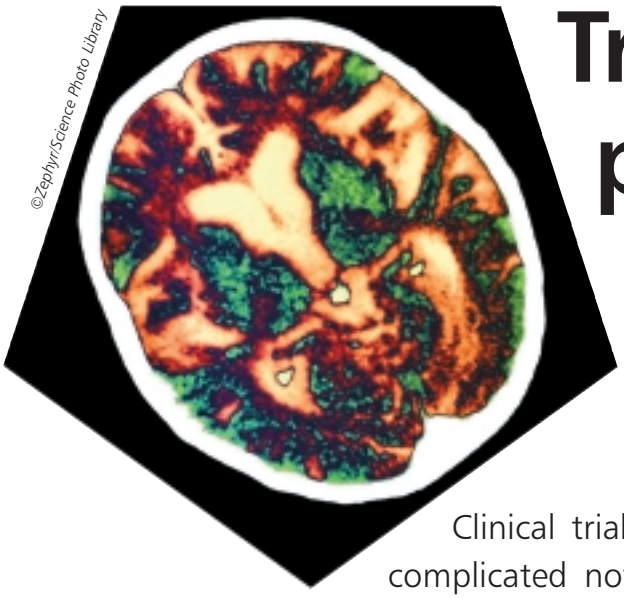

Trials where precision cannot be overrated

Clinical trials into potential Alzheimer's treatments are complicated not only by the disease process itself, but by the array of scales used to assess patients' rates of deterioration. **Dr Michael Bowden** suggests strategies to ensure that any treatment effects are due to the drug's utility rather than poor study execution

Pharmaceutical clinical trials are often conceptually easy but practically difficult, none more so than those investigating Alzheimer's disease. In recent years, we have seen a number of anti-dementia drugs show great promise, then fail in Phase II or III trials. Could some of these failures result more from the difficulties of clinical trial execution and the introduction of bias or chance rather than the true utility of the drug itself? I suspect they may, but there are strategies researchers can use to avoid many of common pitfalls in Alzheimer's trials.

There is a good deal of advice on the type and structure of clinical trials into Alzheimer's disease. The regulatory framework for the development and approval of pharmaceutical products for treating it is enshrined in two sets of guidelines. The first, *Guidelines for the Clinical Evaluation of Anti-Dementia Drugs*, was published by the US FDA in November 1990. This set the scene for product development and, as yet, has not been updated. The second, *Note for Guidance for Medicinal Products in the Treatment of Alzheimer's Disease*, was published under the auspices of the European Medicines Evaluation Agency in January 1998. The main points of these guidelines are summarised in the box (see right).

To date, most Alzheimer's trials have been double-blind, randomised, placebo-controlled and parallel group designs. It could be said that for drugs aiming to improve cognition in the same way as the marketed acetylcholinesterase inhibitors, there is almost a template for their development (the situation is far less clear for drugs intended to modify the disease and slow or halt progression).

What makes a good study?

Why do negative trials of efficacious drugs still occur? Of course, clinical trial results can be affected by bias, chance and fraud. Only if these are systematically eliminated can we be confident that the result reflects the truth. Much has been done in recent years to eliminate fraud in clinical trials to the point where this should be practically non-existent in well-

Regulatory guidelines for Alzheimer's studies

- Treatment must have a clinically meaningful effect on core symptoms, such as cognition, behaviour and performance
- Treatment must benefit the patient's ability to learn new and retrieve old information
- A performance-based test instrument for cognition should be used but it must be qualified by global assessment of the patient by a skilled clinician to ensure statistically significant effects are clinically meaningful
- In Europe, a performance-based measure (for example, 'activities of daily living') must be used
- There are no specific recommendations on which scales to use
- It is important to establish a diagnosis of probable Alzheimer's disease and exclude of other causes of dementia, for example vascular dementia
- There is no specific advice on trial design, although there is a strong preference for parallel groups
- To establish safety at the time of application for regulatory approval, at least 1,000 patients should be presented who have been exposed for several weeks with one-third at a dose at or above intended marketed dose for six months to one year

Cover photograph (above): Coloured CT scan of a horizontal section through the brain of a patient with Alzheimer's disease.

conducted and monitored multinational trials.

Bias can be eliminated in several ways. An adequate control arm must be used – preferably placebo, although it is becoming increasingly difficult to conduct placebo-controlled trials of any duration in patients with Alzheimer's disease. Randomised allocation to the treatment groups must be achieved along with satisfactory blinding of the treatment allocation for the investigational site staff, the patient and the caregiver.

Blinding is critical in Alzheimer's trials. The primary and most of the secondary endpoints are assessed using scales such as ADAS-cog, CIBIC, ADCS-ADL. Such scales are notoriously subject to bias and it is crucial that the person rating the scale is not only blinded to the patient's treatment allocation but also to other scales being used to assess that patient. Therefore, several site staff members are required to conduct a proper study – and they must be trained in order to administer the scales properly.

Chance – the killer of trials

While eliminating fraud and bias can be achieved relatively easily, it is far more difficult to remove the element of chance. Any initial trial design should include an assessment of the likelihood of a result occurring by chance. The larger the numbers of subjects involved in a study, the less likely the outcomes are the result of chance.

All clinical trials look at the effect of a particular intervention on the disease process for a given, standardised population. At the outset, the investigators intend to enrol two very similar groups of subjects, one of whom will be given the investigational treatment, and the other who won't. By the end of the trial the intervention group will have experienced a number of events, as will the control group. The investigators hope that these numbers will be different – demonstrating that the intervention has an effect.

So, adequate sample size is important when designing clinical trials. But there is one other thing to take into account when determining sample size – variability. The higher the anticipated variability, both in a patient from one observation to the next or between patients receiving the same intervention, then the higher the sample size required. As we cannot always predict variability in advance, it is important to avoid it whenever possible. In Alzheimer's trials, this can be done by careful selection of patients, by avoiding patients who are 'only just eligible', making sure that the trial only measures what matters, ensuring consistency in the timing of endpoint assessments and ensuring drug compliance.

Careful patient selection

A diagnosis of Alzheimer's disease can only be made post-mortem. When we talk about patients with Alzheimer's disease in clinical trials we are really referring to a probable diagnosis as defined by various diagnostic criteria, such as those in the Diagnostic and Statistical Manual of Mental disorders (DSM-IV). Probable Alzheimer's disease is a diagnosis of exclusion; that is, it is made after other possible causes are ruled out. Clinical trial protocols should contain clear and detailed assessments to rule out the other causes of dementia (see box below).

To be diagnosed with probable Alzheimer's disease, patients must meet criteria compatible with the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) guidelines. These include:

- Dementia established by clinical examination, with a moderate degree of cognitive impairment at screen, as documented by a score of 13–24 on a standardised Folstein Mini-Mental State examination (MMSE)[1]
- Deficits in memory and one other area of cognition (that is orientation, language, praxis, attention, visual perception, problem-solving, social function), documented by reference to items missed on the MMSE examination and/or other mental status testing documented in medical records
- Progressive (rather than stepwise) worsening of memory and other cognitive functions documented for at least six months before enrolment. Acceptable documentation includes a written statement regarding overall clinical impression obtained from any healthcare professional who has had patient contact ≥six months before study entry. Documented information obtained through phone interview of a healthcare professional is acceptable
- No disturbance of consciousness (delirium, drowsiness, stupor) that prevents adequate evaluation of mental status
- Onset of dementia between the age of 40 and 90 years
- Absence of systemic disorders or other brain diseases that could account for the progressive deficits in memory and cognition.

Uniquely in clinical trials, the very fact that the patient has dementia means that the caregiver assumes an important role in the future assessment of that patient. Ideally, the caregiver will remain constant throughout the trial and the study protocol should be clear on how it will deal with a change in carer. It is worth remembering that assessments via scales based on patient observation are highly subjective and each observer will have a different perspective on the disease. Subjects must be cared for by someone reliable, who will be responsible for ensuring drug administration and the

Causes of dementia

Central nervous system
- Cerebrovascular disease – that is vascular dementia
- Parkinson's disease
- Huntington's disease
- Lewy body dementia

Other medical conditions
- Hypothyroidism
- Vitamin B_{12} deficiency
- HIV infection
- Brain injury
- Depression
- Pick's disease

Substance abuse
- Alcoholism (Korsakoff's syndrome)
- Other drug abuse

completion of protocol-stipulated assessments, either directly or through proxy. The same individual should be able to perform this role for the entire study. For most studies the consistency of the caregiver means that patients must not require skilled nursing home care other than for short-term respite.

Avoid the 'just-eligible' patient

At the start of a clinical trial most investigational sites will have a good idea of their 'best' patients, who will be screened and, if eligible, invited to participate. However, the need to speed up patient enrolment for reasons of cost and timely conclusion means that more pressure is being applied to investigators. Consequently sites may trawl for patients. This may not be a problem in many therapeutic areas, but in Alzheimer's research it certainly is. The reason once again lies in the fact that we are using subjective scales to measure the disease. It is well known that the commonly used scales have 'floor-and-ceiling' effects that is at the top and bottom of the scale range the sensitivity to change lessens.

Thus, a patient with mild Alzheimer's disease may have a slow deterioration on a scale such as the ADAS-cog. Equally, a more severely affected patient may well be deteriorating, but this is not reflected in the change on that scale. In clinical trials of mild to moderate disease, the intention is to include patients whose change in disease is most likely to be captured by the scale with a high degree of sensitivity. Accordingly, it is desirable to have a good spread of patients whose baseline disease severity lies within the entry criterion range, for example 13–24 on the MMSE.

Unfortunately, I have seen trials where the only-just-eligible patients are squeezed into this range. If this happens regularly then 'tails' can occur in the distribution of baseline MMSE scores (see Figure 1). These patients are most vulnerable to floor-and-ceiling effects and their over-inclusion can lead to spurious results and even a falsely negative trial, particularly in trials assessing disease-modifying agents.

To conduct with patient	To conduct with caregiver
Morning study drug administration	NPI (neuro psychiatric inventory)
↓ (wait 90min)	↓
ADAS-Cog	ADCS-ADL
↓ (rest 5–10min)	↓
Interview for CIBIC+*	Interview for CIBIC+*
↓	↓
Safety procedures	CGIC (clinician's global impression of change)

*Uses information obtained from both patient and caregiver interview. Note that the patient interview for the CIBIC+ (clinician's interview-based impression of change) precedes the caregiver interview

Figure 2: Illustrative assessment timings for patient visit.

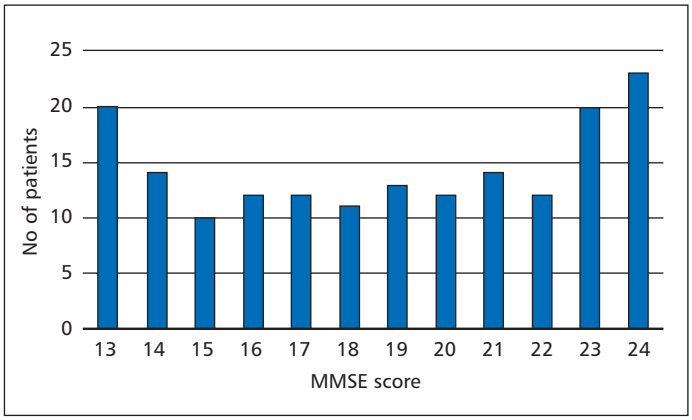

Figure 1: Distribution of baseline mini-mental state examination (MMSE) score.

One solution is to use the latest technologies for data capture and management. This approach enables careful and near real-time monitoring of patient's baseline characteristics and, without compromising blinding, allows the sponsor or CRO to detect rapidly those sites that are including only-just-eligible patients. A quick telephone call to the site staff to remind them of the need to ensure a good distribution of disease severity is usually all it takes to avoid problems further down the line.

Measuring what matters

Many of the scales used in Alzheimer's disease trials are lengthy and complicated to complete. For anyone who is interested, I recommend you sit down with a typical battery of scales and complete them yourself. I guarantee you will become rather jaded by the end. Imagine what is must be like for a patient with Alzheimer's disease. It is well-documented that the quality of data collected by scales deteriorates the more times they are performed. Although it is tempting to include many different scales examining slightly different facets of the disease into the trial protocol, this should be avoided and careful consideration given to the benefit of including scales beyond those necessary to meet regulatory requirements.

Ensure consistency in endpoint timings

Drugs to treat Alzheimer's disease fall broadly into two categories – those that provide a short- to medium-term improvement in the patients' cognition, performance or behaviour, for example the acetylcholinesterase inhibitors; and those that have a putative effect on the underlying disease processes, that is disease modifiers. The former result in a modest improvement, typically around 2–3 points on the ADAS-cog, and the latter should show a reduction in the rate of deterioration on the ADAS-cog, typically around 2–3 points' difference from placebo or natural progression at 12 months.

These are very small differences and can be completely overshadowed by lack of precision in administering a scale such as the ADAS-cog. Indeed it has been said that the desired treatment effect can be masked by the patient drinking a glucose-loaded

glass of orange juice before the scale is administered or by the patient completing the scale in the morning of the first visit and the afternoon of the second. Therefore, the trial protocol should lay down clear rules about the timing of assessments. For example, all psychometric evaluations should begin at a predetermined time, for example 90 minutes after the first morning study drug administration. Illustrative testing sequences for efficacy measures to be completed at each patient/caregiver visit are depicted in Figure 2. Of course, the evaluation of the patient and the carer should be made by the same clinician or rater at each visit.

Ensuring drug compliance

The very nature of Alzheimer's disease makes assessment of drug compliance critical in clinical trials. Many patients will have a competent caregiver who can supervise medication dosing. However, simple factors such as user-friendly packaging and dosing reminders are helpful adjuncts in clinical trials. Many later phase trials use sparse sampling techniques to measure population pharmacokinetics and this also can be used to assess compliance.

In this article I have highlighted the most common issues affecting clinical trials into Alzheimer's disease. Clinical trials of drugs intended to treat Alzheimer's disease are complicated, lengthy and expensive. The desired treatment effects can easily be masked by the introduction of bias and excessive variability, both of which reduce the chance of finding a statistically significant result in favour of the drug. Trials for Alzheimer's disease demand the highest possible standards of precision in their design and execution. This precision must be provided by the sponsor company or the CRO and by the investigational site staff, notably well-trained psychometric raters.

Even with well-conducted trials, it is imperative for the sponsor or CRO to maintain a constant watchful eye on the quality and precision of execution. In this respect, using modern technologies for data acquisition and management is highly recommended. Above all, to be aware of a problem is to have the opportunity to avoid the problem. GCPj

Reference

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