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Informed consent, therapeutic misconception, and clinical trials for Alzheimer's disease

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Introduction to informed consent and therapeutic misconception

A cornerstone of research ethics is the principle of respect-for-persons, by which people who enroll in research trials are supplied with the necessary information so that they can make an informed and voluntary decision regarding their enrollment in the trial.[1] This concept of respect-for-persons has been formalized in the process of informed consent: prior to enrolling in a trial, potential research participants review an institutional review board-approved consent form describing the purpose of the study, risks, benefits, etc. and have the opportunity to ask research staff clarifying questions.[2] If a potential research participant does not possess the capacity to make an informed decision (e.g., children, incapacitated adults), a legally authorized representative can provide informed consent for enrollment in the trial.[3] The process of informed consent is generally achieved via research staff providing adequate information to a person with decision-making capacity and then that person using an understanding of the information to make a voluntary and rational decision about enrollment in the trial.[2]

Concern has been raised, however, that some research participants confuse participation in research trials with routine clinical care. This concept has been described as the "therapeutic misconception" and was first articulated by Appelbaum and colleagues in the 1980s.[4] As patients, people expect a level of personal care where their physicians primarily address the patients' particular needs with a goal of providing individually optimal care.[2] Such optimal care may involve treatment recommendations based on a person's individual circumstances (e.g., past treatments, family history, idiosyncrasies of person's history), dosage adjustments based on individual responses (e.g., dose increase if suboptimal response, dose decrease if intolerable side effects), maintenance of treatment when regimen proves satisfactory, and treatments with relatively well established efficacy and safety profiles.[1,4]

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Research trials, however, are not designed to provide individualized care; the goals are always scientific with an aim of producing generalizable knowledge.[5] Indeed, the protocols of research trials may be directly at odds with the clinical expectation of personalized care: research participants may be assigned to treatment arms randomly, not necessarily based on what treatment may be best suited to their needs; the trial may be double-blinded so that neither researcher or participant are aware of what the participant is receiving; dosing of study medication may be set by the protocol, not the individual participant's response; concomitant medications may be restricted; study medications may be discontinued at the completion of trial, regardless of whether the participant has benefitted; and placebo may be used to improve the scientific assessment, not the participant's condition.[1,2,6] Although there has been controversy regarding a consensus definition, therapeutic misconception is then thought to include beliefs that research protocols will be individualized to the personal needs of the participant, unrealistic expectations of personal benefit through participation in the research trial, and a failure to understand that the primary goal of research is pursuit of generalizable knowledge, not personal care.[5,7]

Therapeutic misconception has been evaluated and confirmed in a variety of clinical trial settings, with some studies evidencing therapeutic misconception in greater than 50% of trial participants.[8] Using close-ended and open-ended questioning as well as qualitative and quantitative analyses, evidence for therapeutic misconception has been found in phase I to phase III trials in diverse research populations ranging from depression to heart disease to cancer.[9–11] For example in an interview-based study of 220 participants enrolled in 84 varied clinical trials (36% hematology/oncology, 18% psychiatry, 46% other), 25% of participants demonstrated therapeutic misconception with respect to individualization of the research protocol, 35% with respect to expected benefit of participation in the trial, and 15% with respect to primary purpose of the study as helping study participants (overall evidence for any therapeutic misconception was 51% of study participants).[12] Factors associated with higher levels of therapeutic misconception include advancing age, less formal education, severity of illness, severity of cognitive deficits, and poor prognosis.[10,13,14]

Decision-making in clinical trials for Alzheimer's disease

Neuropathologically, Alzheimer's disease is characterized by accumulation of abnormal proteins in the brain, notably cerebral plaques (beta-amyloid protein) and neurofibrillary tangles (hyper-phosphorylated tau protein), which ultimately leads to loss of neurons and synapses.[15] Alzheimer's disease is the most common cause of dementia (or major neurocognitive disorder), a devastating terminal illness characterized by neurodegeneration, progressive cognitive impairment, and increasing functional dependence.[16] Treatment options for Alzheimer's disease are limited, and there are currently only two classes of medications approved by the Food and Drug Administration (FDA): cholinesterase inhibitors (e.g., donepezil, rivastigmine, and galantamine) and the N-methyl-d-aspartate receptor antagonist memantine.[15] At best, these medications have shown modest symptomatic improvements in cognitive functioning, daily functioning, and behavior but do little to slow the cognitive and functional decline.[15,17] As the number of people with Alzheimer's disease in the United States is expected to increase from about 6 million to approximately 14 million by the year 2050 with costs of care increasing from around $290

billion to $1.1 trillion in that time frame, there has never been a more urgent need for treatment that can slow or reverse the Alzheimer's disease process.[18]

Significant resources and funding are being devoted to clinical research trials to identify better symptomatic treatments and ultimately disease-modifying treatments for Alzheimer's disease.[19] These clinical trials rely on adequate enrollment of people with Alzheimer's disease, which presents an ethical challenge with respect to informed consent as the progressive cognitive impairment of the disease can affect decisional capacity.[19,20] Given concerns about ability to provide informed consent, it has become common practice for surrogate decision-makers to provide proxy consent for the enrollment of people with Alzheimer's disease in clinical trials, although there can be considerable variability in the application of this practice.[21] For enrollment in a clinical trial via proxy consent, the person with Alzheimer's disease then typically provides assent, which has been defined as evidence of agreement to participate and a minimal level of understanding, although there is no consensus definition.[22,23]

To guide surrogate decision-makers, there is a commonly accepted hierarchy of standards for proxy decisions: 1) explicitly stated wishes of the person (e.g., advance directives); if wishes are unknown, then 2) substituted judgment (e.g., what the person would have chosen if capable based on the person's values, beliefs, past decisions); if the surrogate is not able to make a substituted judgment as preferences are unknown, then 3) best interests (e.g., what appears to maximize benefit for the person).[24,25] When confronted with decisions for a person with dementia such as stopping driving, moving into long-term care, and end-of-life care, it appears that surrogate decision-makers aim to strike a balance between respecting the perceived wishes of the person with dementia (e.g., substituted judgment) and providing for the best interests of the person given the current state of disease progression.[26] It has also been shown that when making medical decisions for a person with advanced dementia, surrogate decision-makers preferentially use a best interests standard (57% of respondents) or see no difference between substituted judgment and best interests standards (37% of respondents).[27]

In focusing more on the decision to enroll in clinical trials for Alzheimer's disease, it appears that there is similarly a complex interplay between substituted judgment and best interests standards.[25] For example in a study of one treatment trial, the majority of surrogate decision-makers (82% of respondents) reported using the stated preferences of the person with dementia or a substituted judgment standard in making the decision to enroll,[28] whereas other studies showed surrogate decision-makers primarily using a best interests standard or some combination of best interests and substituted judgment standards in deciding to enroll a person with dementia in a research trial.[20,29] Common reasons given for enrollment in a clinical trial for Alzheimer's disease include possibility of direct medical benefit to the participant, a sense of altruism in helping others, trust in the clinician/principal investigator and study site, as well as frank desperation given the very limited treatment options currently available.[20,28,30]

A hope for direct medical benefit from participation in a trial does not necessarily indicate therapeutic misconception; for instance, one may express optimism for a therapeutic benefit

while demonstrating an understanding of the primary research goals and focus of participation in a clinical trial, although there is some controversy about what constitutes a "reasonable" amount of optimism.[11,31] Thus far, there has not been any work explicitly investigating therapeutic misconception in the context of clinical trials for Alzheimer's disease.[32] There is significant concern, however, about therapeutic misconception impacting the process of informed consent given known risk factors prevalent in this population including advancing age, cognitive impairment, and poor prognosis with no disease-modifying treatments available.

Current status of clinical trials for Alzheimer's disease

There has not been a new treatment for Alzheimer's disease approved by the FDA since memantine was approved in 2003.[33] In a 2018 review of the pipeline for drug development for Alzheimer's disease, it was noted that there were currently more than 100 agents being studied in phase I to phase III trials in diverse participant populations from cognitively normal to prodromal Alzheimer's disease to dementia due to Alzheimer's disease; the majority of these agents (63%) were noted to be putative disease-modifying therapies (i.e., prevent/delay onset or slow progression of disease).[34] These therapies have a variety of mechanisms of action, but the majority of agents work through anti-amyloid or anti-tau mechanisms.[34] Although clinical trials have shifted more toward participants with preclinical or prodromal stages of disease and have increasingly used biomarker data, there remains an urgent need to develop effective treatments.[34]

The failure rate for clinical trials for Alzheimer's diseases has been estimated at 97% and there have been a number of high-profile trial failures recently.[35] For example, solanezumab, an anti-amyloid therapy, did not significantly affect cognitive decline in participants with mild dementia due to Alzheimer's disease,[36] and verubecestat, an anti-amyloid therapy, did not significantly improve clinical dementia ratings in participants with prodromal Alzheimer's disease and may have worsened cognitive and daily function for some participants.[37] Aducanumab, an anti-amyloid therapy, did not appear to significantly affect cognitive decline in participants with mild dementia due to Alzheimer's disease, although more recent data may suggest a reduction in clinical decline for people with Alzheimer's disease.[38,39] The point here is not to offer further explanation as to the reasons for the failure of these trials (see reference[38] for an example of such a discussion) but to highlight the complex decisional framework underlying enrollment in a clinical trials for Alzheimer's disease where desperation and misconception may inadvertently increase the exposure to risk for this vulnerable population.

How should we think about informed consent for people with Alzheimer's disease?

One of the main concerns raised thus far in this paper has been the infiltration of a therapeutic misconception into the informed consent process for enrollment of a person with Alzheimer's disease into a clinical trial. The concern here is an overestimation of potential benefit with a simultaneous underestimation of the potential risks. Indeed, it has been found that some surrogate decision-makers were willing to enroll a person with Alzheimer's

disease in a clinical trial before receiving any detailed information about the study; such surrogate decision-makers cited desperation and trust in the team conducting the research, essentially minimizing research-associated risks for the participant.[28] In thinking about optimizing informed consent with the goal of moving toward a more realistic assessment of benefits and risks, we can begin to put together an evidence-based, person-centered approach incorporating published qualitative and quantitative data from people with Alzheimer's disease and their surrogate-decision makers as well as expert opinion and consensus.

Who:

The informed consent process should include both the participant with Alzheimer's disease as well as a study partner. For participants with cognitive impairment due to Alzheimer's disease who do not demonstrate decisional capacity, the inclusion of a study partner allows for informed consent through a surrogate decision-maker.[25] Although there is only ever one designated decision-maker, either the person with Alzheimer's disease if deemed to have decisional capacity or the activated surrogate decision-maker if the person with Alzheimer's disease is deemed to lack decisional capacity, it appears that the decision to enroll in a trial is usually a shared decision between the participant and study partner.[30] Given the progressive nature of Alzheimer's disease, decisional capacity should be assessed regularly throughout the course of the trial to assure that the identified decision-maker continues to demonstrate decision-making capacity.

Additionally, it has been argued that to ensure safety for the participant, study partners should also be enrolled and involved in the consent process for participants with preclinical stages of Alzheimer's disease, even though the participants, by definition, do not yet demonstrate cognitive or functional impairment due to underlying Alzheimer's disease at the time of enrollment.[40] This dyadic approach to informed consent makes sense not only from a bioethical and a safety perspective but also from a risks/benefits perspective; for instance, surrogate decision-makers often do not differentiate between risks and benefits from trial enrollment between themselves and the participant with Alzheimer's disease.[28]

How:

With respect to the approach guiding informed consent provided by a surrogate decision-maker, the commonly accepted gold-standard is a substituted judgment. It appears, however, that there is a more complex interplay between a substituted judgment standard and a best interests standard in surrogate decision-making for people Alzheimer's disease, with some surrogates essentially seeing no difference between the two approaches.[27] Evidence suggests that some proxies operate with a more fluid and flexible approach to surrogate decision-making that incorporates an understanding of both past premorbid preferences and current wishes as well as an appreciation for the best interests of the participant based on knowledge of the daily routine and tolerance for various tasks and procedures.[25]

This isn't to say that consenting clinicians should then be more rigid in their approach to proxy consent with surrogate decision-makers, e.g., "will you be using a substituted judgment standard or a best interests standard today?" The idea here is that a pure

substituted judgment standard or a pure best interests standard are often insufficient as guides for surrogate decision-making for people with dementia due to the heterogeneity and complexity of the disease process; indeed, it has been argued that more narrative, longitudinal approaches to surrogate decision-making may be optimal for people with dementia by allowing for a more flexible framework as well as ongoing direct contribution from the person with dementia.[41] Consenting clinicians should certainly be aware of the bioethical standards for surrogate decision-making but should also be aware of their shortcomings when engaging in the consent process with proxies so that there is space for discussion of past and current preferences of the person with dementia as well as discussion of how participation in a trial could impact current quality of life.

What:

Clinical trials for Alzheimer's disease are typically randomized, double-blind, placebo-controlled interventions, so there is usually more than minimal risk to participation for the person with Alzheimer's disease.[19] As clinical trials are shifting further into preclinical and prodromal states of disease, there is concern then that the trials will last longer with an increased exposure of participants to the risks as well as the procedural burden of the trials.[42] Certainly, a discussion of the risks and benefits of participation in a trial is an essential part of the informed consent process, but it is not clear how the consenting clinician should engage the participant and proxy in a realistic discussion of risk when the clinical therapeutic window for the intervention and the subsequent exposure to risk and burden of the trial are essentially unknown.

Given the unclear risk profile of trial participation in the setting of a purported desperation for any intervention that might provide a chance for symptomatic benefit, a more comprehensive approach to the consent process would be to assume some level of therapeutic misconception and tackle that head-on in the informed consent process with potential participants and proxies. Such an approach would not minimize the possibility of some direct benefit through trial participation but would more clearly couch the informed consent discussion in the broader scope of the research goals and methodology of the trial and the associated risks, disadvantages, and burdens of participation. The goal here is to maximize the autonomy of the people with Alzheimer's disease to protect their best interests and to minimize the risk of exploitation through trial participation.[4,6]

How then should we approach the informed consent discussion with an aim of minimizing any putative therapeutic misconception? A first step would be to focus on the investigators, who may themselves also be influenced by a therapeutic misconception.[6] Clinician-investigators may have conflicting interests with respect to enrollment of a person with Alzheimer's disease in a clinical trial: patients and clinicians often converge on the goals of personalized medical care to address the patients' individual needs whereas research participants and investigators may diverge on the goals of participation in a clinical trial with participants seeking direct benefit and investigators seeking generalizable, scientific data.[6] If clinician-investigators conflate participation in a clinical trial with individualized medical care, clinician-investigators may see research as a means to address patients' specific clinical

needs, inadvertently exposing participants to harm under the guise of promoting best interests.[6]

Clinician-investigators should be clear in their own minds that research is not equivalent to medical care. This can be formalized in keeping a distinct boundary between the research teams and the clinical teams and their respective goals. Consenting clinicians-investigators should make clear to potential participants and their proxies that the over-arching goal of the study is for the investigator to collaborate with the participant and proxy in pursuit of science not for a clinician to collaborate with a patient in the pursuit of the patient's individualized medical best interests; practically speaking, the clinician-investigator should remain independent of and neutral in the participant's ongoing medical care.[4,6] This is not to say that trial procedures should not inform routine clinical care (e.g., identifying hypothyroidism on safety lab screening as part of the trial), but that independence should remain between the research team and the personal clinical team, particularly in instances where study data are communicated to the primary clinical team to follow-up and provide individualized medical care if warranted. If there is not primary medical care in place, participants should be referred at the start of the trial.

In focusing on the participants and proxies, attention should be paid to minimizing therapeutic misconception for both as the decision to enroll in a trial is usually a shared process, and a therapeutic misconception could then theoretically influence participants and/or proxies in the decision-making process.[30] A number of approaches have been advanced to further optimize decision-making for clinical trial enrollment for people with Alzheimer's disease with a goal of maximizing autonomy as well as protection from harm.[43] For example in a group of participants with mild to moderate dementia due to Alzheimer's disease, an enhanced consent procedure was trialed using a multimedia approach with video clips as well as corrective feedback.[43] Although this enhanced consent procedure did not show significant benefit with respect to comprehension and decisional capacity, this procedure highlights a creative, person-centered approach to informed consent for people with Alzheimer's disease.[43]

Other approaches to minimize a therapeutic misconception include paying participants who volunteer for a trial to make a clearer distinction between research participation and regular medical care, in which patients are not routinely paid.[6] Paying participants raises concern for coercion, however, particularly given the potential for diminished decisional capacity for people with Alzheimer's disease, but the idea here is that enrollment procedures can be modified to highlight the research focus of the trial.[6] In that vein, it has been argued that potential participants should be asked to explicitly state their motivation for enrolling in a trial, which opens an avenue for conversation and clarification of the research goals of the study by the consenting clinician; proxies could similarly be asked to clarify their motivation in pursuing a clinical trial for a person with Alzheimer's disease.[31]

Conclusions

As the population gets older, fueled by the aging Baby Boomer generation, there will be an unprecedented increase in the emotional, functional, and financial impact of Alzheimer's

disease on patients and their families.[40,44] There are currently no disease-modifying therapies available to reverse or even slow down the Alzheimer's disease process, and significant resources are being devoted to clinical trials to identify targeted therapies for Alzheimer's disease. A critical aspect of a successful clinical trial is obviously adequate enrollment of participants with Alzheimer's disease. Enrollment is complicated in this population, however, by the variable decision-making capacity of people with Alzheimer's disease as well as desperation for any potential therapeutic benefit given the devastating, inevitable decline of the disease.

The concern raised here is that this population is particularly vulnerable to a therapeutic misconception whereby there is conflation of routine clinical care and scientific research such that the informed consent process is compromised, inadvertently exposing this vulnerable population to an under-appreciated level of risk through trial participation. As there is currently no data on therapeutic misconception with respect to Alzheimer's disease clinical trials, a first step would be to more explicitly investigate the motivations for and understanding of clinical trial enrollment with respect to therapeutic misconception for participants and their proxies. This could be done through qualitative interviews of participants and proxies and/or standardized quantitative measurements of therapeutic misconception.[12]

This paper argues for a more comprehensive approach to the informed consent process to proactively minimize a putative therapeutic misconception in which people with Alzheimer's disease and their proxies are enrolled simultaneously in the trial, a flexible approach to surrogate decision-making is used to explore past preferences as well as current interests of the person with Alzheimer's disease, and the research focus of trial participation is explicitly highlighted throughout the consent process. This approach is not meant to dissuade potential research participants or to make the enrollment process more cumbersome. On the contrary, a more comprehensive informed consent process that accounts for the uniqueness of Alzheimer's disease should allow for a more productive and clear relationship between researchers and participants and a minimization of potential harms and burdens for this vulnerable population. The hope here is that communication of more clearly stated expectations of trial participation for people with Alzheimer's disease and their proxies will enhance both recruitment and ultimately retention in the trial, improving the power of and satisfaction in the research endeavor.

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Key points:

1. As there are no available disease-modifying therapies for Alzheimer's disease, large-scale clinical trials are being pursued to identify novel therapies; enrollment is complicated, however, by the variable decision-making capacity of people with Alzheimer's disease as well as desperation for any therapeutic benefit.
2. This paper argues that people with Alzheimer's disease are vulnerable to a therapeutic misconception: conflation of routine clinical care and scientific research, inadvertently exposing this vulnerable population to an under-appreciated level of risk.
3. A comprehensive approach to the informed consent process is described in which people with Alzheimer's disease and their proxies are both enrolled, a flexible approach to surrogate decision-making is used to explore past preferences as well as current interests of the person with Alzheimer's disease, and the research focus of trial participation is explicitly highlighted throughout.