

Perspective

Recruiting to preclinical Alzheimer's disease clinical trials through registries

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Abstract

Participant registries are repositories of individuals who have expressed willingness to learn about studies for which they may be eligible. Registries are increasingly being used to improve recruitment to preclinical Alzheimer's disease (AD) clinical trials, which require large screening efforts to identify adequate numbers of participants who meet enrollment criteria. Recruiting to preclinical AD trials from registries is made more efficient through registry collection of data that permits exclusion of those who will not be eligible and identifies individuals most likely to qualify for trials. Such data could include self-reported disease family history or other risk factors but could also include cognitive, genetic, or biomarker testing outcomes. Few data are available to guide investigators overseeing registries and important ethical questions are likely to arise related to their conduct, especially in registries collecting AD risk information. This article outlines three areas of consideration for registry investigators: informed consent, disclosure, and sponsorship.

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Keywords:

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1. Introduction

Slow recruitment to clinical trials is a consistent barrier to developing improved treatments for Alzheimer's disease (AD) [1–3]. Few interventions have demonstrated effectiveness for improving AD trial recruitment [4]. Potential participant registries are increasingly common interventions that aim to address this challenge by creating repositories of individuals who can be recruited at the start of a new trial [4–9]. Registries represent a potentially important strategy to address the large participant needs of preclinical AD trials [7], which recruit otherwise healthy individuals who are at increased risk to develop cognitive impairment and dementia based on genetic or biomarker criteria [10].

Some registries consist of databases of contact information, allowing investigators to inform large number of

potential participants of new trials rather than (or in addition to) serially engaging in community outreach, social and popular media campaigns, and other forms of recruitment [9]. Other registries include self-reported health information or prospective assessments of cognitive performance. With these data, investigators can prioritize recruitment based on age, family history, previous medical history, or even subjective changes in cognitive performance, all of which may be associated with meeting preclinical AD trial eligibility criteria [11,12]. Within a given health system, registries may link to electronic medical records to access diagnostic and medication information, allowing investigators to more efficiently exclude ineligible participants [13]. Registries may even perform cognitive, genetic, or biomarker testing to identify participants meeting preclinical AD criteria [14,15]. For example, an AD prevention trial is underway that is enrolling apolipoprotein E (*APOE*) $\epsilon 4$ homozygotes specifically [16,17], and eligible participants could be directly identified in registries that perform genetic testing.

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Regardless of the registry model, bigger is better. Greater number of registrants increases the number of potentially eligible trial participants who can be recruited and should expedite the rate of enrollment in preclinical AD trials. Given the increasing number of preclinical AD trials [16,17], national and international efforts are underway to use registries to enrich cohort studies that perform deep phenotyping of participants, including biomarker testing, and can serve as feeders to preclinical AD trials [7]. The “registry-to-cohort” model is being implemented by multinational efforts to enhance the conduct of preclinical AD drug development, such as the European Prevention Alzheimer’s Dementia and the Global Alzheimer’s Platform [7,18] (<http://www.alzforum.org/news/conference-coverage/coming-center-near-you-gap-and-epad-revamp-alzheimers-trials>).

As more registries are initiated, a variety of important questions may arise. Few data are available to guide registry design. Participant preferences related to registry operations are largely unknown and experiences with registry conduct remain nascent. There is a need for normative evaluation of the concept, methods, and use of registries as an intervention to improve preclinical AD trial recruitment. A study by Hunter [19] outlines some ethical concerns for the concept of “prerecruitment,” including the means by which individuals may be recruited to registries. The present article considers issues related to registries used to recruit preclinical AD trial participants. Specifically, registry informed consent, disclosure of AD risk information, and registry sponsorship are discussed (Table 1). Because a wide variety of registry types and methods exist, not all issues raised in this perspective will be applicable to all registries. Nonetheless, the aim of this manuscript is to enhance the discussion around the optimal means to use registries to improve recruitment to preclinical AD trials.

2. Informed consent

Adequate informed consent is generally considered an essential element of ethical research [25]. But which registries should be considered research and which should not? Registries that collect only email or mailing addresses for the purpose of broadly disseminating study announcements may not require ethical review or informed consent. Registries that collect data to instruct trial recruitment, however, may need a consent process, even if the purpose of that data is not to gain knowledge *per se* but rather to facilitate studies that will. The collection and storage of data may carry risks even if data are related only to disease family history or self-reported health information. Disclosing those risks and positioning the potential enrollee to decide if they are willing to absorb them via an informed consent process may be necessary for these registries.

Informed consent is a process, not a document. Consent may be indicated in a variety of ways, including

signing a written form, orally expressing consent, or through voluntary actions [26]. Ethical [26] and regulatory [27] guidelines agree that a review board may grant a waiver of signed consent if the associated risks are no more than minimal. Minimal risk is generally defined as not greater than that associated with routine medical or psychological examination and not requiring written consent outside the research context. But when is the risk associated with enrolling in a registry minimal and when should written in-person informed consent be required?

The Declaration of Helsinki states that although only documentation of informed consent is a requirement, signed written informed consent is preferable [20]. Thus, registries that use fluid or neuroimaging biomarker information such as amyloid positron emission tomography (PET) and cerebrospinal fluid analysis [10], which require in-person visits for data collection, should implement written informed consent. The need for written consent is underscored, given that the collection and storage of biomarker information carries ethical and legal risks that must be addressed in these consent documents to ensure autonomous decision making—including the decision not to enroll for some. These risks have been described more fully elsewhere, as they relate to preclinical AD trials [28–32]. The potential loss of confidentiality and the lack of legal protections against discrimination by insurers and other outside entities could result in harm to registry participants [28]. Unwanted disclosure of AD risk information could result in stigma in the workplace, the clinic, and the home for registrants [29,32].

Securing written in-person informed consent from the very large samples that will need to be enrolled in registries to facilitate preclinical AD trials may not be feasible [18]. Altered methods may ensure practicability when still adhering to the requirements of ethical research [33]. Internet-based registries, for example, may represent a realistic means to establish adequately large populations of willing participants, although there may be risks associated with electronic consent such as participants rapidly scrolling or clicking through consent documents and blithely clicking “enroll,” as they might with a new smart phone application [34]. Comprehension and retention of consent information may differ for screen-based, compared with paper-based, learning [35]. The opportunity to have questions answered may be reduced or delayed. Alternatively, electronic consent is likely to enhance opportunities to use videos, graphics, and other multimedia approaches for more concise and creative means to enhance participant understanding while simultaneously reducing participant burden [34]. Automated quizzes may enable assessment of participant understanding. Giving options for more extensive and detailed information may permit some participants to achieve personal requirements for adequate information in less time, whereas still affording others the opportunity for in-depth understanding of registry operations.

Table 1
Potential ethical issues related to recruiting to preclinical Alzheimer's disease (AD) trials from participant registries

| Issue | Potential challenge(s) |
|--|--|
| Informed consent | |
| Is informed consent necessary? | Lists or databases of individuals willing to be contacted about studies may not carry risk for those included, and therefore may not require an informed consent process. If a registry collects data beyond contact information, an assessment of risk must be performed to determine whether informed consent is necessary |
| When is written in-person consent necessary? | Written in-person consent is always preferred [20], but not always feasible. Investigators and ethical review boards must assess the risk/benefit balance to determine whether risk is adequately minimized to allow remote (e.g., electronic) consent for large registries that may still have the capacity to collect, store, and use sensitive information such as genetic testing results |
| Alternate methods of consent may be needed to achieve necessary sample sizes | Alternate methods of consent, such as electronic consent, may have risks related to reduced participant understanding or opportunity to ask questions before enrollment. Alternatively, novel methods such as video consent and online quizzes may enhance the consent process |
| Disclosure | |
| Previously collected biomarker and genetic information can be used to identify participants eligible for preclinical AD trials | Biomarker study consents may not discuss disclosure of results or may indicate that cognitively normal participants will not be told biomarker results. Individuals who may have explicit desire "not to know" may have enrolled and not wish to be told their results or even offered the opportunity |
| | Disclosure of biomarker results to individuals who underwent testing would require a modification of available disclosure processes [21,22], because pretesting education and counseling would not be possible |
| | The manner in which individuals are selected to learn their biomarker results could risk inadvertent disclosure, before proper informed consent, education, and counseling. |
| Safety of disclosure | Few studies, as yet, demonstrate the safety of biomarker result disclosure [23] Technology may enable reduced burden on expert investigators for full disclosure processes, but the extent to which education, counseling, or disclosure can be safely performed remotely remains an area of active study [24] No studies have examined the safety of automated methods of disclosure, as might be used in Internet-based registries implementing cognitive or genetic testing |
| Integrity of disclosed information | For remotely collected cognitive testing data, a large number of variables, such as the testing modality, the setting in which the participant completes the testing, and other health and lifestyle factors, could result in biased testing results |
| Sponsorship | |
| Ethical review | Some sponsors may not consider registries to be research studies and may therefore not pursue review and approval by an ethical review board [19] |
| Therapeutic misconception | Sponsored registries that cover clinical biomarker test costs for the purpose of research recruitment risk patient misunderstanding and conflation of research and clinical care |
| Conflicts of interest | Sponsored registries that cover clinical biomarker test costs potentially place referring physician investigators in conflicts of interest |

Regardless of the manner in which informed consent is achieved, a clear explanation of the registry methods should be provided. It may also be important to set participant expectations, including that many of those enrolling may never be invited to participate in a preclinical AD trial. The European Prevention Alzheimer's Dementia registry-to-cohort initiative will implement a *staged consent model* (Tromp, AAIC 2016). Participants will first consent to a registry, indicating their willingness to participate in research. Subsequently, registrants will be prepared for risk disclosure and consented into a cohort study, should they choose. After education on disclosure and risk, participants will be invited to decide whether they are willing to learn their biomarker status (although disclosure may not be certain to occur) and to enroll into an intervention trial. Novel mechanisms such as staged consent may be necessary to ensure the ethical conduct of these large efforts toward successful preclinical

AD trials. Consenting at once to enroll in a registry, a cohort study, and then a trial may produce too great a burden for participants, especially because only a portion of those enrolled will advance to subsequent steps of the recruitment pipeline. In addition, the progressive experience of participation, first in low-burden low risk modalities such as remote operation registries and then in more involved studies, may help overcome barriers to recruitment and "nudge" participants to enroll in each new phase [36].

3. Disclosure

The most effective registries will efficiently identify participants who are likely to be eligible for preclinical AD trials so that they can be recruited. Regardless of the type of AD risk information collected, registrants may desire, or even expect, that registry information related to their health will be

returned to them [37-39]. Preliminary studies indicate that the opportunity to receive personal testing results will incentivize some participants to enroll [40] and if these results communicate increased AD risk, this may alter the trial decision-making process toward enrollment [41]. Yet, disclosure of research results requires time, expertise, and resources that may not be feasible in very large registries, especially those operating through the Internet. Addressing these complications should begin at enrollment with thorough informed consent. Cautious development of a recruitment process, and in some cases a disclosure process, may be necessary but particularly challenging if in-person visits with experts will not be performed. Information that might be returned to registrants includes the results of biomarker, genetic, and cognitive tests.

3.1. Biomarker testing result disclosure

Despite increasingly common use in the research and clinical settings, wide-scale biomarker testing in registries may be unlikely because of prohibitive costs of neuroimaging [42] and barriers to procedures necessary for cerebrospinal fluid assays [43]. Some registries, however, may operate more like cohort studies, including the collection of serial biomarkers. Using these registries to identify potential enrollees in preclinical AD trials would require caution, because participants may have enrolled in a study in which there was no expectation of sharing biomarker results and because limited data related to the safety of disclosing biomarker results are currently available [23]. Disclosure of biomarker results will require a careful and deliberate process that ideally should begin before performing the biomarker procedure. A process to disclose amyloid PET results was developed for the anti-amyloid treatment in Asymptomatic AD study (A4), a preclinical AD trial enrolling only those with elevated brain amyloid [44]. This process outlines the need for assessing depression and anxiety before biomarker testing and excluding those at risk for adverse reaction to biomarker information; separation in time between informed consent and biomarker testing and between biomarker testing and disclosure; and careful monitoring for adverse psychological outcomes after disclosure [21]. Recruiting trial eligible participants from established biomarker cohorts would necessitate amendment of this process, including predisclosure counseling and education sessions in which participants consent to learning their biomarker results. Some cognitively healthy older people who initially choose to learn AD biomarker results will change their mind after a thorough education and disclosure process [45]. Knowledge that a test has been performed, however, may increase the desire to learn test results [38]. It is unknown whether those participants who would change their mind about disclosure after thorough education still would do so if the biomarker test had already been performed. Investi-

gators disclosing previously collected biomarker data also need to consider who would be invited to learn their biomarker results, because inclusion of only biomarker positive individuals could result in de facto disclosure.

3.2. Genetic testing result disclosure

Tissue collection, genetic testing, and disclosure of results can be performed without an in-person visit. The disclosure of genetic testing results has been the focus of important research for more than the last two decades, including in AD. The Risk Evaluation and Education for AD (REVEAL) study demonstrated the safety of informing individuals with a family history of AD of their *APOE* $\epsilon 4$ genotypes, using a traditional genetic counseling and disclosure process involving multiple in-person predisclosure sessions, including separate education and counseling visits, and in-person postdisclosure counseling with a genetics or medical expert [22]. The associated time and resource burden may limit the ability to incorporate this approach to sharing genetic testing results in large registries. REVEAL II showed that replacing the in-person education session with a mailed brochure is not inferior to the full disclosure process for *APOE* genetic testing [24,46], although this approach still requires two in-person visits (predisclosure and postdisclosure). Technology may be safely used to reduce the counseling burden associated with the traditional approach, including telephone education and counseling [47] and telephonic disclosure of results [48,49]. Results are expected in the near future from REVEAL III, which examined the safety of telephone disclosure of *APOE* status (<https://clinicaltrials.gov/ct2/show/NCT00462917>). The safety of disclosure of genetic results without predisclosure and postdisclosure counseling of some form is unknown, although direct-to-consumer genetic testing companies implemented such a practice, albeit briefly [50].

Genetic disclosure without adequate counseling could have risks. Participants may lack sufficient information to make fully informed decisions to learn their results. For example, federal protections related to genetic information have particular omissions, including that long-term care insurers are not prohibited from using this information when determining eligibility for policies. A system of education and confirmation of participant preferences and understanding would be needed if a registry implemented remote testing and disclosure. In the absence of counseling, participants may lack the support needed to deal psychologically with learning their genetic status, risking harm to registrants, and violating the principle of nonmaleficence. Ten-to-twelve percent of older healthy people report that they would use AD risk information to instruct suicide planning [51-53]. Beyond the risks to individuals, catastrophic reactions, even if rare, would put the scientific value of a registry at risk, because the occurrence could also have regulatory implications to continued registry conduct. To address these risks and facilitate recruitment to

the “Generations study,” a preclinical AD trial enrolling *APOE* $\epsilon 4$ homozygotes, the Alzheimer’s Prevention Registry investigators recently launched GeneMatch, a program to perform *APOE* genotyping in willing registry volunteers. The program uses online interactive educational programming to ensure informed consent before sending cheek swab testing kits to enrollees’ homes. GeneMatch will disclose *APOE* testing results to a subset of those enrolled, including $\epsilon 4$ homozygotes, heterozygotes, and noncarriers, so that the invitation to learn results is not indicative of genetic status. A substudy will also assess the effectiveness of video teleconference versus telephone counseling and disclosure sessions (<http://www.alzforum.org/news/conference-coverage/know-or-not-know-trial-participants-confront-question>).

3.3. Cognitive testing result disclosure

Open and honest discussion of patients’ cognitive performance is a mainstay in dementia care [54]. The use of remote cognitive testing in registries, however, may create unique challenges in sharing cognitive testing results. Online neuropsychological tests are not equivalent to controlled clinical testing, which is free from distraction, slow Internet speed, and potentially variable testing platforms (e.g., desktop computers, tablets, and mobile telephones). Therefore, normative scores for these new methods may be difficult to achieve and there may be a risk for spurious findings. Measuring within-subject change in cognitive performance may circumvent some but not all these challenges, but informing an individual registrant that their cognitive performance has declined has risks. The amount of information that can be provided with testing results is limited, given that clinical (e.g., changes in medications and clinical depression) and technological factors that could affect testing scores may be unknown to registry operators. Participants who demonstrate sufficient cognitive decline to meet the criteria for mild cognitive impairment [7] may need clinical referral before considering recruitment to research to treat reversible causes of cognitive impairment, address decisions around etiologic testing, and assist patients and families with planning (Grill et al., submitted February 1, 2017). Communicating the need for memory assessment to these registrants in an automated manner may risk psychological reaction, refusal of recommendations, and withdrawal from the registry.

4. Sponsorship

Most registries aim to facilitate science rather than test explicit hypotheses. As a result, few registries are sponsored by federal grants. This may introduce a possibility that registries will not be considered human subjects’ research and create a loophole through which some registries accrue potential participants without ethical review [19]. If an academic institution sponsors a registry, it is likely to require

an independent review from an Institutional Review Board. These registries may also be positioned to serve as sources for recruitment to multiple studies and investigators within the institution. Supporting larger number of studies increases the scientific value of a registry, further justifying the associated risks absorbed by those who enroll [25].

Some industry-sponsored registries have begun to cover the cost of clinical amyloid PET imaging for patients who are interested in participating in future clinical trials for that sponsor. Because amyloid PET adds to clinicians’ diagnostic confidence [55] but is not currently reimbursable, physicians may view the opportunity to help patients undergo etiologic testing that they might not otherwise be able to afford as an incentive to enroll families in these registries. This practice raises several important issues. First, the use of clinical testing for the purpose of trial recruitment could conflate research and clinical care and risk confusion or therapeutic misconception among patients and families. Second, clinicians may be put in a potential conflict of interest. The presence of the registry could alter physician behaviors in referring participants to ongoing or future trials because of feeling debt toward the sponsor. To do so would put patients’ autonomy at risk. Third, covering the cost of scans could be interpreted as an attempt by the sponsor to unduly influence these potential participants and may violate the ethical principle of justice and erode trust

Table 2
Unanswered research questions related to participant registries

| Topic | Research question(s) |
|-----------------------------|---|
| Registry design and methods | <ul style="list-style-type: none"> • What registry designs increase willingness to enroll and to remain enrolled until invited to participate in a preclinical AD trial? • What methods will increase willingness of registry participants to participate in preclinical AD trials, if invited? |
| Participant perspective | <ul style="list-style-type: none"> • Do registry enrollees have expectations related to information they will receive as a function of their enrollment or the probability of being invited to participate in a trial? • How might these expectations need to be addressed to ensure optimal retention within the registry and optimal enrollment to preclinical AD trials? |
| Informed consent | <ul style="list-style-type: none"> • Is electronic consent equivalent to in-person written consent in achieving participant comprehension, understanding, and satisfaction with the enrollment process? |
| Disclosure | <ul style="list-style-type: none"> • If participants are enrolled in a cohort study that involves biomarker or genetic testing for which disclosure was not planned, can participants be safely invited to learn their results as a function of recruitment to a preclinical AD trial? • Does the fact that the test was previously performed affect the decision whether to learn results? • Can biomarker, genetic, or cognitive testing results be safely disclosed to registry enrollees? • Can disclosure be safely performed without expert in-person counseling, education, and/or disclosure? |

Abbreviation: AD, Alzheimer’s disease.

among several stakeholders, including physicians, investigators, patients, and families. Finally, covering the cost of clinical scans for cognitively normal participants (e.g., those with a family history or who know they are carriers of the *APOE* $\epsilon 4$ allele) would violate preliminary recommendations made by expert investigators [31,32,56] and sponsored panels [57], which state that until disease-delaying treatments are available and more is understood about the implications of testing results, clinical amyloid imaging should not be performed in people without objective cognitive impairment. If the sponsored registry intends to support preclinical AD trial recruitment, this would necessitate a careful biomarker disclosure process, as discussed previously.

5. Conclusions

Potential participant registries may enable clinical trials to enroll samples with adequate statistical power and therefore may help ensure the ethical conduct of these studies [58]. Challenging issues may arise in the conduct of registries, however, and in recruiting participants to trials from them. Investigators will need to carefully construct and use registries, especially ones that collect AD risk information, to ensure the safety and well-being of potential trial participants. Balance must be struck between collecting data that permit efficient identification and recruitment of potentially eligible participants and management of the risks that will inevitably be associated with increased data collection.

Registries represent an innovative tool in the pursuit of improved preclinical AD trial recruitment. Yet, many questions remain unanswered related to their use. Whether registries effectively expedite preclinical AD trial recruitment or do so in a cost-effective manner is, as yet, unknown. Rigorous examination of registry effectiveness is needed to inform the field whether larger, more coordinated efforts in establishing and using registries is justified. Furthermore, few data are available to instruct the optimal methods of inviting participants to enroll in registries, inviting registrants to enroll in trials, and managing potential risks around registry conduct. Studies to instruct these issues are needed (Table 2) so that investigators know how best to design and use registries, so that sponsors can consider funding registry efforts, and so that preclinical AD trials can be maximally expedited through these potentially valuable tools.

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RESEARCH IN CONTEXT

1. Systematic review: We reviewed the literature using traditional and Internet sources (e.g., PubMed). Few studies examine optimal registry designs or methods, though recent reviews highlight the increasing use of these novel tools to facilitate recruitment to preclinical AD trials.
2. Interpretation: Novel methods of informed consent may be necessary to recruit the sample sizes necessary to support preclinical AD trials. These methods require, as well as facilitate, new means to ensure participant comprehension. Disclosure of genetic, cognitive, or biomarker AD risk information may be possible or even expected by participants and requires careful planning. Regardless of sponsorship, steps must be taken to ensure ethical registry conduct and participant autonomy and safety.
3. Future directions: Research is needed to understand the effectiveness of registries as a recruitment tool, to improve registry design and maximize the efficiency of preclinical AD trial recruitment, and to elucidate the implications of registry methods to participant safety.

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