The role of placebo control in clinical trials for neurodegenerative diseases

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The role of placebo control in clinical trials for neurodegenerative diseases

Finding effective interventions for neurodegenerative diseases is arguably one of the final frontiers of medicine, in part because of a 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); riluzole, approved in 1995, extends survival by only 2–4 months. Biologically plausible candidate medicines are being tested in clinical trials, although most candidates (either repurposed or bespoke) fail in clinical trials[3]. This highlights the urgent need for a novel approach, apart from two-arm studies, that will deliver efficient (in terms of time, cost and patient resources) and definitive evaluation of multiple promising medicines in clinical trials[4].

Platform multi-arm multi-stage (MAMS) randomized phase 3 trial designs offer demonstrable advantages, because they simultaneously enable the following: 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 the addition of new arms in a continuous trial platform[5]. An example of this in the neurodegenerative disease area is the Motor Neuron Disease Systematic Multi-Arm Adaptive Randomized Trial (MND-SMART; NCT04302870), a MAMS platform, phase 3, double-blind, placebo-controlled trial launched for any neurodegenerative disease[6]. MND-SMART commenced in February 2020, and by August 2023, over 575 people with MND had been randomly assigned in over 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 3 MAMS platform studies over conventional two-arm designs, particularly in rapidly fatal conditions, is that only a single concurrent control arm is needed; from a patient's perspective, this increases the chance of receiving a novel intervention. Thus, if a MAMS trial evaluates three active drugs (as currently in MND-SMART), this represents a threefold lower number of control patients — a substantial reduction.

In phase 3 MAMS platform studies, the size of the control group can be reduced further, or even possibly removed, through the use of one or more of the following

approaches, each with the price of additional (unverifiable in the trial at hand) assumptions: incorporation of randomization ratios that enrich treatment arms[8]; use of 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 provide an expected disease trajectory for people recruited to a trial (assuming no treatment) versus the real trajectory in which the experimental treatment was administered[11]; or pooling of contemporaneous control participants with non-contemporaneous control participants, which allows comparisons of 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. The use of synthetic placebo or non-contemporaneous controls may accelerate a specific trial, but this is at the price of introducing uncertainty into 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. As a consequence, additional trials will be needed, with more patients randomly assigned to the control group; one trial will be accelerated, but the overall pace of identification of effective interventions and their incorporation into standard of care will be slowed. By contrast, studying concurrent controls provides solid evidence of the benefit of effective treatments, which can ultimately then be incorporated into the control arm as the standard of care in a continuing MAMS study.

Reflecting on these points, the 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 randomized trials not only test medicines but also are a critical resource for biomarker discovery, which requires comparison with randomized control data.

Although a placebo control is desirable, MAMS trials need to consider how this will be maintained with the addition of new arms, in which candidate treatments have different routes of administration. A novel approach to this is the use of a pooled placebo, whereby the comparison is known, but blinding is maintained for active versus control, such as in the HEALEY trial for amyotrophic lateral sclerosis, which is testing multiple treatments at once. The pooled placebo approach, although superficially promising, does not solve the problem. First, knowledge of the possibility of randomization to a particular comparator may bias rating scores. More seriously, stopping arms during the trial can be problematic, because if a treatment arm is dropped, then its matching placebo arm must also be discontinued, to maintain blinding. This prevents the collection of data on long-term outcomes for a proportion of the patients receiving the placebo, which reduces the power and 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 the 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, this could lead to an increased chance of false-positive results[12].

There were over 80 ongoing phase 3 MAMS trials registered on the ClinicalTrials.gov website at the time of this 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 an objective primary outcome, such as length of survival, as subjective measures, such as the ALS-FRS(R) (a validated measure of disability), are open to bias in the absence of blinding or a placebo.

Although 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 3 trials to command widespread acceptance in identifying effective therapies. Until such criteria are agreed on, along with approaches to satisfy them, we believe that it is in the best interests of all parties, and of patients in particular, that MND-SMART and similar trials continue with a randomized concurrent control arm.

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Competing interests

The authors declare no competing interests.