LETTER TO THE EDITOR

Smarter adaptive platform clinical trials in neurology: a showcase for UK innovation

Arpan R. Mehta,[1,2,3,4,5] Suvankar Pal,[2,3,4,5] Jeremy Chataway,[5,6,7] James R. Carpenter,[5,8] Mahesh K. B. Parmar[5] and Siddharthan Chandran[2,3,4,5,9]

1 Oxford University Hospitals NHS Foundation Trust, Oxford, UK

2 Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK

3 Anne Rowling Regenerative Neurology Clinic, University of Edinburgh, Edinburgh, UK

4 Euan MacDonald Centre for MND Research, University of Edinburgh, Edinburgh, UK

5 ACORD at MRC Clinical Trials Unit, Institute of Clinical Trials and Methodology, University College London, London, UK

6 Queen Square Multiple Sclerosis Centre, Department of Neuroinflammation, UCL Queen Square Institute of Neurology, Faculty of Brain Sciences, University College London, London, UK

7 National Institute for Health Research, University College London Hospitals, Biomedical Research Centre, London, UK

8 Department of Medical Statistics, London School of Hygiene & Tropical Medicine, London, UK

9 UK Dementia Research Institute at University of Edinburgh, Edinburgh, UK

Correspondence to: Professor Siddharthan Chandran
Anne Rowling Regenerative Neurology Clinic, University of Edinburgh, Chancellor's Building, 49 Little France Crescent, Edinburgh, EH16 4SB, UK
E-mail: siddharthan.chandran@ed.ac.uk

We read with great interest the recent Editorial about smarter adaptive platform clinical trials in neurology.[1] Neurologists, once described as chroniclers of disease and stamp collectors, increasingly now have the tools to begin to slow, stop and potentially reverse progressive neurological conditions, including neurodegenerative disorders. This more sanguine prospect reflects vast and continued progress over the last two decades in our understanding of the cellular and molecular pathophysiology of neurodegeneration. These advances have been catalysed, in part, by the emergence of disruptive technologies, including gene-editing and cell reprogramming.[2] Sydney Brenner remarked in 2008: "We don't have to look for a model organism anymore. Because we are the model organisms."[3] Harnessing patient-derived induced pluripotent stem cell (iPSC) based approaches, combined with gene-editing, has created new and powerful human drug discovery, screening and testing platforms that complement pre-clinical experimental systems. Critically, human-led discovery is likely to reduce the high failure rate of new interventions in human clinical trials that historically has resulted from a failure to translate discoveries exclusively rooted in animal models. Furthermore, it can be scaled to potentially address clinical heterogeneity and opens up the possibility of a personalised medicine pipeline: the effect of a medicine can be estimated prior to administration through the use of patient-derived iPSCs, making it possible to deliver the appropriate medicine to responder patients.[4]

To capitalise on these laboratory-science discoveries there is a need, in parallel, to innovate in clinical trial design, so that the ever-increasing number of promising putative medicines can be rapidly, efficiently, and definitively tested.[5,6] There is much to learn from cancer medicine. Specifically, flexible platform trials that: (i) incorporate simultaneous testing of multiple interventional arms with a single standard-of-care arm; (ii) allow for pre-specified adaptation at interim points of analyses, and which (iii) are designed to be able to include new interventional arms, offer substantial advantages over the standard two-arm trial model. These include major efficiency gains in time, cost and resource to reach definitive Phase 3 outcomes.[7] Notably, the UK has led the way in developing this approach; for example, the landmark STAMPEDE platform trial for prostate cancer has evaluated 8 treatments in 16 years to date, leading to change of standard-of-care 4 times, in a time-frame that is several decades less than that required for a conventional sequential two-arm trial approach.[8] New protocol amendments enabling the evaluation of drugs with different routes of administration by using a master protocol that randomises to different studies for different subgroups of patients each with matched placebo is the future for neurodegenerative trials, together with the seamless evaluation of combinatorial therapies targeting multiple pathways and/or cell

types/cellular compartments. Overall, there is an ongoing need to innovate at each stage of the process, from drug discovery, development and screening, through to trial design, conduct and analysis.

ACORD (A Collaboration Of groups developing, Running and reporting platform trials in neurodegenerative Diseases) is a recently created UK-wide consortium hosted by the MRC Clinical Trials Unit at University College London to share ideas and approaches about how to evolve trial designs for neurodegenerative conditions to address this pressing need.[9] ACORD has already launched pioneering pathfinder multi-arm, multi-stage platform trials for multiple sclerosis (OCTOPUS; EudraCT number 2021-003034-37) and motor neuron disease (MND-SMART; EudraCT number 2019-000099-41; NCT04302870). MND SMART, the largest academic trial in MND in the UK, initially testing two repurposed drugs (trazodone and memantine against placebo), has 17 UK sites, with over 300 people with motor neuron disease randomised since Spring 2020 (despite the COVID-19 pandemic), and has performed its stage 1 interim analysis in March 2022. MND-SMART complements the HEALEY ALS platform trial in the USA and is notable for including survival, as well as functional outcome measures, in a Phase 3 design that obviates the need for further trials to secure MHRA and EMA approval. MND-SMART features broad inclusion criteria (meaning the results are generalisable), liquid investigational medicinal products, and video/telephone assessments—benefits driven by people living with motor neuron disease, sponsored by charities. These and related innovations, such as remote/digital consenting and couriering of medication, have facilitated the recruitment of participants from all areas of the UK (such as the Isle of Wight and Orkney Islands)—people that would have historically struggled to have had the opportunity to participate in a clinical trial for a neurodegenerative disorder. Accordingly, platform trials such as MND-SMART and OCTOPUS bring unprecedented opportunities for discovery and reverse translation through trial-linked biobanking, as well as for innovation of trial operations and outcomes through digital technologies.

To capitalise on these laboratory and clinical advances there is an urgent need to develop and train the next generation of translational clinician-scientists who are expert in novel trial design methodology and delivery. This discipline has, by comparison to mechanistic laboratory research, been comparatively overlooked as ripe for future clinician-scientists. We must move towards recalibrating neurology in the UK towards an interventional specialty, where the default for patients is trial participation (like in cancer medicine).

Data availability

Data sharing is not applicable to this article as no new data were created or analysed in this study.

Competing interest

The authors report no competing interests.

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