PREliminary development of a Multi-Arm, multi-Stage Trial platfOrm for Dementia and mild cOgNitive impairment due to Alzheimer's Disease (PRE-MASTODON-AD)

Research Plan

1. Full Title: PREliminary development of a Multi-Arm, multi-Stage Trial platfOrm for Dementia & mild cOgNitive impairment due to Alzheimer's Disease (PRE-MASTODON-AD)

2. Summary of Research (Abstract)

Research Aim

Using this Application Development Award, we will lay the foundations for a multi-arm, multi-stage (MAMS) platform that will transform our ability to rapidly assess repurposed treatments for symptomatic Alzheimer's Disease. We will establish dedicated PPIE groups and a systematic drug selection process as well as identifying the first three compounds for inclusion into the platform. We will also finalise the set of outcome measures for the trial and complete trial design, including carrying out appropriate simulations.

Background

950,000 people in the UK have dementia, causing major personal hardship and costing over £30 billion/year. Licensed treatments for Alzheimer's Disease (AD), the most common cause of dementia, have not changed in 20 years and offer only modest benefits. Trials of new disease-modifying treatments show promise but increasingly focus on earlier disease stages and show relatively small benefits that vary by gender, ethnicity, and genetic factors. Potential side-effects are significant. Current trials for Alzheimer's dementia are frequently inefficient, biased to underpowered studies, or poorly representative of the wider population with clinical AD. Trials often focus on testing newer compounds rather than repurposing existing drugs for which there is compelling proof-of-concept evidence, and which have a well-established safety profile.

Aim

Our long-term aim is to set up and implement a MAMS platform trial which will, in its first phase, complete evaluation of three leading drugs with proof-of-concept evidence in Alzheimer's Disease. The aim of this proposal is to carry out the initial preparatory work for this platform.

Methods

We will lay the groundwork for establishing this MAMS platform by completing three work packages, each being carried out via a separate group with patient and public representation:

1 Establish a systematic, robust, and sustainable drug prioritisation process and identify leading compounds for inclusion in the first phase of a major AD trial platform.

2 Identify and select measures of cognition and behaviour that reflect meaningful changes in quality of life and activity at home.

3 Complete design, including simulations and use of placebo, of the proposed MAMS platform in preparation for a full funding proposal in 2025.

Timelines for delivery

Our planned grant start date for the proposed work is August 2024 with an end date of 31 July 2025. We would expect to submit a major funding proposal in September 2025 with the aim of starting the platform in 2026.

Anticipated impact and dissemination

Our team's previous platform in prostate cancer (STAMPEDE, commenced 2006) resulted in multiple changes to standard of care, and median increase of 7 years in survival. Our use of this design in Motor Neurone Disease and progressive Multiple Sclerosis has transformed UK clinical research in these fields. We aim to develop a sustainable platform that will provide a new paradigm for PPIE co-production, inclusivity, and drug evaluation as well as harnessing existing and new trials infrastructure to transform the UK clinical dementia research landscape.

3. Background and Rationale

There is a pressing need for new dementia treatments. Licensed AD treatments have not changed for 20 years, and offer only limited symptomatic benefit (e.g., donepezil, rivastigmine, galantamine; memantine) (1). Trials of new disease-modifying treatments show promise but increasingly focus on disease modification mechanisms at earlier stages (2) and most people diagnosed with clinical Alzheimer's disease are unlikely to be eligible for treatment (3-5).

Most current trials testing single interventions require their own funding, personnel & ethical/administrative approvals. After completion, the 'machinery' is dismantled. Thus, the next study needs to start from scratch, analogous to dismantling a stadium after each match. Moreover, this approach requires that many more patients than necessary receive placebo. Narrow inclusion/exclusion criteria (6) and little emphasis on inclusivity/co-design have led to failure to include participants reflecting the real NHS patient population. Finally, industry-sponsored trials tend to assess only new compounds, rather than evaluating existing drugs with good proof-of-concept evidence for repurposing in AD.

These issues will be addressed through a UK-wide platform trial. Platform trials, where multiple intervention arms are simultaneously compared with a single placebo arm, reduce the number of people who are assigned to the placebo arm and maximise study efficiency by using a single infrastructure to evaluate multiple treatments. Specifically, 'multi-arm, multi-stage' (MAMS) trials, pioneered by members of our team, have led to major changes in cancer treatment and have recently been introduced in Neurological settings by ACORD (https://www.mrcctu.ucl.ac.uk/our-research/neurodegenerative-diseases/acord-collaboration). In a partnership between ACORD and Dementia Platforms UK we will carry out the preparatory work for trial development and subsequently another full-scale submission.

Our proposal provides a unique opportunity to overcome the challenges described above, drawing on world-leading expertise in trials methodology (ACORD) and dementia (DPUK) in co-production with patient and public representatives. Drug candidates will be prioritised where there is convincing proof-of-concept evidence for symptomatic benefit and/or disease-modification together with a good safety profile. The multi-stage approach enables comparison of several treatments in parallel arms with a single placebo arm (7). Planned predetermined interim analyses use a common framework to determine safety, tolerability, and early stopping for lack of activity. Our trial platform will aim to implement remote assessments that are acceptable to patients and carers, and applicable across the population. The work described in this proposal will ensure that we are well placed to evaluate the lead existing compounds for treating symptomatic Alzheimer's Disease, and, critically, to detect meaningful clinical effects using methods that are acceptable to people living with Alzheimer's Disease.

Why is this research important in terms of improving the health and/or wellbeing of the public and/or to patients and health and care services?

80% of patients with symptomatic AD in the NHS are not eligible for current pharma-led disease modifying trials, either due to in part to dementia severity (most trials limit entry to MCI or mild dementia only) or co-morbidities. A platform trial focussing on assessing efficacy of drugs with an established safety profile represents a unique and timely opportunity to progress treatments that can be easily made available (8, 9). and be more attractive to candidate patient participants.

Review of existing evidence - How does the existing literature support this proposal?

i) MAMS Platform Trials

A MAMS platform provides infrastructure for swiftly including new treatment arms and allowing timely closure of arms showing no activity (10). We have experience of developing platforms

in other disease areas that have changed clinical practice (7). Through ACORD we have successfully implemented MAMS repurposing platforms in MND (11) and progressive MS (12).

ii) Repurposing

To identify compounds with the greatest promise and minimise bias arising from individuals' interest in specific approaches (13), our team has carried out previous evidence reviews for repurposing in AD with Delphi consensus, involving a panel of international researchers and representatives of patient organisations (14). Two compounds from the 2020 review have progressed to Phase II trials. A further (Alzheimer's Society funded) review is in progress and will be completed by summer 2024. In addition, to select drugs for inclusion in the MND-SMART and OCTOPUS trials, ACORD Members have generated novel, 'living' methods that can be directed towards other neurodegenerative diseases including AD.

iii) Outcome Measures

Classical pen-and-paper outcomes are expensive as they require staff time and clinic visits, and are influenced by cultural background and educational status (15). The COVID-19 pandemic demonstrated that some assessments can be carried out remotely. Technology-based approaches to assess cognitive and behavioural abnormalities in AD can reduce participant burden but is essential to ensure that these are clinically meaningful and do not lead to digital exclusion. We will evaluate newer approaches alongside older outcome measures alongside, selecting those where there is clear validity and acceptability to patients and carers. This will be achieved using the principles established by the NIHR working group (including co-applicant O'Brien) on remote trial delivery (16).

4. Aims and Objectives

The aim of this proposal is to address key issues for a major trial platform, enabling design and preparation of a full funding proposal in late summer 2025. This will be carried out through three work packages (see below).

5. Research Plan/Methods

Research Design

PPIE is central to this proposal and our planned platform. Prior to the start of the proposed work, we will convene a series of meetings of our 'main' PPIE group, led by Pointon, Underwood and Khan, involving people with lived experience of dementia, representatives of key UK Dementia charities, and representatives from the CARE (https://www.kcl.ac.uk/research/community-ageing-research-across-ethnicities-care-network-1) group. This PPIE group will meet monthly throughout the timeline of the proposal.

Work Packages

1) Drug Selection Pipeline

This will establish a systematic, structured, and unbiased drug prioritisation pipeline, which will initially be used to select three repurposed medications with the greatest potential for improving symptoms and/or modifying disease progression. These will then be incorporated into investigational arms in the first phase of the main proposal. Prior to grant commencement we will formalise a process for involving the wider AD community in identifying 'high potential' compounds to include in the first phase of our planned trial platform. This will be disseminated via the main Alzheimer's Charities (ARUK, Alzheimer's Society) as well as other relevant bodies (Dementias Platform UK, Association of British Neurologists, NIHR Dementia Translational Research Collaboration, Royal College of Psychiatrists, UK Dementia Research Institute, Alzheimer's Association International Conference). Industry will also be invited to propose possible treatments, , including via DPUK's Company Partner Forum, The Dementia Industry Group (DIG), and DTRC's Industry Forum. Finally, researchers (including co-applicant Ballard) who are leading an Alzheimer's Society funded review and Delphi process (14, 17) will also contribute (see support letter).

All contributors will be asked to summarise the underlying rationale for their proposed medication and drug CVs will then be generated for each compound, using the Repurposing Living Systematic Review (ReLiSyR) approach developed for the MND-SMART trial (Wong et al., 2022). This consists of a machine-learning assisted systematic review of published clinical literature to aid evidence synthesis. Drugs will then be reviewed by a panel consisting of experts (including specialist Alzheimer's clinicians, basic scientists, and patient/public representation) with expertise across symptomatic and disease-modifying treatments as well as specific pathogenic processes such as Neuroinflammation. Alzheimer's Research UK have confirmed that a member of their team will join the panel and, as for the OCTOPUS platform trial, the platform lead will not be part of this process. The drug prioritisation panel will meet at the start of the grant award period (Aug 2024) and drug proposers will be invited to present the evidence base supporting the use of their compound in Alzheimer's Disease at this meeting. Following the meeting, the panel will shortlist a maximum of 10 initial suggested compounds. Shortlisting will be based scores in the following domains: Efficacy and biological plausibility (including Central Nervous System penetrance); Safety; Feasibility in a platform trial.

Full evidence review will then be carried out for each of the shortlisted compounds, with extended drug information collated for each. This will be based on processes developed in the context of the MND-SMART (18) and OCTOPUS MAMS platforms (12, 19). An Academic Clinical Fellow (ACF) based at Imperial, supported by the funded Research Assistant, will carry out systematic literature searches to enable a robust evaluation process of pre-clinical model work, followed by assessments of known safety and toxicity, target binding and availability, with consideration of early clinical data from AD and other neurological diseases. In addition to pharmacological and therapeutic data the team will also compile relevant practical information that will aid decision-making. This will include access to drug supplies and placebo versions, cost, and/or feasibility of over-encapsulation, as well as considerations relating to pharmacy, distribution, and labelling requirements.

All relevant information will be collated into an extended drug CV for each medication over the course of 3 months. Each CV will be reviewed in detail by two panel members and presented to the wider panel, at a second meeting in December 2024. At this point, each compound will be discussed in detail and three selected for potential inclusion into the platform trial. Candidates will first be scored, primarily on efficacy and safety, but also on ease of administration, tolerability, safety, and monitoring requirements. A key consideration for inclusion, as assessed by the patient/public representative panel members, will be patient acceptability of any proposed intervention. In addition, we will ensure that issues specific to a platform trial setting are considered, such as selecting medications that have different pharmacological mechanisms and the feasibility of being able to prepare a shared placebo (discussed in a MAMS trial placebo workshop convened by ACORD, Jan 2024).

This two-step process will be repeated in 2025 to shortlist and evaluate further compounds for potential inclusion later in the trial process as well as relevant new evidence for previously discussed drugs. If any of the compounds evaluated in this second round of the process are considered to have extremely high promise, and can feasibly be included at platform commencement, then they may replace one or more of the original shortlist. To ensure the platform's sustainability, this process will be repeated annually during the course of the platform.

2) Outcome Measure Selection

Outcome measures in AD trials continue to be based on pen-and-paper instruments designed decades ago. Although electronic and remote cognitive testing approaches have been developed, these tend to consist of computerised versions of existing cognitive tests or techniques. These can be arduous and problematic for use with diverse populations (20) and do not map onto everyday function (21).

Recently there has been movement towards developing more accessible remote and technology-based outcome measures for neurodegenerative disease. For the planned trial platform, we aim to use a set of measures that i) are sensitive to change across multiple stages of disease, ii) are acceptable to patients and carers, iii) have face-validity and currency value in the AD research community, iii) have recognised minimal clinically important difference values iv) cover the breadth of Alzheimer's symptomatology. To achieve this, our outcome measure subgroup, led by Dunne and including PPIE representatives as well as other experts.

In our previous submission, we included the Alzheimer Disease Assessment Scale – Cognitive (ADAS-Cog), the Neuropsychiatric Inventory (NPI) Questionnaire and the Bristol Activities of Daily Living Scale (BADLS) as primary outcome measures. These scores all fit the criteria above but will be supplemented by additional digital outcomes. Examples of include computerised cognitive neuropsychological tests that have been validated (22), as well as remote side effect questionnaires that have previously been implemented in trials with cognitively impaired participants. Using an analogous approach to the drug selection process, we will prepare outcome measure summaries for commercial and non-commercial measures of cognition, non-cognitive symptoms, and activities of daily living. The CV information which will include level of validation, availability, appropriateness across levels of cognitive impairment, cost, and applicability amongst underrepresented participant groups. We will also liaise with MHRA to ensure that primary outcomes measures are pre-approved.

3) Trial Design

In our full submission, we proposed a placebo-controlled platform trial, with three active treatment arms (n =295 per arm). This was based on data from the Critical Path (https://c-path.org) Alzheimer's data set and preliminary data from the ongoing NIHR NorAD trial (23). As per other ACORD platforms, our platform design also included a staggered start for the treatment arms with the third arm starting after 18 months. For this proposal, in response to the board's suggestions, we shall carry out statistical simulations including the required sample size as suggested by the NIHR EME Board, using the Critical Path dataset as well as NorAD data (available from Aug 2024). Using our original design as the template, the trial design team led by Carpenter and the funded Grade 8 statistician, as well as external triallists and statisticians with expertise in platform trial design, will also address the need for placebo, predicted dropout rate, and strict criteria for adding/removing trial arms, including toxicity.

Core Development Team

Our core development team, including the 3 Co-Is, PPIE representatives and work package leads will meet monthly over the course of the grant. Taking further PPIE input into account, we will revisit key issues including those raised by the board, including consent strategies, hypotheses underlying mechanistic work, and the need for placebo. The team will also scope developments in the field, particularly relating to the introduction of new treatments and diagnostic approaches in the NHS and how the trial will integrate with these.

6. Dissemination, Outputs and Anticipated Impact

This proposal, if funded, will provide the critical groundwork for a MAMS trial platform in symptomatic Alzheimer's Disease. The key impact will come from accelerating the assessment of a range of symptomatic treatments with a view to providing patients with efficacious medications as swiftly and efficiently as possible. Using the outputs from this award we anticipate a full application in late 2025, with the aim of starting such a trial in 2026.

7. Project/research timetable

Pre-Award:	Call for treatment proposals from AD community
	PPIE Group Meetings x 2
Aug 2024:	Grant Commencement (Monthly Core and PPIE Meetings)

	Drug and outcome subgroup meetings Scoping and statistical design
Dec 2024	1st Drug and outcome subgroup review meetings Design refinement according to selected treatment/outcomes
Feb 2025	Drug and outcome subgroup meetings Preliminary preparation of full platform proposal
June 2025	2nd Drug and outcome subgroup review meetings Finalisation of platform proposal (and Stage 1 submission)
Aug 2025	End of grant

8. Project management

The project has leadership from across the UK Dementia trials landscape. CI is Malhotra (ACORD, DPUK, UK DRI, NIHR TRC-D) with co-leads Carpenter (ACORD) and Raymont (DPUK, Deputy Chair NIHR TRC-D). They will lead the project with support from co-applicants and input from the MRC Clinical Trials Unit at UCL, DPUK and ACORD members.

9. Ethics/Regulatory Approvals

Ethics and regulatory approvals will not be required for this stage of work.

10. Project/research expertise

This proposal draws on world-leading expertise across platform trial design and dementia research and includes researchers and clinicians from throughout the UK.

11. Success criteria and barriers to proposed work

Success criteria

a) PPIE-informed drug selection and clinical trial design that maximises participant inclusion

Barriers to proposed work:

a) Delays in completion of financial contracts and agreements

b) Insufficient candidate treatments

We will mitigate against these barriers through advance planning to address these issues. As soon as we aware of the proposal outcome, we will begin to prepare contracts and ensure suitable staff are ready to be in post. We will reach out to the AD community in advance of the grant and convene meetings of key groups prior to funding start date.

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