The role of placebo control in clinical trials for neurodegenerative diseases

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Finding effective interventions for neurodegenerative diseases is arguably one of the final frontiers of medicine, in part because of failure to study the complex nervous system using human experimental medicine systems.[1] Notwithstanding emergent promising medicines for the treatment of Alzheimer's dementia,[2] there are no truly effective disease modifying therapies for motor neuron disease (MND), noting that riluzole, approved in 1995, extends survival by just 2-4 months. Biologically plausible candidate medicines are being tested in clinical trials, although ~90% of candidates (either repurposed or bespoke) fail in clinical trials.[3] This highlights the urgent need for a novel approach, away from two-arm studies, that will deliver efficient (time, cost and patient resource) and definitive evaluation of multiple promising medicines in clinical trials.[4]

Platform multi-arm multi-stage (MAMS) randomised phase III trial designs offer demonstrable advantages, because they simultaneously enable: definitive evaluation of multiple treatment arms against a single control group; early cessation of treatments that show no sign of activity through multiple staged analyses against pre-determined futility outcomes; and addition of new arms in a continuous trial platform.[5] An example in the neurodegenerative disease area is the Motor Neuron Disease Systematic Multi-Arm Adaptive Randomised Trial (MND-SMART; NCT04302870), a MAMS platform phase III double-blind, placebo-controlled trial launched for any neurodegenerative disease.[6] Commencing in February 2020, by August 2023 >575 people with MND have been randomised in >20 UK hospitals. Alongside the Phase 2/3 HEALEY platform trial (USA; NCT04297683), this heralds a new era of trial innovation for neurology.[7]

A practical advantage of phase III MAMS platform studies compared with conventional two-arm designs, particularly in rapidly fatal conditions, is that only a single concurrent control arm is needed; from a patient perspective this increases the chance of receiving a novel intervention. Thus, if a MAMS trial evaluates 3 active drugs (as currently in MND-SMART), this represents a 3-fold reduction in the number of control patients—a substantial reduction.

In phase III MAMS platform studies, the size of the control group can be further reduced, or even possibly removed, using one or more of the following approaches, each with the price of

additional (unverifiable in the trial at hand) assumptions. These include: incorporation of randomisation ratios that enrich treatment arms;[8] using a synthetic placebo of historical control data from previous trials,[9] real-world data from disease registers,[10] or validated prognostic models that predict disease outcome and give an expected disease trajectory in people recruited to a trial (assuming no treatment) versus the real trajectory where the experimental treatment was administered;[11] or pooling of contemporaneous with non-contemporaneous controls, allowing for comparisons to be made with participants receiving different routes of administration and/or dosing schedules.

The key test for each of these approaches is whether they will accelerate the identification of medicines that objectively, definitively and persuasively improve outcomes for people living with MND. Use of synthetic placebo or non-contemporaneous controls may accelerate a specific trial, but this is at the price of introducing uncertainty in the robustness of trial results; it may introduce bias as it is not guaranteed that the control group is comparable to the active group. This is likely to lead to disagreement over the reliability of results, with consequent difficulties in obtaining regulatory approval and widespread use—the ultimate aim. In consequence, there will need to be further trials, and more patients randomised to control; one trial is accelerated, but the overall pace of identification of effective interventions and their incorporation into standard-of-care is slowed. By contrast, incorporation of concurrent controls provides solid evidence of the benefit of effective treatments, which can be incorporated into the control arm in a continuing MAMS study.

Reflecting on these points, people living with MND who co-produced MND-SMART have considered the pros and cons of the use of a control group, including a placebo. Their feedback included the attraction of being on an active intervention, but also an acknowledgment that the absence of harm is vitally important, noting that some potential candidate treatments may be unpredictably harmful, as well as ineffective. People with MND expect to receive the current best standard-of-care and understand that randomised trials not only test medicines, but are also a critical resource for biomarker discovery, which requires comparison to randomised control data.

Although placebo-control is desirable, MAMS trials need to consider how this will be maintained with the addition of new arms, where candidate treatments have different routes of administration. A novel approach to this is the use of a pooled placebo, where the comparison is known, but blinding is maintained for active versus control, such as in the HEALEY trial for ALS, which tests multiple treatments at once. The pooled placebo approach, although superficially promising, does not solve the problem. Firstly, knowledge of the possibility of randomisation to a particular comparator may bias rating scores. More seriously, stopping arms during the trial can be problematic, since, if a treatment arm is dropped, then its matching placebo arm must also be discontinued, to maintain blinding. This prevents collection of data on long-term outcomes for a proportion of the placebo patients, reducing power and the value of the trial. To address this, HEALEY will use a Bayesian approach to model heterogeneity in the rates of progression of shared controls over time and across regimens through inclusion of hierarchical random effects.[7] A simulation study found this method worked well when the event rate was similar across different placebos. However, if there were differences between the different placebos, then this could lead to an increased chance of false-positive results.[12]

There are >80 live phase III MAMS trials registered on clinicaltrials.gov at the time of writing; over half lack a placebo-control, and only a third have full placebo-control blinding. An open-label study without placebo-control would be reliable only with a objective primary outcome, such as length of survival, since subjective measures, such as the ALS-FRS(R) (a validated measure of disability), are open to bias in the absence of blinding or placebo.

While there is widespread agreement on the need to continue research in developing and evaluating proposals to reduce the number of concurrent control patients, there is currently no agreement on the criteria that need to be met and how to set about satisfying such criteria. Premature elimination of concurrent control arms will damage the ability of Phase III trials to command widespread acceptance in identifying effective therapies. Until such criteria are agreed, along with approaches to satisfy them, we believe that it is in the best interests of all parties, and patients in particular, that MND-SMART and similar trials continue with a randomised concurrent control arm.

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Competing interests

The authors have no conflicts of interests to declare.

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