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Neuroimaging to assess safety and efficacy of AD therapies

Derek Hill
Medical Imaging Science, UCL and CEO IXICO Ltd, London, UK and Centre for Medical Image Computing, UCL, London, UK

During the last two decades, neuroimaging methods have become widely used to study the natural history of Alzheimer's disease and also as a means of assessing safety and efficacy of novel treatments. Widely used safety and efficacy end points are described, along with their level of maturity. The North American Alzheimer's Disease Neuroimaging Initiative (ADNI), and similar activities in Europe, Japan, and Australia, are natural history studies that are providing new insights into the use of imaging end points in clinical trials. While the results of these trials are not yet all available, a recipe for successful deployment of imaging to assess eligibility, safety and efficacy is emerging.

Keywords: imaging biomarkers, longitudinal imaging, MRI, PET

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1. Overview

Testing safety and efficacy of candidate drugs is a key challenge for many major pharmaceutical companies as they develop novel treatments for Alzheimer's disease and related disorders. The North American Alzheimer's Disease Neuroimaging Initiative (ADNI), and similar activities in Europe [1], Japan, and Australia [2], are natural history studies that are providing new insights into the use of imaging end points in clinical trials.

While imaging methods are not yet widely used for clinical assessment in Alzheimer's disease, imaging has a key role to play in the study of disease progression and response to treatment that has become established over the last two decades. A spectrum of imaging methods can be used to assess eligibility, safety and efficacy, with the most common approaches based on MRI and positron emission tomography (PET) modalities, with some interest in also using latest-generation volumetric CT. The use of imaging includes assessment of the following:

- *Eligibility* – through amyloid load, baseline hippocampal volume, absence of white matter disease, or absence of microhaemorrhage
- *Efficacy* – through downstream 'structural' effects such as brain atrophy
- *Function* – through FDG-PET and contrast MRI
- *Change in amyloid load* – through PET molecular imaging
- *Safety* – through signs of encephalitis, microhaemorrhage and vasogenic oedema.

These approaches are discussed below, along with implications for trial design and operation.

2. Assessment of eligibility

Many putative Alzheimer's disease therapies specifically target amyloid pathology. It is therefore important to exclude subjects who have dementia with other causes – in particular vascular dementia, which is also quite common. Imaging is, therefore, frequently used to assess eligibility for trials. The most basic approach is to use clinical MRI imaging with local radiological assessment to exclude subjects with evidence of substantial vascular disease. More sophisticated approaches involve

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exclusion of subjects with more than a specified number of microhaemorrhages (using a combination of MRI methods usually including T2* weighted imaging).

There is increasing interest in treating patients who do not yet meet the full diagnostic criteria for Alzheimer's disease, on the grounds that treating patients who meet those diagnostic criteria may be less successful due to the advanced state of the pathology and the amount of irreversible neuronal damage present. Several pharmaceutical companies are, therefore, designing trial protocols that require the recruitment of patients who do not meet the full criteria for Alzheimer's disease but have mild cognitive impairment (MCI) or prodromal Alzheimer's disease. In these cases, imaging can be used at baseline to detect evidence of early downstream consequences of the disease (such as hippocampal atrophy from structural MRI) or to directly image amyloid plaques through the use of PET amyloid tracers (discussed later). These more sophisticated methods involve imaging methods that are typically beyond those used in standard clinical imaging and therefore require careful site training and normally also central assessment of the images to ensure consistent interpretation and measurement. In MCI or prodromal Alzheimer's disease trials, these imaging methods are often combined with non-imaging measures such as cognitive testing (to collect evidence of progressive cognitive decline) and CSF amyloid markers to achieve high conversion rates to Alzheimer's disease in the control group.

3. Assessment of efficacy through downstream 'structural' effects such as brain atrophy

One of the most established down-stream effects of Alzheimer's disease is brain atrophy. Atrophy can be assessed either globally by making measurements on the entire brain [3-6], lateral ventricles, locally using measurements of local brain regions (such as the hippocampus [7]) or using cortical thickness [8] or voxel-by-voxel approaches [9,10]. To use structural change as a measure of efficacy requires both large cohorts and fairly long trials. A typical trial design involves imaging over at least 12 months with around 100 subjects per arm [11]. The large number of subjects required limits these approaches to late-phase trials or large proof-of-concept trials. Some sponsors use structural MRI end points in earlier-phase trials that have fewer subjects per arm to get baseline data and ensure the methodology is worked up ready for a subsequent pivotal trial.

4. Function through FDG-PET and contrast MRI

An alternative to measuring efficacy from downstream structural effects is to measure the effect of treatment on more short-term effects such as brain metabolism or blood volume, which can be measured with imaging methods including FDG-PET [12] and contrast MRI [13]. There are strong advocates of these measures, which have the potential to detect a drug effect more rapidly than structural methods. However, because many other factors besides disease progression and treatment response can affect these measures, trial design issues are currently less well understood. The ADNI trial is likely to provide useful data on required sample sizes from FDG-PET imaging.

5. Amyloid load through PET molecular imaging

Relatively recently, PET imaging techniques that can directly image amyloid pathology have been introduced. Their availability remains limited to specialised PET centres, but these have great potential value for treatments that target the amyloid cascade: they can be used not only to ensure that amyloid pathology is present at baseline, but also potentially to assess change in amyloid load as the disease progresses and treatment is given. The most widely used amyloid imaging agent to date is called Pittsburg Imaging compound B (GE's PIB) [14-16]. This is a carbon 11-labelled tracer that most PET centres cannot use because it lacks a cyclotron in close proximity. Fluorine-labelled amyloid imaging agents are becoming available and are currently under study (e.g., [17]).

6. Safety, through signs of encephalitis, microhaemorrhage and oedema

Some experimental Alzheimer's therapies have associated risks of adverse events that can be detected on imaging. This is especially true of the methods based on immunotherapy. The widely cited AN1792 201 trial [18] was terminated due to adverse events that could have been detected using imaging, and there has subsequently been an increasing use of imaging to provide a safety end point, though not in all trials. Current safety imaging approaches typically involve the use of a battery of MRI methods, including T1, T2-FLAIR, diffusion MRI, and sometimes also T1 post-contrast imaging.

7. Implementation issues

Imaging end points can have a high profile in trials. They have been prominently mentioned, for example, in press releases for recently completed trials from both Elan/Wyeth's bapineuzumab and Pfizer's atorvastatin. Imaging is also expensive due to the costs of data collection as well as the need to pay an imaging CRO or academic core lab to coordinate sites, perform data transfer and analyse end points. It is therefore important for sponsors to carefully consider how imaging can deliver value in the trial, and select an approach that will ensure quality results and meet regulatory requirements. Many sponsors are also keen to determine whether imaging end points and other measures be combined to increase power.

The key challenges to effective use of imaging in Alzheimer's disease trials are:

- Choice of imaging modality and end point to assess drug efficacy (and, where appropriate, safety)
- Standardisation of methods, so that between-site variability does not dominate subject variability, and so that instrument and operator-induced between-scan variability does not introduce variability that masks disease effects
- Incentivising imaging sites to follow instructions, given that these departments are almost always administratively independent from investigators
- Rapid data transfer and quality control (QC) with queries raised, to ensure compliance and arrange re-scans if needed
- Achieving sufficiently short timelines to enable imaging results to inform inclusion or impact on dosing
- Selection of eligibility assessment methodology
- Selection of end-point methodology (which image analysis method from the literature has the greatest statistical power?)

The ADNI project [19] has looked at many of these issues, and the results that are now entering the literature are providing useful guidance to inform trial methodology. However, the conclusions from ADNI are not yet clear as the full analysis results have not yet been published. Also, because ADNI does not involve any therapeutic intervention, there are some factors it cannot study, such as safety assessment. From a methodological point of view, it is not clear whether all aspects of ADNI methodology, some of which are hard to use in a commercial trial, are essential.

8. Expert opinion

There are some important learning points from our own experience with multiple Alzheimer's disease trials, and that are also emerging from the ongoing natural history trials such as ADNI:

• *Selection of modality and end points*. It is important to remember that the key end point to assess efficacy in an AD trial is going to be a measure of cognition. It is unlikely that any drug will be approved on the basis of 'improvements' in imaging end points unless cognitive end points also show improvements. Imaging end points, however, have the potential to demonstrate a biological substrate to any cognitive benefit that might provide evidence of disease modification. The interim analysis from the ADNI data suggests that structural MRI end points may have higher statistical power than FDG-PET for detecting a drug effect in the Alzheimer's or MCI population. MRI has the advantage that images for both structural and safety end points can be collected at the same visit. Structural MRI, however, requires long study durations to provide evidence of potential efficacy. Functional modalities may provide a more rapid assessment of proof-of-mechanism, though that remains controversial. Direct amyloid imaging remains challenging to use in multicentre trials because of limited availability. The high cost also reduces its use, but it certainly has a role in providing evidence of amyloid pathology in the brain, and may also provide evidence of change in amyloid load longitudinally. One of the great achievements of ADNI is the placement of a large amount of carefully collected data onto websites from which it can be downloaded for analysis. This is providing a resource that can be used by algorithm developers to test their novel methods for calculating MRI and PET end points. This is likely to lead to methods that have greater statistical power than those that are more established.

The widespread availability of scanners capable of acquiring volumetric CT images with higher resolution than MRI and in a shorter scan time (reducing the risk of motion artefacts) means that there is scope to reassess the potential of CT to make longitudinal measurements in neurodegeneration.

• *Site management*. Where longitudinal imaging is used, sites must use standardised sequences and must not change practice over time. The greatest risk of poor data is from operator error rather than instrument drift in MRI. While phantom measurements can help reduce instrument variability, this approach is not a panacea; in some circumstances, phantoms can introduce new errors, especially if these phantoms are not used properly or are damaged. Furthermore, thorough site qualification, training, and management are essential. For sites to follow instructions, the imaging departments (as well as the investigators) need to be incentivised to produce good-quality data. It is also important to put procedures in place to optimise communication between the imaging sites and investigators. Training, and then regular and effective communication with the sites, can help in this; but sponsors also need to consider the real additional costs to sites of collecting, de-identifying and transferring data to the imaging CRO. Some commentators are concerned that, as trials go more global, fraud may become a greater risk, and that steps need to be put in place to detect fraudulent data submission of image data. The image data and metadata in images offer many opportunities to look for evidence of fraud, though medical image-specific fraud detection methods are not yet established.

• *Data management*. Rapid data transfer – electronic, where possible – and quality control are essential to enable problem data to be detected sufficiently rapidly to allow for a re-scan (e.g., if motion artefact makes the MRI scans unusable), and to provide sites with timely feedback as to how well they adhere to the imaging protocols. Rapid data handling also facilitates rapid turnaround for safety and eligibility assessment.

• *Selection of the imaging core lab*. Image analysis for AD trials is usually centralised. It can be performed either by a commercial organisation (an imaging CRO) or by an academic core lab. The academic core labs are most likely to have access to academic state-of-the-art methods and know-how, but less likely to have high standards of regulatory compliance and may not always a have rigorous QC procedures. Imaging CROs, in contrast, may have high-quality procedures, and be free of any potential conflict of interest, but can have less scientific expertise.

• *Engagement with imaging experts*. There are numerous aspects of the collection and analysis of imaging data that need to be correct. Many of the end points need quantitative analysis as opposed to radiological assessment, and so imaging for Alzheimer's clinical trials requires a different approach to collecting data than clinical imaging in Alzheimer's disease.

There is strong evidence that imaging can have great value in Alzheimer's trials if deployed properly, and there is now sufficient experience of imaging for Alzheimer's disease in both natural-history and therapeutic trials for a clear recipe for success to be emerging. The results from the ADNI trial, as they are published, will provide important further guidance for trial design related to both efficacy and eligibility.

Declaration of interest

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Affiliation

Derek Hill
[†]Address for correspondence
[1]Professor of Medical Imaging Science, UCL and CEO IXICO Ltd, London, UK
E-mail: derek.hill@ixico.com
[2]Centre for Medical Image Computing, UCL, London, UK