Utilising Large Data Sets and Extended Trial Observations To Close the Alzheimer's Evidence Gap

PEER REVIEWED

One of the most widely recognized limitations of traditional randomized clinical trials (RCT)s is that the observation period and treatment courses reflect only a fraction of the natural history/progression of the disease being investigated on an often miniscule and idiosyncratic subset of patients. Investigators and patient phenotypes frequently do not map into the post-approval setting as they are chosen to enhance assay sensitivity, and the visit structure including restrictions on concomitant medications, patient management procedures, and study duration constrain the range of outcomes which can be measured.[1] This is not surprising as RCTs are designed for statistical rigor and specifically to ensure adequate internal validity based on a distinctive set of highly selected enrollment constraints and treatment delivery conditions which are designed to reduce or eliminate both bias and confounding factors.

In fact, RCTs, are considered the hallmark of evidence-based medicine which forms the basis for translating research into practice, and as such must possess internal validity to ensure that the differences observed between treatment groups are related to the intervention(s) tested in the trial. However, to also ensure some degree of generalizability and clinical utility once market authorization has been achieved, the results must be relevant to a definable group of patients in a clinical setting; and it is this lack of external validity that is the most frequently cited criticism of RCTs by clinicians and systematic reviews. This may provide one possible explanation for the poor adoption of recommended guidelines stemming from RCTs resulting in an ever-widening evidence gap between research and clinical practice. External validity can be enhanced in RCTs through the use of eligibility criteria that are as broad as possible when randomizing patients, and in a post-marketing setting through a construct called "pragmatic trials".[2] Once randomized, patients in longitudinal studies often drop out differentially and not at random, and often do not adhere to assigned treatments, or may even receive post randomization supplementary treatments. Importantly, both attrition and selection bias are the two major sources of bias that represent major threats to internal validity and when these occur the benefits of randomization often dissipate[3].

Additionally, the high complexity and costs of conducting RCTs restrict the use of very large numbers of patients and that in itself introduces selection bias. This partiality can be due to patient factors related to geography, trial access, health insurance, the availability of past medical records, and the economic resources that would permit and support participation in RCTs. In RCTs of Alzheimer's disease (AD) studies examining the rates of patient eligibility have suggested that as little as 10–27% of potential AD patients are trial eligible[4,5]. Regrettably, only a small portion of AD patients are even marginally aware of research opportunities and many are unable or unwilling to participate. Many older adults live alone and may not have access to a caregiver who can accompany them to study visits and aid with various procedures. Indeed, AD trials require not one but two participants – the patient and a study partner – and enrolment of this dyad is imperative in ensuring clinical trial success.

Of interest substantive differences have been noted between enrolled AD samples and the general AD population which primarily reflect the idiosyncratic subject entry/eligibility criteria specific to any given AD study. More often than not the diagnosis of AD in clinical practice as opposed to research setting is based on an individual clinician's distinctive diagnostic approach rather than any specific research criteria. The greatest challenge for most investigators is how to properly select the right patients for a particular AD study and appropriately translate that patient's medical data and history into protocol-specific entry criteria. This becomes even more important in oligosymptomatic disease presentation in early AD where the patient's spontaneous reports of cognitive impairment are very often rare, inconsistent, and may not have not been taken seriously.

Even for those patients who are willing and able to enter RCTs actual enrolment into the trial faces many other obstacles including proscribed medical comorbidities, extensive use of prescription and over the counter medications, and behavioural complications of AD which may all be exclusionary. In practice the use of such strict enrolment criteria and enrichment designs may paradoxically end up excluding the exact cohort of patients most likely to actually use or possibly even benefit from the drug, and essentially exclude those patients who are most likely to provide the richest data sets (e.g., those most likely to utilize healthcare services) of interest to payers and clinicians. During clinical development and long before observational studies begin, an effort should be made to include a broader, more representative cross-section of the population that is ultimately likely to receive the drug therapy. Additionally, some AD patients are anxious about biomarker related procedures such as lumbar puncture for cerebrospinal fluid examinations or MRI/PET imaging procedures, whereas other subjects might have difficulties with extensive and numerous psychometric tests that often require three to six hours to complete and can result in frustration and emotional anguish upon confrontation of deficits. In the end RCTs in AD are designed to test verum in a very specific patient cohort utilizing very strict eligibility criteria. So, even after a large positive registration trial, the number of patients that the results of an RCT may apply to could be relatively small[6].

Arguably it is important to make painstaking efforts to include as many of those patients with the most frequent comorbid illness and those taking the most common comorbid medications as possible, as these patients are also the ones most likely driving utilization costs and are therefore are ultimately the most informative. Enrolling "super" AD subjects who are exceptionally healthy except for their AD does not tell us much about the typical patients who will eventually be taking the drug once it is approved, let alone those in the "deeper end of the pool" who have "messy" multiple and severe comorbid illnesses that ultimately drive utilization costs.

Linking Real-World Evidence with Large Multidimensional Data Sets

There are several broad approaches to help enrich data sets to include information on more typical patients who more greatly resemble those who will ultimately receive the drug. These include Real-World Evidence (RWE) studies, pragmatic trials (conducted post-approval), platform trials and extended observations that go beyond the constraints of a randomized investigation. Table 1 presents the methodologies that have garnered a renewed interest in recent years thanks largely to payer and regulatory concerns regarding the deficiency of practical and valuable data on drugs already approved.

Options, Alternatives and Enhancements to Traditional RCTs

Methodology	Description	Reference
Real-World Evidence Study	Linking fragmented data sets to build virtual study populations	https://www-healthaffairs-org.ezp-prod1.hul.harvard.edu/doi/pdf/10.1377/hlthaff.2017.1579
Extended Observations	Following a study population beyond trial endpoints to understand disease progression and impacts longer term	https://www.nejm.org/doi/pdf/10.1056/NEJMoa1615869
Pragmatic trials	A trial whose purpose is to evaluate the effectiveness of an intervention with the view to informing a decision about a healthcare policy or practice	https://trialsjournal.biomedcentral.com/track/pdf/10.1186/s13063-018-2895-x
Platform Trials	To study multiple-targeted therapies in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm	https://onlinelibrary.wiley.com/doi/epdf/10.1111/dom.13417
Basket Trials	To study a single-targeted therapy in the context of multiple disease subtypes	https://onlinelibrary.wiley.com/doi/full/10.1111/dom.13417

Table 1. Options, Alternatives and Enhancements to Traditional RCTs

Simply put, RWE is the capture and analysis of the actual experience of medical practice. Most often based upon electronic medical record (EMR) data and drug and/or treatment-centric data, RWE provides a retrospective view of exactly how drugs are used "in the wild" without the constraints of rigorous RCTs and the associated monitoring processes. Many drug developers are looking to the rapidly evolving field of real-world evidence (RWE) to serve as the critical bridge between these disparate domains.

Assuming that clinical trial research has covered a significant proportion of the total timeline of the disease progression, as shown in Figure 1A, the next opportunity is to increase the dimensionality of data as shown above in Figure 1B. A single study rarely samples sufficiently long outcomes – even an entire program would not likely cover the full transitions in clinical care that might take place. Here, there are many options but, in general, the goal is to bridge the data and methodology gap between drug development and clinical care. Techniques include the use of same/similar measures over extended time frames or the use of new measures over similar time frames (see figure 1.)

While these two can often appear similar, they are in fact quite distinct with differences in data collection platforms, staff training, monitoring conventions, methods of data aggregation and analysis, and regulatory requirements to enable the trials. In a post marketing environment, physicians are limited by practice apology and by payers to the types and frequency of diagnostic tests they can perform. In RCTs, costs are also important but can be secondary to concerns that extraneous data collection can confound clinical trial data interpretation and results[7].

A Path Forward

The art and science of RWE is rapidly evolving as many hope RWE will fill the data divide between medical practice and biomedical product development for topics ranging from drug safety endpoint development to the regulatory review of generic drugs[8,9]. That said, it is also clear that RWE alone is also inadequate as the only basis of drug review and approval due to its retrospective and fragmented nature but, when linked with large data sets, RWE can serve as a solid basis of medical evidence. Recent regulatory guidance on the topic provides a mosaic of opportunities both in terms of facilitating approval, but particularly in describing the impact of novel therapy on systems of care. The key lies in exactly how to link and pull these complex stories together to gain a comprehensive view over time and across a fragmented health system, of a single patient journey as well as the aggregate experiences of larger populations.

This can be done and has been recently demonstrated in a recent study in combining RWE and large genomic databases to provide an in-depth view and guide for a single cancer patient[9]. By linking RWE, large scale genomics databases, data from independent labs and specialty genomics sequencing companies, these researchers were able to recreate the entire longitudinal patient journey for a single cancer patient despite the complex, fragmented and non-standardized nature of all the data sources. Notably, one methodology that involves simply extending observations outside the scope of a traditional RCT has shown great promise in gathering data sets important to payers and regulators in economically efficient and practical manner and will be discussed in more detail.

Extended Observations and Patient Reported Data

As previously noted, RCTs have a highly selective focus and short

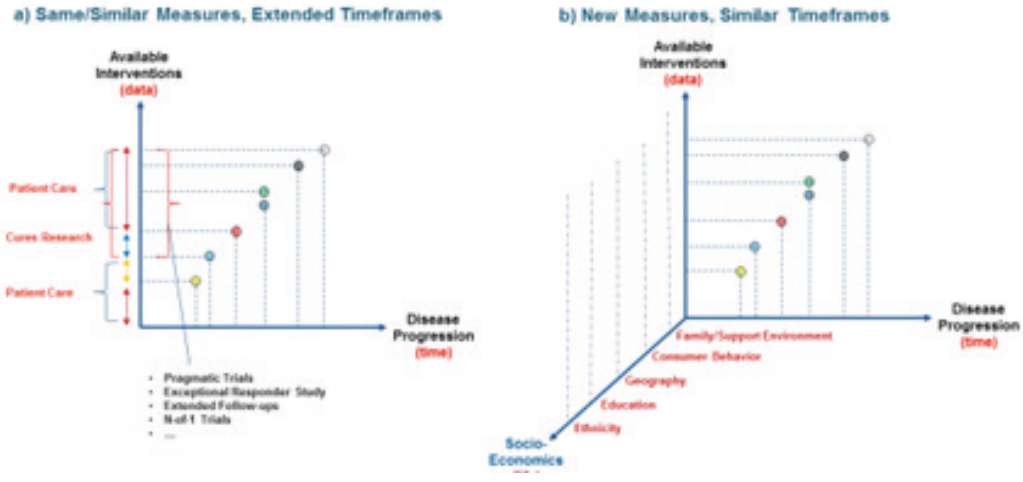

Figure 1. Options for Covering a Greater Proportion of Patient Journey (A) and increasing Data Dimensionality (B)

duration which limits understanding of disease history, progression or trajectory. Most importantly, traditional strategies to optimize the timing of interventions using nomenclature which would resonate with providers as opposed to investigators are limited to coarse and subjective labels such as early or late AD. Overcoming these limitations to provide a comprehensive and enhanced perspective on disease course, symptom progression and treatment efficacy over the full-time course of disease progression could be transformational for patients and progress is being made in that endeavor. For example, recent work using the Alzheimer's Disease Neuroimaging Initiative (ADNI) has shown that highly fragmented data can be linked and modeled algorithmically to demonstrate a comprehensive view of AD progression over 20 years or more[10]. While retrospective investigation of large data sets has inherent limitations, these challenges may be greatly reduced when coupled with prospective data collection especially when key variables missing from a retrospective study are prioritized within the prospective study[11].

There are many options, both novel and long-standing, for capturing and studying a greater percentage of the AD disease journey as summarized in Figure 1. Starting with the more established methods, it has long been known that patient and caregiver diaries were suitable and valuable as research collection tools despite being seldom used[12]. Methodologies that exploit the concept of patient-reported data (PRD) continue to mature and are now highly digitized and used across a wide swath of healthcare from complex chronic diseases, such as cystic fibrosis and cancer, to complex underserved populations and even dentistry and other healthcare disciplines[13,14]. Although these tools have matured greatly over the years, their usage remains traditional and restricted, and they are most often primarily limited to utilization within RCTs. While there are many reasons for this, economics and liability top the list. RCTs in AD are sponsored and all incurred costs are reimbursed by the sponsor in research for neurodegeneration and it is unclear if medical payers would reimburse PRD activity as an essential part of the course of care. It is also unclear who is ultimately responsible for following up on interesting or odd data or who would follow up if something important is missed. One set of models that appears effective are those implemented by patient advocacy organizations and registries. These groups are capable of self-funding extended data collection and have become pivotal in the research and development continuum[15].

Having available tools and business models obviously aids the cause but most researchers remain uncertain as to how best to implement these. As previously discussed, one creative and novel approach would be to simply extend a study database by offering an alternative observational PRD-based protocol to patients that are screened out of traditional RCTs. Regulatory agencies have more recently requested better characterization of potential patients who screen fail and follow-up with longer-term outcomes offers an attractive model to pursue. Another potential benefit of this would be to gather information on natural history and disease course that could be used to design and power future studies, especially when disease trajectory is not linear, and the nature of assessments that would be most sensitive clinically is not uniform across the disease trajectory.

An alternative might be to offer a voluntary observational protocol for all patients that complete or drop out of trials regardless of whether they responded or even dropped out of the clinical trial; and this alternative could also be extended to those patients who are screen failures reflecting the most common and salient reasons for screen failure such as use of a concomitant medication or past medical history or those who fail for some reason idiosyncratic to the study such as past exposure to the study drug. All of these groups and subgroups are potential cohorts for future prospective or retrospective study but only if they are engaged and tracked. Prior studies already cited have shown that patients can and will stay engaged for decades or until their demise. Further, these studies need not be limited solely to patient-reported measures. Under proper informed consent procedures, these observational studies can be built to enable future data collection of almost all types including electronic medical records, imaging, surveys and even data types that are not yet foreseen[16].

Practically speaking the following schema in Figure 2 could be followed whenever possible for all patients who screen fail or drop out early with the ultimate goal of gathering important PRD and reducing loss to follow up to zero.

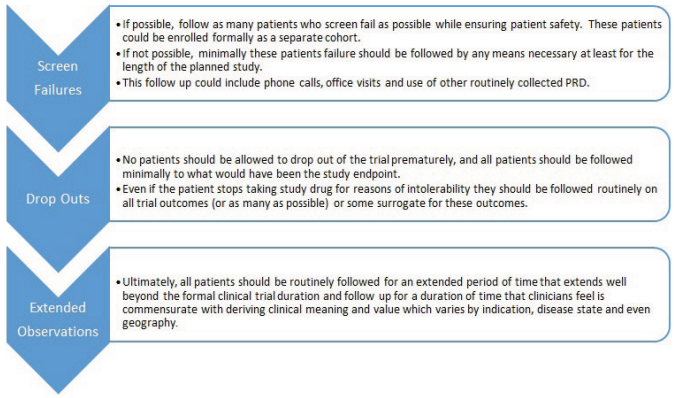

Figure 2. A Schema for Optimizing Patient Data Throughout an RCT

An Example of Utilizing Large Integrated Data Sets to Limit Loss to follow up and Extend Observations in an Early AD RCT

Patients in early AD RCTs are typically younger than their mild to moderate AD counterparts, have characteristic pathophysiologic changes of AD and subtle detectable abnormalities on sensitive neuropsychological measures, but no functional impairment, and as such may continue to be employed and socially active. The diagnostic criteria for Early AD, sometimes referred to as Prodromal and/or Mild Cognitive Impairment (MCI) due to AD, have recently been developed and include evidence of amyloid burden and/or neurodegeneration. Although amyloid PET scanning or CSF amyloid measurement is integral for identifying subjects who are more likely to develop AD the expense and relative limited availability of PET scanners uniformly throughout various geographic regions, and the regional variations in obtaining lumbar punctures limits their widespread application for many AD trials. Screening for amyloid positivity is now a routine part of enrolment criteria in clinical trials. However, this one criteria may effectively eliminate approximately 1 out of 3 patients with MCI[17]. Additional screening criteria regarding cognitive function, concomitant medications and illnessxes has routinely resulted in extremely high screen failure rate (approximating 75–85%) driving up costs and timelines of early AD RCTs. And unless this same type of rigor (confirmed by imaging or CSF) is utilized by general practitioners to diagnose patients who will ultimately receive these AD drugs it is very likely that once approved these medications will be utilized in a population with nominally the same diagnosis that nevertheless is markedly different from the one that led to the drug's approval.

One suggestion to help remedy this problem of poor generalizability is simply to follow those patients who screen failed for various reasons (lack of biomarker, concomitant medication, concomitant illness, lack of a reliable caregiver etc.) minimally for the length of the trial period in order to better understand the natural history of the disease but also for an extended period of time after the conclusion of that trial. Following these patients outside the confines of the RCT through the use of large related data sets may help limit the cost of the study, will be virtually unobtrusive to patients, and help extend generalizability. These patients could serve as a "control arm" in support of a current study in terms of healthcare utilization (especially if it is a rare disorder); help plan post marketing studies;

help characterize a pool of potential patients for future clinical trials which may have a much more liberal set of eligibility criteria; and importantly help establish the burden of disease against which to model drug effects. Obviously, patients who met criteria and enter the trial could also be followed in this manner whether they drop out early or complete the study.

As noted patients in early AD trials may still be active socially and may even still be employed. Many of these patients have health insurance and even supplemental health insurance in addition to Medicare. By chance it might be expected that approximately 10–20% of subjects in any given large RCT for early AD conducted in the United States would be covered by a single health care insurer provider depending on geography. This estimate can be greatly increased by simply changing geography to match a single payer market penetration or by including data from more than one payer, or even by obtaining provider data from patients who may belong to specific organizations such as the American Association of Retired Persons (AARP). Data from payers tends to be broad but not very deep, meaning that there is data on many patients, but the quantity and quality of that data may be limited to top diagnostic codes and procedures that are paid for by the provider. Routinely collected data from managed care companies on procedures can be used to infer if the drug continued to show overall benefits on an individual patient level. Less compellingly would be differences between dose groups or the active comparator versus standard of care which continue to exist.

This type of payer data can also be supplemented by other large data sets that can be integrated with payer data and includes data related to social media, activity, driving, etc. Of course, there must be a way to integrate these disparate databases as data silos have greatly limited the realization of health data benefits. One such solution is to use a "token" that can be applied to individual patients to enhance trial datasets, enabling researchers to connect trial data sets to other large and diverse health care, marketing and social data sets or any de-identified datasets pooled from multiple real-world sources in a passive observational study without compromising patient privacy, enabling new avenues for researchers and a better understanding of the patient journey.

Disparate datasets often need to be de-identified in order to be exchanged. In the process of de-identification, it is possible to leverage the underlying identifying information to generate anonymous identifiers or "tokens" that can be used to link corresponding patient records across datasets. These tokens are essentially hashed and encrypted combinations of those identifying elements. Hashing the underlying identifying elements ensures that a bad actor cannot reverse the token to identify the patient. Encryption is a second layer of security that results in tokens which are specific to a given site (so that a breach anywhere in the network of tokenized data does not put anyone else's data at risk). While it is not possible to reverse the hash, site-specific tokens can be decrypted and re-encrypted so that records can be linked across sites.

To take a simple example, imagine that a man named John Smith, who was born on January `1, 1950 exists in both an EHR dataset and a diagnostic lab dataset. If all of John Smith's identifying information was removed from both datasets, there would be no way to link his records. However, by creating tokens from first name ("John"), last name ("Smith"), gender ("M") and birth date ("January 1, 1950"), it is possible to create two hashed and encrypted tokens for John Smith. At the EHR data source, the record might correspond to AA0001. At the diagnostic lab, the record might correspond to BB0001. When this data is transferred to the sponsor, however, both tokens will be decrypted and re-encrypted such that each record will be identified with the token CC0001. In the sponsor's environment, all CC0001 tokens correspond to the same de-identified individual (in this case, John Smith).

To enhance a traditional RCT, a sponsor might begin by tokenizing the clinical data that is collected during the clinical trial. By then using the same method to tokenize the various real-world data sources that the sponsor will leverage as part of the enhanced clinical trial, the sponsor can link the traditional clinical trial data to other real-world data which are routinely collected outside of RCT setting may be useful in tracking clinical state and many of those suggested below have been shown to be closely related to patients' overall level of cognition and function. These include the following examples in Table 2, but the suggested outcomes are only limited by the types of data available and the creativity of the researcher:

Data Type	Element	Source(s)	Rationale
Traditional Healthcare Datasets	Claims	Medicare QE data, IBM Watson Health, DRG, etc	Diagnoses of AD / MCI / Dementia, prescription Rx data
	EHR	Allscripts	Rich narrative data on disease severity / imaging results
	Labs	Quest, Prognos	Lab IE Criteria
Consumer / Marketing Datasets	Prevagen Purchases	Loyalty programs (e.g. Walgreens, Safeway)	Strong indicator of self-diagnosed cognitive decline
	Change of Postal Address	USPS Change of Postal Address Database	Recent institutionalization may indicate cognitive decline
	Gas Purchasing Behavior	Credit card data (e.g. Mastercard)	Gas purchasing can be used as proxy for loss of driving ability
	Search behavior for Assisted Living facilities / nursing homes	Digital marketing segments (e.g. Clickagy)	Interest in assisted living / nursing homes indicative of loss of function

Table 2. Example of Possible Data Sets and Their Utility in AD trials

Discussion

Patients who are enrolled in early AD RCTs are typically assigned to one of two to three medication dose groups or placebo (as monotherapy or added therapy to an underlying drug like a cholinesterase inhibitor or memantine). In an early AD RCT of a disease modifying agent, or even for a drug that would prevent the onset of dementing symptoms in a population of patients likely to develop these, trial durations are often long and typically the duration is 18–24 months. Therefore, attrition of upward of one third of the sample would be expected. This attrition is problematic in the trials as there is always a chance to see non-random differences in drop-out rates and missing data, as well as poor adherence to treatment over long treatment durations. It is therefore important to attempt to track these patients over time to what would have been their pre-established endpoints by using traditional RCT endpoints whenever possible, and when not possible by using integrated data sets that are available to the researcher. The availability of large integrated data sets has resulted in a renewed interest in the use of such real-word data to supplement RCTS and bridge the widening evidence gap between research and clinical practice.

Additionally, even for those early AD patients who complete the RCT much can be learned by following them for an extended period of time past the traditional 18–24 month treatment period of the RCT. Specifically, data garnered from this extended period of time can help assess if the drug has disease modifying effects that persist long after the cessation of study drug. Compared to patients on approved symptomatic treatments which do not alter the underlying course of the disease, a drug which is a true disease modifier will continue to show benefit even after the drug is discontinued and long after the trial is formally over supporting a claim for disease modification. This clinical benefit could be evidenced across varied sets of medical and social media data that track clinical state dependent upon the type of data that the researcher has access to, and reasonably could even be accompanied by evidence of a delay in the progression of brain neurodegeneration as seen by imaging

or CSF biomarker if available. Extended observations may also help differentiate dose groups that were very similar in terms of efficacy and safety upon conclusion of the RCT and help to determine which dose(s) will ultimately be used for marketing purposes or provide better evidence for add on versus monotherapy.

Of course, it is helpful if there is an existing literature to support a link of various types of data to cognition or function; that the data have some level of face validity; or be related to some clinically meaningful outcome accepted by healthcare practitioners or regulators. For example, the FDA has become much more interested in real-world outcomes and have recently encouraged the development of novel approaches to the integrated evaluation of subtle early AD functional deficits/impact that arise from early cognitive impairment such as facility with financial transactions, and adequacy of social conversation[18]. These can be tracked by formal outcome measures during a RCT or even outside of the trial using data from large data sets without steadfast requirements as to the exact type of data nor linkage to disease. In fact, by relating this type of data back to clinical trial outcomes and patient characteristics it is possible to discover data relationships that support or predict longer term outcomes that are as yet unknown. All of this should be done in an effort to close the evidence gap between the data evaluated by regulators for approval which is by definition derived from idiosyncratic RCTs, and the real-world data used by health care providers, payers and consumers to inform clinical practice.

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