate identification of health disparity groups in administrative or EHR data is particularly salient in ePCTs because study participants do not have the opportunity to self-report or corroborate information. Instead, ePCTs often rely on how these demographic data are represented in systems, which vary with regard to accuracy.

Interventions introduced on a systems-level must also be tailored to PLWD and their caregivers from various sociodemographic and cultural dimensions, yet the literature provides little guidance on the types of adaptations needed. Therefore, when it comes to diverse populations, the implementation of ePCT often occurs in an “evidence-vacuum.” This creates unique challenges for historically underserved and underrepresented populations and threatens the “readiness” of moving evidence-based programs from efficacy

to pragmatic designs because these programs are not founded on representative and inclusive populations.^{9,10}

It is imperative that a health equity lens be central to the design of AD/ADRD studies so that the inclusion of health disparity populations be considered early, often, and thoughtfully in ePCTs from inception to end. A recent infusion of research funds and increased national and international attention to AD/ADRD signals prioritization of ameliorating the effects of AD/ADRD on PLWD and their caregivers. However, it is critical that AD/ADRD trials aim for true population representation, achieved through concerted efforts to represent health disparity populations and establish effectiveness of non-pharmacological programs.

This paper aims to highlight specific aspects of ePCTs that have vast implications for health equity in the generation of good quality research. To this end, the Health Equity Team (HET) contributes to the overall mission of the National Institute on Aging (NIA) Imbedded Pragmatic Alzheimer's disease (AD) and AD Related Dementias (AD/ADRD) Clinical Trials (IMPACT) by developing and implementing strategies to address health equity in the conduct of ePCT to ensure that the Collaboratory is a national resource of all Americans with dementia. As a first step, this report reviews what is currently known about the inclusion of health disparities populations of people living with dementia (PLWD) and their caregivers in ePCTs, highlights unique challenges related to health equity, and suggests priority areas in the design and implementation of ePCTs to increase the awareness and avoidance of pitfalls that may perpetuate and magnify healthcare disparities. The focus in many of the examples presented is on race/ethnicity because these are the groups for which there is the most peer-reviewed work and evidence base. Concerns raised about transmitting inequities may not occur and operate in the same way for other health disparity groups. Still, important continued work for the HET will be to evaluate challenges across health disparity groups.

Healthcare disparities for PLWD and family caregivers

There is growing evidence of disparities in the epidemiology and health outcomes in AD/ADRD populations. Black Americans are twice as likely and Latinos are 1.5 times more to have dementia compared to non-Latino white Americans.^{1,11–13} Among community-dwelling persons with dementia, black Americans and Latinos have higher levels of neuropsychiatric symptoms of dementia.¹⁴ Studies have found that Latino family caregivers endorse higher levels of psychological stress compared with their white non-Hispanic counterparts.^{15,16} The economic impact of dementia may be felt disproportionately by minority ethnic families, particularly black American, Latino and American Indian and Native Alaskan families because on average, these groups have less disposable income and suffer from higher rates of poverty.¹⁷ Minority ethnic older adults are more likely to be misdiagnosed¹⁸ and less likely to receive cognitive enhancers as part of their dementia care.¹⁹ There are also marked and persistent racial and regional differences in the quality of care provided to PLWD. For example, black Americans (compared to white Americans) with advanced dementia and those living in the Southeastern US (compared to those living in other regions) are far more likely to receive aggressive, costly interventions of questionable clinical benefit at the end-of-life, such as tube-feeding or hospitalizations.^{11,20–27} These

differences have persisted from 2000–2014.^{36,40} Access to dementia care and the quality of this care varies widely for PLWD and their informal family caregivers. Minority ethnic older adults are more likely to be housed in nursing homes and long-term care facilities that are under-resourced and racially segregated.^{28–30} The quality of care delivered in nursing homes that serve predominantly minority ethnic PLWD is lower, and these nursing homes are more likely to be afflicted by serious deficiencies such as low staffing ratios, low occupancy rates, and financial instability.^{29,30}

While traditional efficacy trials test a drug or treatment under highly controlled conditions, ePCTs test effectiveness in real-world settings under conditions that are not as controlled. By design, all PLWD served by a given HCS should be eligible for inclusion in ePCTs regardless of background. However, the regions from which HCS or clusters (e.g., nursing homes) are selected, nature of the intervention, and other factors such as residential racial segregation and high racial/ethnic concentration in institutional settings (e.g., nursing homes), have important implications for health equity. Because ePCTs emphasize research conducted in usual clinical care settings and workflow, deliberative efforts are needed to prevent exclusion of minority ethnic populations in ePCTs.

Usual considerations of adapting interventions to different cultural contexts apply in ePCTs. For instance, evidence-based behavioral interventions require substantial effort to adapt to culturally-sensitive materials and delivery of programs. While frameworks have been developed to guide the cultural adaptation process³¹ and characterize types of adaptations,³² these have not been widely used in intervention studies of non-pharmacological interventions for PLWD and family caregivers.^{33,34} Further, evidence on best strategies for adaptation or tailoring may also be sparse.³⁵ To this end, implementation science approaches may be helpful in guiding the adaptation process with respect to diverse populations³⁶ and process evaluation may also be valuable in understanding how interventions are experienced across diverse segments of the population and various stakeholder groups.

Specific health equity considerations in AD/ADRD ePCT design

Below and in Table 1, the Pragmatic Explanatory Continuum Indicator Summary (PRECIS-2) framework³⁷ and its domains are used to highlight health equity considerations in the design of ePCTs

1. Eligibility criteria

ePCTs typically aim to enroll all individuals in a clinical setting with minimal eligibility criteria. Thus, inclusion of health disparity populations in ePCTs is dependent on the demographic profile of the clinical site within a HCS. Assessment of patient demographics within randomized sites is needed to determine if they comprise a representative subset of patients served by an HCS as well in the HCS catchment area. Aiming for representative samples relative to ADRD burden for minority groups is an important design strategy to improve precision of estimates, and in many cases, can help ensure adequate samples to power comparisons of effectiveness. Oversampling of disparities populations may also be needed to address gaps in evidence. Moreover, accurate identification of specific

demographic groups from the HCS's EHR may not be complete or accurate with regard to sociodemographic information.

2. Enrollment/recruit/retain

While there is considerable literature about the challenges of recruiting diverse participants at the individual-level, there is a paucity of prior work describing recruitment of minorities within "clusters" of care settings within HCS which themselves may have distinct values and perceptions of research. Clearly, researchers need to engage and recruit HCS or units within HCS that serve diverse PLWD and their families. For example, to the extent that HCS/units are segregated with respect to race/ethnicity, balancing or stratifying clusters at randomization based on known proportions of minorities may be important, particularly when outcomes may be associated with race/ethnicity.

3. Setting

To the extent that AD/ADRD disparities (e.g., in access or quality of care) exist within the routine clinical care of a clinical setting HCS, there is substantial risk that these disparities will be reproduced in implementing the intervention in the context of an ePCT. For example, minority ethnic older adults are more likely to reside in nursing homes with lower quality of care and fewer resources.²⁹ Thus, recruitment and outcomes may be adversely impacted by existing disparities at the nursing home level.³⁸ Lack of trust and communication barriers may be particularly important to address with ethnically and culturally diverse PLWD and their caregivers in settings with less culturally and linguistically competent care to avoid poor recruitment and intervention fidelity.

4. Organization

Traditional efficacy trials often rely on research infrastructure and personnel to ensure strict adherence protocol for relatively straightforward interventions. In contrast, ePCTs for AD/ADRD aim to embed often times complex interventions into to the usual clinical care flow of front-line providers in a HCS. Taken together, there is greater risk in ePCTs for provider biases and factors that further complicate implementation, such as language or health literacy barriers that perpetuate inequitable delivery of the intervention.

5. Flexibility (delivery)

Despite training, implementation protocols, and incentives, ePCTs, the ultimate delivery of the intervention in an ePCTs is intentionally flexible and up to the discretion of the clinical providers. Thus, existing disparities in access or quality of care that already exist within HCS are likely to be reproduced in ePCT. Provider background and cultural perspectives may affect implementation delivery, and resources needed for successful training.

6. Flexibility (adherence)

The ability of many HCS to culturally and linguistically tailor evidence-based interventions may be very limited without technical assistance and stakeholder engagement, leading to ad hoc and uneven adaptation and adherence to the interventions by PLWD and their caregivers from diverse populations.³⁹

7. Follow-up

Participant follow-up in ePCTs is reliant on existing HCS practices, patient-level transitions and reporting, continuity of care, and completeness of administrative secondary data sources (e.g., claims). To the extent that disparities already exist in these entities, they have the potential to translate into differential follow-up among minorities and potentially affect the validity of the trial results in these groups. Moreover, differences in mortality among PLWD may influence observed disparities when considering losses to follow-up in ePCTs. These factors should be deliberated in the design of the ePCT as well as its analysis.

8. Primary outcome

Outcomes assessed must be relevant and important to health disparity populations, who should be viewed as key stakeholders in the research design process. In addition, instruments to assess selected outcomes should be translated and validated for use in linguistically and culturally diverse populations. Process evaluation may be important to help understand how evidence-based trials are experienced by diverse populations and how providers deliver interventions to diverse populations.

9. Primary analysis

Leveraging of existing/minimal data collection in ePCTs is likely to obscure important mechanisms of action that may be at play for minority groups in key patient and caregiver-centered outcomes. It is important to do the up-front work with stakeholders to identify important measures and hypothesized mechanisms to supplement collection efforts or, at the very least, acknowledge these data limitations in discussing and framing trial results. Process evaluation—along with other qualitative approaches—can help identify mechanisms and opportunities to improve intervention implementation to meet the needs of diverse populations.⁴⁰ In addition, subgroup analyses hinge on having sufficient participants to enable subgroup comparisons and should be planned for in the design of ePCTs, and pre-specified in the statistical analysis protocol. Optimally, studies need to be powered to allow meaningful examination of effectiveness by race/ethnicity or other groups. If underpowered, analyses may show lack of differences in effectiveness by subgroup when they do in fact exist. Further, subgroup analyses may falsely suggest the intervention is less effective for minorities if there is differential delivery or implementation of the intervention.

Additional considerations

The concept of *Value* as it pertains to ethnic and cultural considerations may not be adequately captured in the PRECIS-2 domains. While the domain of *Primary Outcome* focuses on relevance to participants, this may again fail to consider the relevance across PLWD in randomized HCS. It may be worth scoring interventions on the *Breadth of Value*; that is, relative to burden assumed, a higher score to a set of outcomes relevant to participating HCS, clinicians, PLWD and their caregivers, and lower scores for outcomes relevant to a single or narrow set of stakeholders. In this way, elements of systemic and institutional culture to better characterize health equity may once again be crucial for other aspects of ePCT viability, such as implementation and dissemination, bioethics, appropriate engagement of additional stakeholders, and development of outcomes and technical data.

Research priorities advanced the field of health equity in ePCTs

Achieving health equity in ePCTs should be driven by overarching ethical principles such as social justice and inclusion. Given the nature and complexities of ePCTs, if left unexamined, can undermine access to start-of the art research in real-world settings, and dilute stakeholder preferences around outcomes that matter to them. Good scientific practice includes representation of diverse groups with heterogeneous experiences in dementia assessment, treatment, and delivery of care. Examining heterogeneity—both between groups and within groups—affords scientific advancement by considering putative mechanisms of action that may play a key role in the prevention, treatment, and care of dementia.

Health equity cannot be achieved passively, it requires a concerted investment of resources. However, these investments will yield important gains by resulting in a more inclusive and improved science. ePCTs are central in ensuring that PLWD, their families, and the providers and organizations that serve them, receive focused, timely, and acceptable care. In conducting ePCTs, inclusion of adequate samples of minority groups is a critical design issue that needs to be addressed up-front. Partnering with HCS or agencies that serve larger numbers of ethnic minority or other diverse populations should be considered. This is particularly important given the “evidence vacuum” that exists for many diverse populations. These considerations will have implications for study costs as recruitment of disparities populations will be more resource-intensive but critical to rectify inadequate existing evidence for the efficacy of interventions. Equally critical is the role funders must play to ensure accountability in design strategies to ensure adequate samples of minority groups in ADRD research. These strategies will only be effective insofar as funders and stakeholders are able and willing to enforce health equity goals.

1. Health equity should be addressed in each PRECIS-2 domain and by explicitly addressing health equity at multiple levels (e.g., PLWD and caregivers, frontline providers, HCS) within domains. ePCTs would be encouraged to look at multiple levels of change based on the unit of analysis or intervention and assessing the degree to which health equity was attained.
2. ePCTs have the opportunity to advance the field by extending our knowledge and expanding into underrepresented communities. Study participation exclusions (comorbidities, age, language, health literacy) in traditional efficacy trials do not reflect the complexity of PLWD. Study designs should incorporate and directly address health equity considerations early in the pilot phase to address recruitment and retention, cultural and linguistic considerations, workforce enhancements, and adherence measures. When a gap in evidence exists for underrepresented groups, draw from existing frameworks in the area of implementation science to guide adaptation of evidence-based treatments. This would ideally occur at the pilot-testing stage prior to large-scale implementation.
3. ePCTs should, whenever possible, be sufficiently powered and ensure that all analyses are conducted, reported, and published by sex and race/ethnicity. If these data are collected, they need to be reported. In the same vein, compliance

and regulatory agencies need to hold studies accountable for lack of reporting, and/or reasons for failure to meet diversity and inclusion target accrual goals.

Disparities in quality and access must be monitored in the conduct of ePCTs. Because our knowledge of disparities in healthcare and services for PLWD and family caregivers is still relatively new, this knowledge will help inform the field more broadly. While much of the thinking and discussion centers around minority ethnic populations, achieving health equity for other health disparity populations—rural residents, low SES populations, and sexual and gender minority groups—will require exposition of considerations that may not overlap with those of minority ethnic groups. Future work should consider a broad and intersectional treatment of health equity implications in ePCT design for these important health disparity populations.

As such, the HET of the Collaboratory is well poised to increase the knowledge base to guide, support, and monitor Collaboratory-funded ePCT pilot studies to ensure issues related to health equity are integrated into the design and conduct of research. Pilot awards are the cornerstone of the Collaboratory's activities, and as such, constitute an important group to reach, inform, and train. The HET will be instrumental in developing and disseminating guidance and training materials for pilot awardees related to integrating issues related to health equity into the conduct of ePCTs among PLWD and their caregivers. In addition, the HET will coordinate with other Collaboratory Cores to ensure issues related to health equity are integrated into all aspects of ePCT research for PLWD and their caregivers.

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Table 1:

Considerations in Efficacy vs. Pragmatic Trials Using the PRECIS-2 Framework

| Domain | Efficacy Trial Considerations | Pragmatic Trial Considerations |
|--|---|---|
| Eligibility Criteria <i>Who is selected to participate?</i> | Strict inclusion criteria <i>Health Equity considerations:</i> Strict inclusion criteria may exacerbate exclusion of minority populations (e.g., English speaking, etc.). | Broader, no restrictions on comorbidities with AD/ADRD <i>Health Equity considerations:</i> Minority group inclusion is challenging due to eligibility occurring at HCS. Accurate identification of demographic characteristics in EHR/ admin data is a major challenge. |
| Recruitment <i>How are participants recruited?</i> | Recruit at individual-level <i>Health Equity considerations:</i> Adequate numbers recruited to ensure sufficient sample size using best practices for recruiting minorities. | Recruit at system/cluster-level <i>Health Equity considerations:</i> Ensure HCS/sites serve minority populations willing to participate. |
| Setting <i>Where is trial being done?</i> | Conduct trial in settings conducive to research <i>Health Equity considerations:</i> Study sites conducive to efficacy trial conditions may be less likely to serve minority populations. | Conduct trial in applicable real-world settings <i>Health Equity considerations:</i> Many HCS/sites of care are segregated; assess and ensure sufficient race/ethnic group population in site/system. |
| Organization <i>Expertise/resources needed to deliver intervention?</i> | Modify/impose on clinic workflow <i>Health Equity considerations:</i> Modifying clinic workflow provides opportunities to correct conditions that result in disparities in clinical care. | Use existing clinic workflow <i>Health Equity considerations:</i> Usual clinical workflow may result in a continuation of conditions that give rise to disparities, including potential provider bias. |
| Flexibility (delivery) <i>How should intervention be delivered?</i> | Implementation up to investigators <i>Health Equity considerations:</i> Strict study protocols and fidelity assurance between data collectors limits differential implementation between study subjects. | Implementation up to providers <i>Health Equity considerations:</i> Leaving intervention delivery up to providers may lead to replication of existing disparities in access or quality of care. Background and training of providers may impact delivery. |
| Flexibility (adherence) <i>Measures to ensure participants adhere to intervention?</i> | Adherence specified by investigators <i>Health Equity considerations:</i> In well-designed trials monitoring of adherence to study protocols limits differential implementation between study subjects. | End users decide how to engage with intervention <i>Health Equity considerations:</i> Tailoring or adaptation of evidence-based interventions to diverse populations may be ad hoc or may not occur at all. Adherence to intervention may be uneven as a result. |
| Follow-up <i>How closely are participants followed-up?</i> | Number of follow-ups chosen by investigators <i>Health Equity considerations:</i> Ability to monitor whether minority study participants are more likely to be lost to follow-up during study period. | No more follow-ups than is standard in usual care <i>Health Equity considerations:</i> Unclear if monitoring of minority groups will occur to assess sustained outcome effects or differential rates of attrition/retention in the course of standard/ usual follow-up care. |
| Primary Outcome <i>How relevant is it to participants?</i> | Investigators select outcomes <i>Health Equity considerations:</i> Outcomes are selected by the investigator teams a priori and may or may not be relevant to minority populations. | Select outcome important to all stakeholders <i>Health Equity considerations:</i> Outcomes must be relevant and important to minority populations. Instruments to assess outcomes must be translated and validated for linguistically and culturally diverse groups. |
| Primary Analysis <i>Are all data included?</i> | Consideration of non-adherence, etc. <i>Health Equity considerations:</i> Subgroup analyses may allow for examination of non-adherence and differential implementation. | Intent to treat analysis leveraging existing data or minimal data collection <i>Health Equity considerations:</i> Limited data collection threatens assessment of mechanisms that may differ between minority groups. Subgroup analyses require sufficient minority participants to enable comparisons and |

| Domain | Efficacy Trial Considerations | Pragmatic Trial Considerations |
|--------|-------------------------------|--|
| | | may falsely suggest lower effectiveness for minorities if there is differential delivery/implementation. |

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