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The Patient in Your Alzheimer's Disease Study May be in Another: Duplication and Deception in Clinical Trials of Alzheimer's Disease

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Abstract

Duplicate and deceptive subjects, a significant issue in CNS studies, are not often considered in Alzheimer's Disease (AD) clinical trials. However, AD patients and their study partners may be motivated to take advantage of different mechanisms of action, increase odds of receiving active treatment, and/or obtain financial compensation, which may lead them to participate in multiple studies. CTSdatabase reviewed memory loss subjects (n=1087) from January 2017 through May 2019 to determine how many attempted to screen at multiple sites. 117 subjects (10.8%) visited more than one site within two years. When these potential AD subjects went to additional sites, it was predominantly for non-memory indications (often MDD or schizophrenia). For those that participated in studies, the rate of duplication approached 4% of screened AD subjects. This data indicates that significant numbers of AD subjects attempt to enroll at multiple sites, which confounds efficacy and safety signals in clinical trials.

Key words: Professional research subject, deception, duplicate subjects, dual enrollment.

Introduction

Duplicate and professional subjects are well described in many indications, particularly in psychiatry and pain, where subjective endpoints facilitate entry of those who may magnify or falsify symptoms (1, 2). Motivations for participating in multiple studies vary, however financial gain, i.e. collecting research stipends, defines the "professional subject" (3). Duplicate subjects, defined as those that participate in more than one study simultaneously or within a timeframe prohibited by the protocol, may have other motivations (2). Duplicate enrollment affords patients the opportunity to increase their chance of receiving active medication or to take advantage of the different mechanisms of action (MOA) of investigational products available at different sites and in different protocols.

Subject registries, including CTSdatabase (CTS) and Verified Clinical Trials (VCT), are used in clinical trials for both healthy volunteer and patient studies, particularly schizophrenia, Major Depression (MDD), migraine and fibromyalgia. In addition, CTS and VCT can be used together on a single platform, SubjectRegistry.com. Consent for these databases are IRB-approved and presented to the research participant with the study informed consent document (4, 5).

However, use of a subject registry is much less common in studies of Alzheimer's Disease (AD) and other memory indications (as a group, we will refer to all those prescreening or screening for an AD study or memory loss indication as "memory subjects") (6). Many AD researchers may be unaware of or do not recognize the importance of duplicate subjects in their studies. This is alarming given the large number of clinical trials for AD. As of May, 2019, there are more than 400 simultaneous AD clinical trials listed on clinicaltrials.gov, many of which compete for the same subjects (7). If memory subjects participate simultaneously in multiple studies and take more than one investigational product, they may be at increased risk of adverse events. Conversely, if memory subjects do not take their study medications, as is often the case with professional subjects, the study will lose power to detect efficacy (2). In either case, data integrity may be compromised. Therefore we set about to better characterize subject duplication and deception in trials of AD.

Methods

In order to determine if there is currently available data on duplicate and deceptive memory subjects to inform researchers, we performed a literature search using Scopus, Google Scholar, and Medline for publications from Jan 1, 2015 to July 22, 2019. We searched using the keywords: professional research subject, duplicate enrollment, deception and nonadherence. In particular, we looked for information on duplicate and professional subjects in AD studies. To supplement these more recent publications, we used Lee's extensive 2018 review detailing earlier studies (8).

We accessed data from CTS, a subject registry

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containing over 60,000 CNS subjects, and reviewed those screening for memory loss studies (n=1087) between Jan 1, 2017 and May 30, 2019 to determine how many attempted to screen at more than one site. Investigative sites enter subjects' authorized partial identifiers into CTS and an algorithm determines the likelihood that matching identifiers are the same person. When someone is found to be a "virtually certain" match, the odds are less than 1 x 10-7 that the match could be attributed to chance. We analyzed all virtually certain matches that occurred at different (i.e. unique) sites, for the same indication (AD/Memory) as well as for other indications (such as MDD or schizophrenia).

Results

Our literature search combined with Lee's review found over one hundred reports of subject deception, which included concealment, fabrication or collusion (e.g. participants sharing proprietary study information to help gain admission into studies). Of these reports, there was only a single poster specifically addressing duplicate and professional memory subjects (6,8).

CTS identified 1087 subjects who presented for a memory study between Jan 1, 2017 and May 30, 2019. Of these, 117 subjects (10.8%) went to at least one additional site within two years. When these memory study subjects frequented a second site, it was more often for a non-memory indication (most commonly MDD or schizophrenia) than for a memory indication (Fig 1).

The following brief examples are presented here to highlight the issue in AD studies.

Example 1

A 65-year-old woman participating in an AD with Agitation study screened for a Migraine study at a different site. She was screen-failed from the Migraine study, but remained in the AD study. Three weeks later, while still enrolled in the AD study, she screened for a Treatment Resistant Depression study at a third site. All three sites were within a 20 mile radius.

Example 2

A 52-year-old man with several years of progressive memory impairment (MMSE of 24/30 and CDR of 0.5) screened for an AD study in Southern California. He denied any significant medical conditions or any previous clinical trial participation, but his labs showed an ALT/AST three times the upper limit of normal. He was then found to have completed five Healthy Volunteer studies at different clinics, as recently as two months prior.

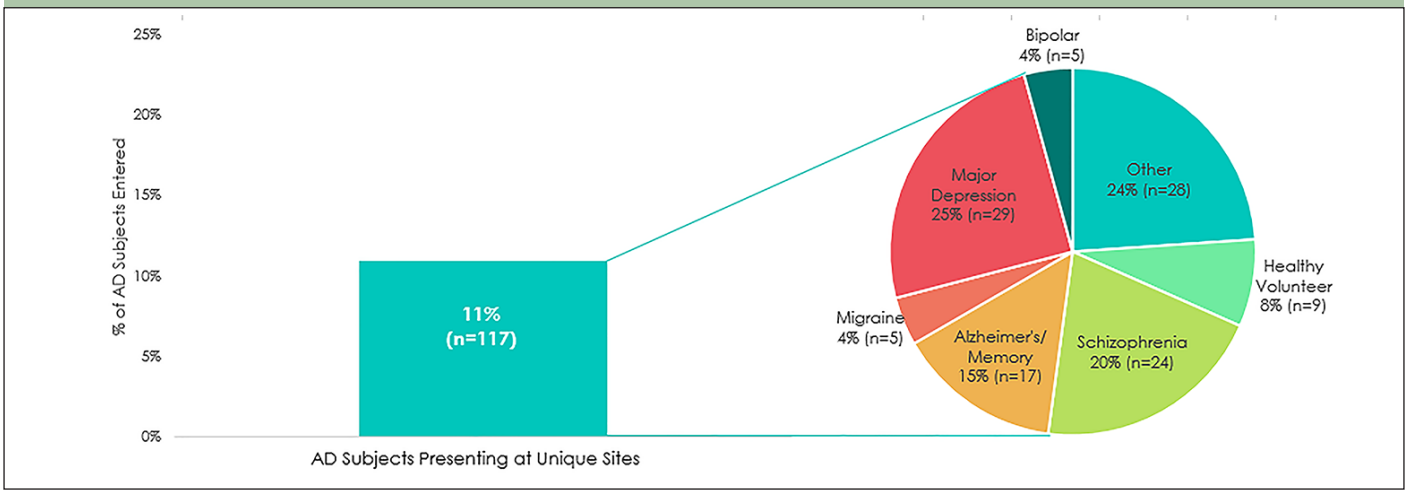
Example 3

A 76-year-old man screened for an AD study in South Florida despite having already completed the same study at different site several months earlier. After being turned down from re-enrolling in the study, he attempted to enter a "sister" study with the same compound and design at a third site.

Discussion

Given the high prevalence and devastating nature of Alzheimer's Disease and the hundreds of failures in Alzheimer's Disease studies, it is not surprising that patients with memory loss and their caregivers would try to participate in multiple trials (9, 10). Specifically, the recent failures of aducanumab, crenezumab and several BACE inhibitors may lead these patients and their caregivers to resort to desperate measures (11). As questions remain about the MOAs and preventive strategies that will ultimately be effective in treating AD

Figure 1. Within a two-year period, 11% of Memory Subjects presented to a unique (i.e. different) site, often for an indication other than AD



(12), patients and caregivers may seek to take advantage of multiple mechanisms at once, e.g. combinations of anti-amyloid mAb, BACE inhibitor, anti-Tau or novel MOA compounds. In fact, the EU/CTAD Task Force unanimously agreed that the treatment of AD will most likely involve combination therapy and that sequential or simultaneous targeting of multiple pathways should be investigated in clinical trials (13). Alternatively, patients might attempt to enroll multiple times in studies using the same investigational product in order to increase their chance of receiving active medication. In either of these situations, data integrity is affected and there could be unknown and potentially catastrophic effects to subject safety.

These duplicate subjects, as described above, may over-enroll in an attempt to improve the course of their disease. One could also understand a depressed, cognitively impaired patient seeking to participate in both AD and MDD studies. However, there are also professional subjects (and their study partners) who are knowingly deceptive in their presentation. For example, we have seen subjects who deny previous study participation while simultaneously enrolled in Cognition in Schizophrenia and Early AD studies (6).

Previous work has described duplicate and professional subjects of all ages and numerous indications (8). Affective and psychotic disorders, such as MDD and schizophrenia, as well as pain indications, such as fibromyalgia and migraine, may be particularly vulnerable to subject deception because of subjective endpoints. Furthermore, inpatient and healthy volunteer studies have significant problems with deceptive and professional subjects because of the large stipends offered. It has been shown that even a modest stipend, as low as $5.00, may induce potential subjects to change their presentation in order to qualify for a study (2,14). Smartphone apps and social media that list inclusion/exclusion (I/E) criteria and detail compensation facilitate this deception and increase the opportunity for professional subjects (5,15).

Even relatively small numbers of duplicate subjects found in memory studies are sufficient to affect safety and data integrity in AD studies. Shiovitz (2016) described how small amounts of misinformative data produced by professional subjects can lead to a loss of study power, primarily due to nonadherence (2). McCann (2015) also described how deceptive subjects who enter studies destined to succeed or fail can negatively affect a study's success (1). Steps that might be taken to mitigate the effects of duplicate subjects may have limitations or consequences. An ideal approach would be a national registry of research subjects, akin to ClinicalTrials.Gov, that could securely identify duplicate enrollment without identifying the subject or putting their personal information at risk. This has previously been proposed for healthy volunteers in Phase 1 trials but would also be appropriate for Phase 2-4 study participants (16). To date, the authors are not aware of any movement toward the creation of such a national database. In fact, central study databases such as ClinicalTrials.Gov may inadvertently increase the ability of professional subjects to easily locate all clinical trials and to learn the I/E criteria in order to aid their deception.

Many pharmaceutical sponsors use their own methodologies to internally track subject identifiers and prevent subjects from attempting to re-enroll in the same or similar studies (17). However, these are not in real time and do not track subjects across different pharmaceutical sponsors. Furthermore, HIPAA, GDPR and a company's internal requirements make such data acquisition difficult. To mitigate these shortcomings, use of one or more HIPAA and GDPR-compliant private subject registries at screen and throughout study participation would allow the tracking of these subjects.

Offering payment for study participation is important but also potentially problematic, as increasing levels of payment may encourage the professional subject. From a practical standpoint, if potential subjects are not compensated for their time and expenses, recruitment goals will never be met and subject populations that should be represented in clinical trials are excluded. It is important for trials to include those who require financial compensation as well as those of independent means who are able to take time away from work and family (18). To ensure that there is adequate reimbursement without undue coercion, the Institutional Review Board (IRB) will review all proposed compensation to subjects. However, it is the investigator's responsibility to understand not only the issues of undue coercion and adequate reimbursement, but also how some levels of payment may affect subject deception and dual enrollment.

A few caveats must be mentioned regarding our data collection. First, these are pooled results that reflect both subjects who screened for studies and some of those who presented for memory studies and never enrolled (i.e. only prescreened). While the amount of data that comes from subjects who prescreened and those who consented for AD studies is almost evenly divided, we are unable to present this data separately due to agreements with sponsors. Including prescreening subjects may overestimate the number of duplicate subjects entered into studies. Second, only a limited number of sites and sponsors performing AD trials mandate the use of CTS, which is likely to significantly underestimate the number of duplicate memory subjects in our dataset.

In conclusion, a small but significant number of AD patients attempt to enroll in multiple clinical trials which can confound efficacy and safety signals, as well increase patient risk. The number of duplicate and deceptive subjects in AD studies may approach 4% of screened subjects. It is important to consider the potential effects of such enrollees when designing and executing AD studies. Among other strategies, eliminating detailed I/E criteria and specific compensation from websites may impede

professional subjects in their pursuit of co-enrollment. Patients and caregivers should be encouraged to converse with their investigator before they consider participating in studies elsewhere; periodic reinforcement that participation in other studies is prohibited as it may harm the study and the patient may also be helpful.

When designing AD studies, taking into account the number of subjects that provide misinformative data by not taking study medication (when not administered parenterally) is important when calculating sample size. Pharmacokinetic sampling and adherence technologies rather than pill count alone may better characterize adherence to study medication. Finally, mandating a check for concurrent enrollment at screen using an available subject registry is an effective way to reduce the numbers of these inappropriate subjects and circumvent their negative effects on the success of AD trials.

Those who work to design and conduct successful protocols for AD patients should always be cognizant of the enormous effort and dedication of patients and their caregivers who participate in clinical trials. However, researchers must also recognize that although the vast majority of these patients are partners in finding effective treatments, there are those whose reasons for participating in studies are not altruistic. This includes patients motivated to find a treatment compound that works for themselves and/or their loved ones at any cost, as well as a few who may be professional subjects and are purposely deceptive.

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Conflict of interest disclosure: Dr. Shiovitz has ownership interest in and is President of CTSdatabase, LLC.

Ethical standards: All data reported in this study has been collected from patients who have signed an appropriate IRB or Ethics Committee approved consent form.

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