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Resources, Methods, and Data Infrastructure to Promote Research in Dementia Care, Caregiving, and Services

Short Running Title: Resources, Methods, and Data in Dementia Research

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Key Points

- Strategies to identify persons living with dementia should fit the research purpose.
- Embedded pragmatic trials are well-suited to dementia research.
- Consent requires capacity assessment and appropriate surrogates when indicated.

Why Does This Matter?

New approaches and data sources hold promise and perils for dementia research.

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Abstract

Background: The National Institute on Aging (NIA), in conjunction with the Department of Health and Human Services as part of the National Alzheimer's Project Act (NAPA), hosted a *2020 Dementia Care, Caregiving, and Services Research Summit Virtual Meeting Series* on August 13, 2020. This paper reflects three presentations related to *Theme 6: Research Resources, Methods, and Data Infrastructure*. Dr. Bynum discussed the challenges of identifying people for population- and health care-based research, including how definitions of dementia have changed over time, the opportunities and challenges inherent in the use of electronic data sources, and the need to fit data collection strategies to research goals and questions. Dr. Travison provided an overview on the growing use of embedded pragmatic clinical trials (ePCTs) and how to enhance their impact in dementia research. Dr. Wendler presented on the ethical considerations relevant to consent for dementia research, including assessment of decisional capacity and the role of decisional surrogates.

Conclusions: The availability of claims data, electronic health records, and other sources of "existing" data have made the use and development of embedded pragmatic clinical trials both easier and more appealing. Among other things, they offer advantages in terms of lower cost and generalizability to real world settings. This is turn has necessitated the use of informatic and analytic approaches to account for some of the limitations and complexities of such data, including multilevel clustering and the need to link and jointly analyze data from the person with dementia and those of their care partner. As part of this process, it will be important to broaden the scope of who is assessed for decisional capacity, make those assessments more study specific, and

assist surrogates in making decisions based on what the individual would have chosen for themselves if capacitated (i.e. substituted judgement).

Keywords

Alzheimer's disease, dementia, health care generated data, decisional capacity, embedded pragmatic trials

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INTRODUCTION

This paper is based on presentations related to *Theme 6: Research Resources, Methods, and Data Infrastructure*, presented on August 13, 2020 as part of the *2020 Dementia Care, Caregiving, and Services Research Summit Virtual Meeting Series* convened by the National Institute on Aging (NIA) in conjunction with the Department of Health and Human Services as part of the National Alzheimer's Project Act (NAPA). The three presentations focused on: 1) identifying people with dementia for population and health care research, 2) opportunities and challenges relating to the use of embedded pragmatic clinical trials in dementia research, and 3) ethical considerations surrounding obtaining consent and using surrogate decision makers in dementia research. Cross-cutting themes include weighing the costs and/or greater convenience of various approaches (e.g., electronic data sources, surrogate decision makers, pragmatic clinical trials) against the need to focus on the overall goals of the research and the needs and desires of persons living with dementia and their care partners (e.g., finding the best Fit to Research).

Identification of People Living with Dementia for Population and Health Care Research

There is no single best approach to identifying persons for dementia-related research studies; rather, the optimal identification strategy will match the overall objectives and individual requirements of the study, such as inclusion and exclusion criteria, costs, and other trade-offs. In other words, the means of identifying research subjects for dementia studies needs to *fit the research purpose*.

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Two overarching types of medical research are population surveillance and health care research (see Figure 1.) The purpose of public health surveillance is to assess public health status, track conditions of public health importance, define public health priorities, evaluate public health programs, assess disparities, identify risk factors, and inform policy development.[1] In population-based research, one first identifies a representative sample and then individuals within the sample are classified as “cases” or “non-cases” based on standard and reproducible diagnostic methods (e.g., blood pressure for the condition of hypertension). Health care research, in contrast, is concerned with how people access and utilize services, including testing new interventions, implementing and disseminating proven interventions, monitoring care quality, and monitoring access to care relevant to underserved and at-risk groups.

Both of these research approaches depend upon, or are focused on determining, the diagnosed prevalence of a condition within a local environment. Medical research uses epidemiological studies to inform more biologically detailed and etiologic studies regarding the nature of a disease. Prevalence data can be used secondarily to focus clinical studies on populations at high risk, or alternatively can use comparisons to the general population to identify disparities in treatment or outcomes and to determine how generalizable a study sample is. For medical care purposes, a key feature of disease prevalence studies and the resulting data is to reflect the local community without bias induced by differences in care seeking. Thus, the foundation of all dementia research then is the accurate determination of who is (and who is not) a person living with dementia.

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Who is a person living with dementia?

In the case of Alzheimer's disease, which has traditionally been defined as a syndrome based upon clinical features, identifying potential research participants involves standardized measures of cognition, physical function and, in some approaches, clinical adjudication by experts. These classification strategies must be both consistent over time and accurately reflect disease characteristics across geographies and diverse populations.

Over the past few decades, however, there have been repeated changes in the clinical guidelines and diagnostic criteria used to define the presence of Alzheimer's disease and related disorders (Figure 2). The diagnostic criteria used to define and identify a disease or condition, as well as the interpretation and operationalization of those criteria in clinical and research settings, necessarily determines the measured incidence and prevalence of that disease or condition. This is especially true for a condition such as dementia, which typically has a gradual onset and variable progression. Determining when cognitive decline has become sufficiently severe to cause limitations in activities of daily living (ADLs) (a key element of most clinical diagnostic criteria) is challenging. Determining when the "dementia threshold" has been crossed leads to variation in case definition and prevalence estimates across clinicians and researchers.

Given the variability in definitions, thresholds, and assessment tools, it is essential to identify the specific features of persons living with dementia that are most important in terms of meeting the purpose of any given study. One study may focus on people with a dementia syndrome, defined by cognitive and functional loss; another

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may center on people with dementia of a specific type or cause, such as Alzheimer's disease or Parkinson's; and yet another may highlight people at risk for developing dementia, such as people with mild cognitive impairment (MCI). These disease constructs are important to distinguish from each other because they often lead to differences in the types and sources of data collection, the researchers' interpretation of findings, and the way stakeholders interpret study results.

Challenges in Identification for Population-Based Studies

Ideally, case identification strategies will result in the final sample being as representative as possible of the targeted population. A truly representative study often needs a large sample, which carries significant expense. Variation in measurement across and within studies is also a challenge. For longitudinal studies, harmonization is extremely important, as nomenclature and diagnostic definitions change over time. It is estimated that 62% of community dementia cases go un-detected, due to stigma, access to care, the belief that cognitive losses are "normal" with aging.[2] Lastly, there remains limited biological data that are determinative of dementia or specific types of dementia. This is particularly the case for racially and ethnically under-represented populations who are less likely to volunteer for studies that require biologic data.[3] A critical first step then in study design is thinking about the disease construct and how it fits with specific study questions being addressed. A second critical step is using clear nomenclature about the chosen construct and understanding how that construct and data processes could impact interpretation. For example, a study may enroll people with the clinical syndrome of dementia which should not be interpreted to be synonymous

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with Alzheimer's Disease only without further evidence of causal type within the study sample.

Table 1 presents the four basic categories of data collection for epidemiological identification of Alzheimer's disease and related dementias, along with the pros and cons of each with regard to precision, cost, risk levels, and recruitment barriers. These are considerations researchers must evaluate when deciding how best to fit their research purpose to their data collection resources.

Challenges in Identification for Health Care-Based Studies

Over time, data obtained through the provision of medical care have become more routinely available. *Administrative claims data* contains information about diagnosis as documented on the bill submitted for payment by clinicians and health care facilities. The *electronic health record* (EHR) can contain billing information, structured medical documentation (e.g., problem lists and past medical history), as well as clinical notes. The potential value and availability of electronic health data has increased with developments in the field of data science. The newest source of information relevant to determining disease risk or prevalence is *biomarker data*, often collected as part of epidemiological research or, more recently, for other clinical studies.

The cost efficiency of using data that are already being collected as a part of routine medical care is attractive, especially in the case of a disease such as dementia that predominantly affects people old enough to qualify for Medicare, which captures 97% of US adults aged 65 and older, but there are other advantages as well. For example, Medicare requires a diagnosis in order to pay a claim, reducing the likelihood

of “missing” diagnostic information. Moreover, Medicare data are centralized with an established process for obtaining access for research purposes.

Challenges remain, however, in the use of health care generated data for research purposes. The most significant, whether for billing or EHR data, is dependence on the clinical process for identifying affected people, as this process has inherent limitations and biases. Many factors can impact the likelihood of a person receiving a diagnosis. These include factors related to the patient (e.g. the person’s symptoms, beliefs about those symptoms, and their access to healthcare), the care partners (e.g., diagnostic skills, experience with the disease, personal biases about the disease, and availability of consultative expertise), the system (e.g., availability of diagnostic technologies and payment for those services), and societal influences (e.g., the benefits and risks of having the disease label). Notably, these factors also change over time and in response to policy changes, such as which services are paid for and how much they cost. Also, while “missing” data is not likely when using diagnostic codes, the prevalence of certain diagnostic codes found in health care data may not reflect true disease prevalence. Similarly, the types of biases present in any given set of healthcare data may not be the same across other data sources or studies.

Finally, while EHR data are timely and cost effective, they are often of poor or uneven quality or carry built-in bias. For example, algorithms used to identify persons living with dementia may have lower accuracy for minority populations and/or those with more limited healthcare access,[3-5] Medicare claims data may not be timely and may have lower sensitivity for early stage disease.[6,7] For this reason, even previously validated definitions and algorithms for identifying populations and outcomes related to

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dementia must be validated again locally (and in each healthcare system) to account for variations across settings and purposes. When data quality issues are discovered, it may be possible to mitigate them by combining with other data, using advanced statistical approaches such as imputation, or by performing sensitivity analyses.

Summary

As new diagnostic approaches and data sources become available, it is essential that researchers carefully consider the issue of how people living with dementia are identified, making sure that these methods work over time and across subpopulations to accurately reflect the prevalence and the experience of being a person with dementia or their care partner. Inexpensive data are actually more costly if the inherent biases lead to incorrect conclusions that end up negatively impacting the lives and well-being of persons with dementia.

Opportunities and Challenges For Embedded, Pragmatic Clinical Trials Among People Living With Dementia And Their Care Partners

Unlike traditional clinical trials, which are separate from clinical care, embedded pragmatic clinical trials (ePCT) are conducted within healthcare systems using existing processes and structures (i.e. “embedded” within routine clinical care). They often utilize randomization of sites and/or providers, and the interventions are implemented by health system personnel through the existing communication and monitoring channels.

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Potential Advantages

The potential advantages of ePCTS are multifold. ePCTs can lower costs and increase efficiency compared to traditional clinical trials. By maximizing the degree to which the results were obtained in real-world conditions, it is reasoned, the applicability of the findings to real world conditions is maximized also. They might, for instance, enforce fewer exclusions, so that individuals who would typically be excluded from participation in medical research are included. In endeavoring to make use of routinely collected data, ePCTs lower the data collection burden, making it easier for the research design to be deployed in diverse and lower-resourced settings, a fact that can also lead to greater consistency with real life circumstance. ePCTs, being pragmatic, may also allow for greater flexibility with regard to participant adherence to intervention.[8,9] While this might be considered a drawback in a traditional trials model (due to, for instance, potential negative effects on fidelity), in a pragmatic trial it is acknowledged that receipt of the intervention by any given end user will vary. Another advantage of ePCTs is that, being so “close” to medical care provision, tend to focus on patient-important outcomes. This increases the relevance of the results to the lives of PLWD and caregivers and potentially also increases willingness to participate in the research. Finally, the close attention to detail that is required to maximize the research/clinical care “fit” when conducting an ePCT brings awareness to the potential tension between these two domains (e.g., the clinical outcomes most relevant to a specific patient population may not be routinely collected). As such, embedding trials within healthcare delivery organizations allows for greater assessment of the effectiveness of healthcare delivery while acknowledging system-level costs and

opportunities, making sure that the costs and benefits of the intervention are explicitly considered.

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Potential Challenges

Hand-in-hand with the benefits of ePCTs come numerous challenges related to the overall research setting and design, measurement, and the interpretation of results. Interventions deployed at the level of institutions or systems are assigned to groups of participants that then necessarily share certain characteristics. The statistical 'clustering' that exists within these patient subsamples can be accommodated by contemporary data-analytic methodology, but the design of ePCTs can be particularly challenging in this regard, as clusters and the experience of patients within them may be highly specific. The so-called cluster-crossover and stepped-wedge trial designs offer possible avenues for ameliorating these challenges; by exposing participant clusters to both intervention and comparison control regimes, these designs facilitate within-group comparisons in a way that classical parallel-group trials cannot. The use of tailored and/or dynamically evolving interventions can further enhance relevance for particular patient subgroups, though they do add complexity.

A key challenge relating to measurement is that subjective states of well-being, which may be quite relevant to PLWD and care partners, are unlikely to be included in the standard medical records, and this can necessitate the addition of primary data collection. For instance, in describing the protocol an ongoing trial of a dementia care model to improve the quality of life of PLWD and their care partners, Bristol and colleagues detail ascertainment of measures of well-being for both PLWD and care

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partners beyond what is readily available in the electronic record. Investigators must balance the appeal of a fully pragmatic approach with the importance of person-centered measures. When data are needed about care partners, researchers will require a mechanism for linking each PLWD to their care partner, a potentially substantial challenge when data are obtained from the electronic record.

With regard to data analysis and interpretation, a potential limitation is that discriminating between mechanisms of action and reasons for heterogeneity of effectiveness across subpopulations can prove difficult. Administrative or other routinely collected data, the use of which may enhance the pragmatism of a design, not capture directly the intervention's primary mechanism, or may be unable to capture patient-important elements of its effectiveness. In some cases, contemporary design and modeling strategies can address these limitations. For example, modeling strategies that explicitly consider the PLWD/care partner dyad and the intervention's effect on each dyad member in light of their interdependence can capture not only these effects, and may shed light on mechanisms of action by charting the evolution of these these effects with time. A downside of such analytical approaches is the need for enrollment of sufficiently large participant groupings.

Summary

ePCTs are highly promising for testing novel interventions to improve the health and well-being of PLWD and their caregivers. However, they are present challenges in obtaining fidelity of interventions and in measuring patient-important effects and outcomes.

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Consent for Research Involving Individuals with Dementia: Some Ethical Challenges

Obtaining appropriate informed consent is critical to ethical research, but special challenges exist in the context of consent for dementia research, especially involving assessment of decisional capacity and determining who qualifies as an appropriate surrogate.

Assessing Decisional Capacity

It is frequently assumed that, absent evidence to the contrary, adults are able to consent for themselves. Standard approaches for assessing the ability to consent therefore tend to focus on individuals perceived to be at risk for decisional incapacity. The U.S. National Bioethics Advisory Commission, for example, recommends assessing potential subjects who suffer from "mental disorders that may affect their decision-making capacity."[10] Using this type of approach, members of at-risk groups receive formal assessment while others receive little, if any, assessment. This approach raises three ethical concerns. First, ethical research requires that individuals actually *give* valid consent, not simply that they have the capacity to do so. This distinction is important because individuals who have decisional capacity can still fail to give valid consent, often as a result of failing to understand material aspects of the proposed research, such as the risks or the alternatives. Second, this approach often does not define who is "sufficiently at risk" to merit a capacity assessment, a shortfall that will inevitably lead to the arbitrary targeting of some groups over others. Third and relatedly, such arbitrary targeting has the potential to stigmatize certain groups. A better approach may therefore

be to assess everyone, whether they fall into a predefined at-risk group or not, to ensure they give valid consent, and to do so prior to enrollment and periodically thereafter.[11]

Choosing an appropriate method for assessing whether individuals provide valid consent is also important, because diagnoses and standardized tests of cognitive capacity (e.g., Mini Mental State Examination) have been shown to be poor arbiters of decisional capacity.[12-13] These assessments should be functional and study-specific. That is, individuals should be assessed to determine whether they have the functional capacity to consent to the specific study in question. Independent of the specific disease etiology, this requires that the individual understands the material aspects of the study, including the risks, potential benefits and alternatives, is able to make a reasoned decision regarding enrollment and continued participation based on their preferences and values, and is able to communicate this decision. The nature and extent of this assessment should be tailored to the study's risk-benefit profile. For example, for a minimal risk study, an investigator might simply ask potential participants why they want to enroll in the study, engaging in more in-depth follow-up only when an individual's response raises concern. Increasingly formal and in-depth assessments should be used as the risks of participation increase and the potential benefits decrease. For studies that pose significant risks without the potential for clinical benefit, researchers should consider having the evaluation conducted by someone independent of the research team.

Because comprehension can be influenced by a range of factors (e.g., quality of the explanation, time of day, level of anxiety, comfort with the setting), researchers should prospectively take steps to increase the chances that a person will be able to

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provide valid consent. This might include conducting the assessment in a comfortable and private setting after the study has been explained to the individual. Moreover, when individuals are found not able to consent, assessors should consider whether a change in one or more of these factors might make a difference, such as conducting the assessment when the individual is more rested or providing additional explanation of the information they did not understand the first time.

Finally, while assessment of decisional capacity typically focuses on research subjects, the decisional capacity of their surrogates should be considered as well, as they are a critical safeguard to the conduct of ethical research.

Identifying Appropriate Surrogates

A finding that individuals lack decisional capacity raises concern that investigators might enroll them in studies that conflict with their preferences and values. To address this concern, individuals who lack decisional capacity should be protected against “unwanted” research involvement. Existing data suggest that, in the presence of an appropriate surrogate, many (but not all) individuals are willing to participate in research even after they lose decisional capacity, especially when the risk/benefit ratio of the research is favorable for them.[14-18] Appropriate surrogates are those who know the individual well and use substituted judgement, wherein the surrogate attempts to make decisions based on their best understanding of what the individual who lacks capacity would have chosen for themselves had they retained capacity. Substituted judgement is enhanced when individuals are encouraged to document their preferences and values as much as possible during the early stages of the illness. While most

advance directive forms focus on documenting preferences regarding clinical care, some explicitly solicit preferences regarding research participation (e.g., NIH Advance Directive) and others permit the inclusion of research preferences.

Rather than relying on surrogates, some commentators advocate “supported” decision-making, in which individuals with decisional incapacity retain the authority to make their own decisions with the support of advisors.[19] These recommendations are based on the claim that all individuals, independent of capacity level, have a right to make their own decisions. However, this view is controversial and its application to clinical trials requires future research. Recommendations have also been made to engage surrogates early on in decision-making, before decisional capacity has been lost, and to then keep them involved for the duration of the study. Via this “seamless” approach, the person losing capacity will be eased into the loss, rather than having an abrupt and potentially emotionally stressful change from making their own decisions to being explicitly notified that they no longer are able to make decisions for themselves.[20]

Summary

The consent of all research subjects should be assessed, not just selected “at-risk” populations. These assessments should be conducted in ways that maximize the chances that a person is able to provide valid consent. They also should not rely on standard cognitive tests, but rather should be tailored to the specific study in question. When they are needed, surrogates should be familiar with the person’s preferences and values and use substituted judgement to make decisions for incapacitated individuals.

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DISCUSSION

There are many new and exciting changes in the field of dementia research, including wider use of extant data and embedding clinical trials within routine medical care. While promising in terms of lower costs, enrollment flexibility, diversity of setting deployment, and flexibility in intervention adherence, we cannot as a field lose sight of key issues such as case identification and ensuring that the research is conducted in an ethical manner. For some of the complexities involved in these contemporary designs, new modeling strategies and data capture methods may boost the ability of researchers to more accurately identify cases (and dyads) and estimate the heterogeneity of effects, including over time. Close attention to the relevance of these design features to the patient population, setting, and clinical problem will, as always, do much to determine the eventual success or failure of the research endeavor.

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Figure 1. Diversity of Research Purpose

Figure 2. Who is a Person Living with Dementia?

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Table 1. Epidemiologic Identification Strategies and their Pros and Cons

	Dementia Syndrome	Alzheimer's vs Other Etiology	Mild Cognitive Impairment vs Dementia	Biological Alzheimer's Disease
Measurement Requirements				
Objective cognitive performance	x	x	x	-
Role or IADL/ADL function	x	x	x	-
Clinical evaluation	-	x	+/-	-
Biological markers	-	-	-	x
Data Collection Considerations				
Diagnostic precision	Low	Higher	Low	Uncertain
Cost	Low	High	Low/high	Highest
Risk to participant (ethics)	Low	Low	Low	Higher
Recruitment barriers (diversity)	Low	Medium	Low	High

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Population / Epidemiology Research
• Measure burden of disease • Assess disparities • Identify risk factors • Inform etiology • Inform policy development

Health Care Settings Research
• Test new interventions • Implement and disseminate proven interventions • Monitor quality care improvement interventions

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