

## OUTCOMES FOR DISEASE MODIFYING TRIALS

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### Introduction

We have arrived at an exciting time in the evolution of treatments for Alzheimer's disease with the opportunity to evaluate the translation of scientific knowledge into the clinic. The emphasis in most future pharmacological trials will probably focus upon disease, as opposed to symptomatic, modification. What is disease modification? Possibly the best definition is the arrest or slowing down of the underlying neurodegenerative processes, and to many this means reducing the effects of the amyloid load in the Alzheimer disease sufferer's brain, e.g. by stimulating its removal, reducing its pathological impact or reducing production. Strategies to prevent neurofibrillary tangle formation, or to compensate for it once they have been created, are also under investigation. In addition there are non-amyloid and non-tangle treatment mechanisms in development. Examples include the gamma-secretase inhibitors and modulators, immunotherapy, GSK-3 inhibition and cell cycle related hypotheses. Clinical trials to evaluate disease modification will need longer studies than those used in symptomatic drugs, larger cohorts and ideally access to biomarkers. However, to clinicians, the benefits to patients and their families i.e. clinical outcomes, are going to be paramount.

### Trial Design

Trial design and selection of subjects has an important influence on the choice of outcome measures. The European Task Force consensus (1) on trials for disease modifying drugs concluded that patients with mild AD would be the ideal subjects, but that the "MCI" population should be avoided as it is more heterogeneous and progresses more slowly, although the amnesic form might be a disease modifying target, especially if there was a suitable biomarker. Patients in the more moderate stages of AD progress more rapidly in some outcome measures and could be considered for inclusion.

Although randomised start or withdrawal designs (2) are favoured by some they are more difficult to undertake, e.g. they require longer term follow up, and are likely to experience more subject drop out which may affect interpretation, especially if it occurs differentially in the pre and post start or withdrawal phases compared to the initial period.

The classic randomised, parallel, two arm placebo-controlled design is therefore favoured, adopting a trial duration that is a balance between the time required to show a disease modifying effect and the need to minimise the attrition rate that is often

part of longer trials. In addition financial considerations need to be considered, as longer trials are more costly. Those participating would need to be able to continue with other pre-existing treatments, such as cholinesterase inhibitors or memantine as long as they have been taking a stable dose, e.g. for at least 3 months.

If the NICE recommendation (3) that cholinesterase inhibitors should only be prescribed for those with an MMSE in the range of 10-20 is adopted, this will need to be factored into the trial design as mild patients may slip to this range during the trial, and wish to start on treatment, which will affect the assessments of the study drug.

A disease modifying trial could use a "time to event" design or compare rates of progression, or possibly both. Both the event itself being studied in a "time to event" trial, and the length of delay to that event need to be clinically relevant. A delay of less than 6 months is unlikely to qualify as significant given the overall duration of the disease progress. It will also be more meaningful if the treatment can be shown to enable those to whom it is given to remain in the mild category for longer.

For trials comparing progression rates, e.g. comparing slopes of progression, the analysis needs to take into account the effect of attrition as it may be affected by a last observation carried forward type of phenomenon. If those who drop out early are included in the analysis, carrying forward their last observation may bias the outcome if they are in the active treatment group, as they may have dropped out at a time when their ability would be better than it would have been at the end of the trial period, even if allocated active treatment. For this reason it is very important to retrieve those who drop out.

### Choice of outcome measures

We need to use clinically relevant outcome measures across a range of domains. Symptomatic treatments, such as those modulating neurotransmission, are likely to have a more limited effect which will reflect the role of the neurotransmitter systems involved. Disease modifying approaches should show evidence of a more global pattern of efficacy as they are targeted at neuronal survival in general rather specific systems. If it is not possible to show evidence of an impact on multiple domains, this would question whether or not the drug being evaluated is in reality disease modifying.

The endpoints should include cognition, functional ability (adl), neuropsychiatric symptoms, possibly a more global measure and a carer burden scale, and probably quality of life measures. In addition, regulators and funding authorities will

increasingly require evidence of cost effectiveness in the future. Delaying the transition from one stage of the disease to another could be included in a “time to event” protocol, e.g. using the Clinical Dementia Rating Scale or crossing a boundary defined by a score on the MMSE.

It has been apparent for a while that some of the most frequently employed assessment scales have different levels of sensitivity to change at different stages of the disease. It is therefore important to optimise the procedures, e.g. to supplement the ADAS-cog with a more sensitive test battery for subjects with early disease as was built in to the design of the Elan immunotherapy trial. There are a range of assessment tools to measure the other domains, and the same principle may apply.

### **Biomarkers**

A biomarker is defined as a characteristic that it is possible to measure objectively, and is assessed as an indicator of normal biological or pathogenic processes or pharmacological responses to a therapeutic intervention (4). In our context it should have at least 80% sensitivity and specificity. Clinical endpoints, as already described, measure how a subject functions or feels, or even how they progress or survive. Surrogate endpoints substitute for clinical endpoints and are also used to predict clinical change. Biomarkers have been adopted as surrogate endpoints in clinical trials in other areas of medicine, e.g. in MS, but are less well validated in AD. In an ideal world a biomarker for use as an outcome measure in phase III trials in AD would be a simple blood, or possibly urine, test. A more complex measure may be useful in earlier proof of concept studies.

At present a number of potential biomarkers are vying with each other for use in AD trials. These include CSF biochemical entities related to beta-amyloid and tau which have shown significant sensitivity and specificity levels, and isoprostanes,

as examples. They are also being explored in blood, and isoprostanes also in urine. Structural neuroimaging has been incorporated into many trials for many years, and is becoming increasingly sophisticated, although the results are sometimes unexpected. The newer techniques attempting to demonstrate changes in brain amyloid load, and also the increasing exploration of functional MRI may lead to new clinical gold standards, but presently need more evaluation.

### **Conclusion**

Progress is being made in the design of trials to evaluate potential disease modifying drugs, and we are gaining valuable experience from the few studies that have recently been undertaken. This has contributed to our understanding of the principles of trial design, and emphasised the need to develop more sophisticated, and perhaps sensitive, approaches to outcome measurement. At present most studies are using traditional clinical outcome measures in trials of extended duration, often supplemented by additional cognitive protocols, and analysing differential rates of progression, e.g. with a slopes analysis. Biomarkers, e.g. neuroimaging and CSF amyloid peptide and tau markers, are increasingly incorporated into trials, usually as secondary or exploratory outcome measures.

### **References**

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