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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.

Keywords: Recruitment; Preclinical Alzheimer's disease; Clinical trials; Registries

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 systm, 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*) ε4 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.