EXPERTS-ALS NHS Sheffield Teaching Hospitals NHS Foundation Trust University of Oxford University of Sheffield | Clinical Trials Research Unit School of Health & Related Research	**A multi-centre, Bayesian phase II, open label, randomised drug prioritisation platform trial using blood neurofilament light (NFL) chain levels as a surrogate outcome for biological efficacy in patients with ALS** **EXPErimental medicine Route To Success in Amyotrophic Lateral Sclerosis (EXPERTS-ALS)**
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Sheffield Clinical Trials Research Unit (CTRU)

A multi-centre, Bayesian phase II, open label, randomised drug prioritisation platform trial using blood neurofilament light (NFL) chain levels as a surrogate outcome for biological efficacy in patients with ALS

EXPErimental medicine Route To Success in Amyotrophic Lateral Sclerosis (EXPERTS-ALS)

This document describes a clinical trial, and provides information about procedures for entering participants. The protocol is not intended for use as a guide to the treatment of other patients. Amendments may be necessary; these will be circulated to known participants in the trial.

Authorisation Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, CTRU (and/or any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

Protocol authorised by:

Name, Role and Organisation	**Signature**	**Date**
Christopher McDermott, Chief Investigator, University of Sheffield	Approved via email	10th January 2025
Alessia Dunn, Sponsor Representative, Sheffield Teaching Hospitals	Approved via email	8th January 2025
Peter Jüni, Methodologist, University of Oxford	Approved via email	30th January 2025
Jennifer Petrie, Study Manager, University of Sheffield	Approved via email	7th January 2025

Contents

Abbreviations

Definition of terms

AE	Adverse Event
CCC	Confirmation of Capacity and Capability
AR	Adverse Reaction
CA	Competent Authority
CHI	Community Health Index
CI	Chief Investigator
eCRF	Electronic Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
DMEC	Data Monitoring and Ethics Committee
DSUR	Development Safety Update Report
EC	European Commission
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials Number
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
MS	Member State
NHS R&D	National Health Service Research & Development
NIMP	Non-Investigational Medicinal Product
PCF	Peak Cough Flow
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
PSC	Programme Steering Committee
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
RCT	Randomised Control Trial
REC	Research Ethics Committee
rFVC	Remote Forced Vital Capacity

rPCF	Remote Peak Cough Flow
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVC	Slow Vital Capacity
TMF	Trial Master File
TMG	Trial Management Group

1. General information

1.1 Investigator details

Chief Investigator

Professor Christopher McDermott
Professor of Translational Neurology
NIHR Research Professor
Sheffield Institute for Translational Neuroscience
University of Sheffield
385a Glossop Rd
Sheffield
S10 2HQ

c.j.mcdermott@sheffield.ac.uk
0114 226 1049

Co-chief Investigator

Professor Martin Turner
Professor of Clinical Neurology and Neuroscience
Nuffield Department of Clinical Neurosciences
Level 6, West Wing
John Radcliffe Hospital
Headley Way
Oxford
OX3 9DU

martin.turner@ndcn.ox.ac.uk
01865 223 380

Co-applicants

Name	Institution
Professor Ammar Al-Chalabi	Kings College London
Professor Siddharthan Chandran	The University of Edinburgh
Professor Linda Greensmith	University College London
Professor Dame Pamela Shaw	The University of Sheffield
Professor Kevin Talbot	University of Oxford
Dr Alexander Thompson	University of Oxford
Professor Peter Jüni	University of Oxford
Dr Bruno da Costa	University of Oxford
Professor Cindy Cooper	The University of Sheffield
Ms Diana Papaioannou	The University of Sheffield
Dr Ruben van Eijk	UMC Utrecht
Dr Andras Lakatos	University of Cambridge
Dr Helen Devine	University of Newcastle upon Tyne
Professor Jonathan Mill	University of Exeter
Professor Stuart Allan	The University of Manchester

Name	Institution
Dr Tom Massey	Cardiff University
Honorary Professor Carolyn Young	The Walton Centre NHS FT
Professor Andrea Malaspina	UCL Institute of Neurology
Mr Lee Millard	PPI representative
Mrs Nicola Waters	PPI representative

Participating Centres

Site	Principal Investigator
NHS Lothian (Edinburgh) *NHS Forth Valley (Participant Identification Centre)*	Dr Suvankar Pal
The Newcastle upon Tyne Hospitals NHS FT	Dr Tim Williams
Royal Devon University Healthcare NHS Foundation Trust	Dr Tim Harrower
The Walton Centre NHS FT, Liverpool	Dr Siva Sathasivam
Cambridge University Hospitals NHS FT	Dr Rhys Roberts
Northern Care Alliance NHS FT	Dr Amina Chaouch
Sheffield Teaching Hospitals NHS FT	Prof Christopher McDermott
Cardiff and Vale University Health Board (South Wales) *Participant Identification Centres (PICs):* *Swansea Bay University Health Board* *Aneurin Bevan University Health Board* *Cwn Taf Morgannwg University Health Board* *Hywel Dda University Health Board*	Dr Tom Massey
Oxford University Hospitals NHS FT	Prof Martin Turner
University College London Hospitals NHS FT	Prof Andrea Malaspina
King's College Hospital NHS FT	Prof Ammar Al-Chalabi

1.2 Clinical Trials Research Unit

Name	Role	Institution	Contact Details
Diana Papaioannou	Trial Oversight	University of Sheffield	d.papaioannou@sheffield.ac.uk 0114 222 0766
Cindy Cooper	Trial Oversight	University of Sheffield	c.cooper@sheffield.ac.uk 0114 222 0743
Peter Jüni	Lead Statistician	University of Oxford	peter.juni@ndph.ox.ac.uk
Bruno da Costa	Statistical Modelling	University of Oxford	bruno.dacosta@ndph.ox.ac.uk
Jennifer Petrie	Trial Manager	University of Sheffield	j.petrie@sheffield.ac.uk 0114 222 0676
Rachel Glover	Trial Manager	University of Sheffield	r.e.glover@sheffield.ac.uk 0114 222 4265
Rowena Seaton Kelly	Research Assistant	University of Sheffield	r.seaton.kelly@sheffield.ac.uk 0114 222 0675

April Carne	Research Assistant	University of Sheffield	a.r.carne@sheffield.ac.uk 0114 222 0792
Lizzie Bailes	Research Assistant	University of Sheffield	elizabeth.bailes@sheffield.ac.uk 0114 222 0893
Joseph Bretten	Research Assistant	University of Sheffield	j.bretten@sheffield.ac.uk 0114 222 0826
Alice Flanagan	Trial Support Officer	University of Sheffield	a.flanagan@sheffield.ac.uk 0114 222 0738

1.3 Sponsor Details

Name and address of Sponsor
Sheffield Teaching Hospitals NHS Foundation Trust
Clinical Research and Innovation Office
D Floor
Royal Hallamshire Hospital
Glossop Road Sheffield, S10 2JF

Contact details of Sponsor representative
Alessia Dunn
0114 271 2550
alessia.dunn@nhs.net

1.4 Laboratory Details
EXPERTS-ALS Oxford Laboratory, Nuffield Department of Clinical Neurosciences, University of Oxford, Level 5, West Wing, John Radcliffe Hospital, Headley Way, Oxford, OX3 9DU.

EXPERTS-ALS University College London (UCL) Laboratory, UCL Queen Square Institute of Neurology, Queen Square, London, WC1N 3BG.

1.5 Role of the Funder
The funder has reviewed the research protocol but will have no role in data collection, analysis, data interpretation, report writing or in the decision to submit the report for publication. The funder has approved the selection of members for oversight committees.

1.6 IMP Supplier
N/A – hospital stock to be used

1.7 Protocol amendments

Protocol Version	Changes
2.0	● Presence or history of any psychotic disorder added as an exclusion criteria for ropinirole (Appendix 4) ● For metformin (Appendix 2) – added assessment of renal function at week 12 for participants over the age of 65 years and/or with impaired renal function at screening

	● Minor update to number of participants required for futility analyses 1 and 2 (Figure 1 and Section 11.2) ● Corrected site details for NHS Lothian and Royal Devon University Healthcare NHS FT
3.0	● Addition of the details of the qualitative sub-study (Section 12.1) ● Clarification of remote FVC procedures allowing a window of +/- 3 days around their follow-up date (Table 2 and Section 9.9) ● Amendment to the timepoints at which the samples and data for future research will be collected (Table 2, Figure 3 and Section 9.8) ● Addition of "drugs which are known to independently alter NFL levels" to exclusion criterion 2 (Section 5.2) ● Addition of the collection of CHI numbers (instead of NHS numbers) for participants at Scottish sites (Section 14) ● Addition of patient contact card information (Section 7) ● Addition of the requirement for sites to record hospitalisations due to ALS progression in the CRF (Section 10.2 and Figure 4) ● Minor amendment to Figure 4 to make it clear that all AEs require an assessment for relatedness to an IMP, not just SAEs
3.1	● Addition of further details about the qualitative sub-study, including the background and rationale for the study, the research questions and aims, and the procedures for approach, consent to share contact details and scheduling of interviews (Section 12.1)
3.2	● Update to the Clinical Trials Research Unit staff and contact details (Section 1.2) ● Addition of four PIC sites in Wales ● Addition of the ISRCTN number to the Trial Summary table ● Corrections to Sections 9.1 (Table 2) and 9.9 to clarify that rFVC and rPCF should be completed within 7 days of the appointment date, as specified in the exploratory objective ● Correction to Section 9.5 (PCF) to clarify that scores greater than 880 L/min should be recorded as 881 L/min ● Minor amendment to Section 9.9 to clarify the training instructions for rFVC ● Minor clarifications to the IMP appendices (appendix 2, appendix 3 and appendix 4)
4.0	● First enrolment date updated (Trial Summary) ● Exploratory objectives and associated outcomes, statistical analysis updated (Trial Summary, Sections 3.2, 8.3 and 11.1) ● Exclusion Criteria 3 and 6 updated for clarity (Trial Summary and Section 5.2) ● Addition of salbutamol and doxycycline as new IMPs (Trial Summary and Appendices 5 and 6) ● Blinding section updated to clarify that there will be an unblinded trial statistician (Section 4.1) ● Gender identity added to the list of demographic information (Sections 4 and 5.5) ● Clarification of re-enrolment guidelines for patients who are randomised to an arm which is dropped before they start treatment (Section 5.7)

	● Clarification of prescribing and dispensing guidelines if they are done in advance of a study visit (Section 6.4) ● Moved the timing of the stool sample, food diary and lifestyle questionnaire from screening to baseline (Figure 3, Table 2 and Section 9.8) ● ECG added at screening for salbutamol (Figure 3, Table 2 and Appendix 5) ● Amendment to the scheduling of study visits if initiation of study drug is delayed (Section 9.2) ● Addition of the option for SVC to be measured at screening if patient unable to generate an FVC (Section 9.5) ● Addition of the option for qualitative interviews to be completed over email (Section 12.1) ● Update to ropinirole dosing chart (Appendix 4) ● Minor typographical errors corrected throughout

Trial Summary

Study title	EXPErimental medicine Route To Success in Amyotrophic Lateral Sclerosis (EXPERTS-ALS)
Sponsor	Sheffield Teaching Hospitals NHS Foundation Trust
Funder	National Institute for Health Research Efficacy and Mechanism Evaluation (NIHR EME)
ISRCTN	15525855
Project start date	1st September 2023
Project end date	31st March 2027
Hypothesis, aims and objectives	To evaluate, in a multi-centre open label experimental medicine trial, the ability of candidate drugs to lower blood NFL levels to a relevant extent as the basis for prioritising formal testing in a Phase III RCT **Primary objectives:** To determine 1. Whether a candidate drug is associated with a relevant decrease from baseline in mean group NFL levels. 2. How a candidate drug ranks compared with concurrently or previously randomised competitor drugs on its effect on mean NFL levels. **Secondary objectives:** 1. To evaluate the safety and tolerability of candidate drugs in patients with ALS. 2. To assess the effect of candidate drugs on standard clinical measures of daily functioning (e.g. ALS revised functional rating scale ALSFRS-R) and clinical (King's) stage. 3. To create an ALS sample bioresource for further research. **Exploratory objectives:** 1. To explore survival at 12 months without non-invasive ventilation >22 hr/day or invasive ventilation, and compare it with the median prediction of survival without non-invasive ventilation >22 hr/day or invasive ventilation from the European Network for the Cure of ALS (ENCALS) survival prediction model. 2. To explore the effect of candidate drugs on disability and quality of life. 3. To explore respiratory function assessments and determine the feasibility and validity of remote, unsupervised respiratory function assessment as compared with supervised assessments. 4. To explore participant and site staff (Principal Investigators, Research Nurses) understanding and experience of the EXPERTS-ALS platform trial design including barriers and enablers for recruitment and retention.

Study design (including randomisation)	A multi-centre, randomised, open-label, multi-arm platform trial that enables comparisons between drugs. Participants will be randomly allocated to one of the current treatment options for which they are eligible. A member of the local study team will perform the randomisation by accessing a web-based randomisation system provided by the Sheffield CTRU (SCRAM)
Internal pilot/feasibility criteria	Site set up (number of centres set up and recruited their first participant): <6 centres (red), 6-10 centres (amber), 11 centres (green). Participant recruitment: <60% (red), 60-99% (amber), 100% (green). Proportion of NFL results (primary outcome) useable/verified: <80% (red), 80-90% (amber), >90% (green).
Setting	The study will be a UK multi-centre, academic-led study involving 11 centres of excellence in ALS care and research.
Participants (to include eligibility criteria)	**Inclusion criteria:** 1. Diagnosis of ALS according to Gold Coast criteria. 2. Age at least 18 at the time of consent. 3. ENCALS prognosis risk score of -6.0 to -2.0 as calculated from the results of the screening visit. See study-specific Research Manual for more details. 4. Those taking riluzole must be on a stable dose for at least 30 days prior to the baseline visit or must have chosen not to take it for the study duration. 5. Must be able to be randomised to at least two of the open arms after reviewing contraindications, current medication and the IMP-specific eligibility criteria as detailed in the IMP-specific appendices. 6. Fertile persons must use adequate contraception if required by the IMPs (see Section 5.8 and IMP-specific appendices for details). 7. Persons of childbearing potential must have a negative pregnancy test prior to randomisation. **Exclusion Criteria:** 1. Clinically significant history of unstable or severe cardiac, oncological, hepatic or renal disease or other medically significant illness which, in the opinion of the local investigator, is a contraindication to participation. 2. Presence of an active disorder (other than ALS) or currently taking a drug which is known to independently alter NFL levels. 3. Treatment with IMP in any other investigational drug trial within 30 days prior to screening 4. Pre-existing use of current EXPERTS-ALS IMPs or drugs in the same class as current EXPERTS-ALS IMPs that would

	result in the patient not being able to be randomised between a minimum of two arms. 5. Contraindications to IMPs that would result in the patient not being able to be randomised between a minimum of two arms. Refer to IMP-specific appendices for details. 6. Use of non-invasive ventilation >22 hr/day or invasive ventilation. 7. Pregnant or breastfeeding. 8. Unable to comply with trial procedures.
Intervention and control groups	The EXPERTS-ALS protocol describes an overarching trial design to evaluate the effect of candidate drugs on blood NFL levels in patients with ALS receiving usual standard of care. The protocol is deliberately flexible, allowing: ● as broad a range of ALS patients to be recruited; ● participant randomisation between only those treatment arms that are not believed by the enrolling doctor to be contraindicated (e.g. by particular co-morbid conditions or concomitant medications); and ● treatment arms to be added or removed according to the emerging evidence from within the trial. The current treatments arms are: ● Metformin ● Nifedipine ● Ropinirole ● Salbutamol ● Doxycycline
Primary outcome(s)	Change in blood NFL levels from baseline to weeks 18 and 24.
Secondary outcome(s)	● Change in ALSFRS-R score from baseline to weeks 12 and 24 ● Progression in King's Stage from baseline to week 24 by 1 stage or more ● Adverse events and serious adverse events during the trial (definitions in Section 10) **Exploratory outcomes:** ● Survival at 12 months without non-invasive ventilation >22 hr/day or invasive ventilation, compared with the ENCALS median prediction of survival without non-invasive ventilation >22 hr/day or invasive ventilation. ● Change in WHO Disability Assessment Schedule (WHODAS 2.0) and Quality of Life (WHOQOL-Bref) at 24 weeks (or early discontinuation of treatment) against a natural history cohort. ● In person forced vital capacity (FVC) and peak cough flow (PCF), compared with remote FVC and remote PCF where readings are available within +/-7 days of each other.

Duration of recruitment period & first enrolment date	First enrolment date: November 2024. Duration of recruitment period: 43 months.
Duration of follow-up	24 weeks.
Target sample size	Total target recruitment is 700 participants.
Definition of end of trial	Database lock of the last arm(s) to be included in the trial.

2. Introduction

2.1 Background

Amyotrophic lateral sclerosis (ALS), the commonest form of motor neuron disease (MND) is an adult-onset neurodegenerative condition, with a UK prevalence of at least 5000. It is characterised by progressive loss of motor neuronal input to the muscles of (variably) limb, speech, swallowing and ultimately respiratory function (1). Despite the provision of multidisciplinary care, the very modest survival benefit of the UK's only licensed disease-modifying drug for ALS – riluzole - plus the selective use of non-invasive ventilation, median survival from symptom onset is only 30 months. During this time, individuals become increasingly dependent on others for all activities of daily living, with an unparalleled burden of physical and emotional distress, associated with very high societal cost. It is a clinically and pathologically heterogeneous disorder (2).

At present, the majority of those receiving a diagnosis of ALS will not have the opportunity to take an experimental therapy during their remaining lifetime. For the minority that do, current outcome measures for trials rely on insensitive endpoints such as tracheostomy-free survival or demonstration of a clinically meaningful reduction of the rate of disability accrual measured using the revised ALS functional rating score (ALSFRS-R). These requirements necessitate Phase III randomised-controlled trials (RCTs) involving 300-600 participants followed for at least 12 months (3). With a median survival of 30 months from symptom onset, those people living with ALS who can access such a trial will typically have the opportunity to do so only once within their shortened lifespan, with a significant proportion of participants assigned to the placebo arm.

This model of drug testing, involving over 150 drugs over more than 30 years, has resulted in the licensing (in some countries) of three drugs, all with small absolute clinical benefits of questionable meaningfulness to daily function or quality of life, namely riluzole, edaravone, and combinatory tauroursodeoxycholic acid/sodium phenylbutyrate. Meanwhile, a significant group of those living with ALS resort to routinely accessing untested, potentially harmful supplements and drugs via unregulated sources and consistently voice concern about being asked to participate in placebo-controlled studies based on non-human signals of benefit.

The development of cellular and small animal models of disease, coupled with access to repurposed drug libraries and high throughput screening platforms, has resulted in an increasing number of drugs showing encouraging pre-clinical signals. There is currently no systematic approach to prioritising drugs showing a signal in pre-clinical studies for human testing. Beyond the commercial space there are limited resources for academic-led efficacy trials. Therefore, there is an urgent need to develop a drug prioritisation strategy for the considerable financial and human capital investment required for a Phase 3 RCT to be used to best effect.

Through large, multi-centre, collaborative ALS biomarker cohort studies and developments in assay sensitivity, blood levels of neurofilament light chain (NFL) has been established as a reliable correlate of the *rate* of disability progression in ALS (as measured by the slope of ALSFRS-R decline). Higher levels of NFL are associated with faster rates of disability progression (and shorter survival) and vice versa. In individual ALS patients, rates of disability progression tend to be stable across most of the disease course; their individual NFL levels are increased and tend to remain constant over time in established symptomatic disease (4–

6). This underpins the rationale for considering significant lowering of group NFL level through drug administration as a likely indication of disease-modifying drug activity and amelioration of the processes causing motor neuron injury (7). Given the current absence of highly effective disease-slowing therapies for ALS, the disease-based evidence for this rationale comes indirectly, nonetheless convincingly, from other disorders. This includes rapid reduction in the very high NFL levels associated with HIV-associated neurodegeneration in response to highly-active anti-retroviral therapy (HAART) (8) and after fingolimod therapy in multiple sclerosis with both clinical and MRI response markers (9). However, recent trials of the antisense drug tofersen in ALS patients due to pathological variants in *SOD-1*, demonstrated not only target engagement with consistent lowering of both CSF SOD1 protein levels, but also a significant reduction in plasma NFL levels in the treatment arm over the 28 week study and a clear effect in the placebo group when transferred over to active drug (10). Importantly, the drop in NFL levels occurred several months before any sign of clinical benefit. Ahead of the necessary longer-term follow-up of treated patients, in a landmark statement the USA FDA panel were unanimous in agreeing with the assertion that NFL in this study is "a biomarker reasonably likely to predict clinical benefit". The USA ALS Association noted the wider implications of this recognition of "a change in the course of the disease" for the use of NFL lowering to build early confidence in human benefit of candidate drugs (https://www.als.org/blog/heres-why-fda-committees-recommendationtofersen-matters-everyone).

Importantly, the recognised occasional variability of longitudinal NFL levels takes the form of a small rise prior to stabilisation in the early symptomatic phase, typically in those associated with more aggressive rates of disability progression (7). This makes the chance of a type 1 error (falsely concluding that a drug is associated with NFL lowering when it is not) negligible. The theoretical concerns that i) small disease modifying benefits might be overlooked because this methodology represents an unreasonably 'high bar' or ii) that a highly therapeutic drug might (somehow) not be associated with a fall in NFL levels, are not relevant for an approach that is seeking only to detect evidence of potentially large therapeutic effects and to prioritise the growing pool of untested candidates. The inclusion of nested biomarker work can consider individual 'responders' and 'non-responders' within apparently unsuccessful drugs at group-level and allow consideration of wider biochemical and network changes attributable to the IMP that might inform future candidates.

2.2 Rationale for current study

This protocol describes one part of a larger programme of work, as summarised below:

- Workstream 1: IMP identification. This will identify and prioritise compounds to be tested in the platform.
- Workstream 2: Drug prioritisation platform trial (this protocol). This is a Bayesian Phase II open label, randomised platform trial, using blood NFL levels as a surrogate outcome for biological efficacy alongside other exploratory endpoints.
- Workstream 3: Nested biomarker development studies. Samples will be collected from participants in the platform and stored for use in future biomarker development studies. Note that any future analysis of the samples will only be undertaken when the appropriate ethics approvals are in place.

The EXPERTS-ALS platform is designed as a randomised, open-label, multi-arm trial with a biomarker-based endpoint. It aims to prioritise drugs for further testing based on their ability to lower NFL levels and to also identify drug-specific adverse events. The dynamic Bayesian modelling proposed leverages comparative NFL data between the different drugs

that are running at any one time. The NFL assessor will be blinded to IMP allocation. A fully blinded study is not warranted, given that the primary outcome measure is objective and the overall aim one of prioritisation for definitive RCT. There is no placebo arm by intention. EXPERTS-ALS is not designed to show clinical efficacy and cannot do so to a level that would currently be needed to support licensing. This can only come from Phase III RCTs, for which there are insufficient patients, clinicians, trial support staff and financial resources to study the growing pool of pre-clinical candidates. The patient community have indicated the EXPERTS-ALS design is appealing, in i) offering more newly diagnosed patients access to studies with solely active drug candidates, ii) ensuring that only those drugs with human signals of likely clinical benefit are offered in later (necessarily) placebo-controlled studies to improve the chance of success, and iii) doing so in a more rapid time frame.

2.3 Treatment options

The protocol allows assessment of the effect of multiple different treatments on NFL levels in patients with ALS as a surrogate marker of therapeutic disease modification. Further details, including justification for the choice of treatment options, are provided in the IMP-specific appendices. Participants will continue to follow standard of care, including regular ALS outpatient clinic visits, and they may remain on a stable dose of riluzole (as a NICE standard of care) throughout the duration of the trial if they have elected to take this.

2.4 Modifications to the treatment arms

A working group including experts from academia and industry will prioritise drugs for inclusion in EXPERTS-ALS based on disease relevance (the drug must target a relevant pathway in ALS pathogenesis likely to be disease-modifying), safety profile (the drug must have a clear toxicity profile) and CNS penetration (the drug must have pre-clinical pharmacodynamic evidence of blood brain barrier (BBB) penetration). Further details on the criteria for selection of new drugs can be found in Appendix 1.

New arms will be added to the protocol and submitted to MHRA, REC and HRA for approval via substantial amendment based on recommendations from the working group. Arms will be added in advance of them needing to be activated and may be added via amendment in groups but then activated singly or in groups as appropriate. The decision to activate recruitment to a new arm (from those which have been approved by MHRA, REC and HRA) will be made by the Trial Management Group (TMG).

Each trial arm will end when the last participant recruited reaches the 24 week follow up visit, or if the arm is dropped for futility or potential harm, whichever occurs first, unless the arm meets the criteria to be retained as the “current reference” as documented in the statistical analysis plan (refer to Section 11 for more details), in which case it will be carried forward for additional recruitment. The sample size is not fixed and is detailed in section 11. The DMEC will make recommendations to the TMG regarding the selection of the current reference drug in accordance with the details in the DMEC charter. Participants randomised to arms which are dropped for futility may continue in the trial for follow up but trial treatment will be stopped.

It may be necessary to pause recruitment to individual arms, multiple arms or the entire trial (for example, to allow follow up data to be collected and/or interim analyses to be completed) and this decision will be made by the TMG. The TMG will also be responsible for the decision to re-open recruitment or permanently close arms. Arms which are permanently closed will be removed with a future substantial amendment.

If a candidate drug is associated with no relevant decrease in group NFL level from baseline at 18 to 24 weeks, it will be dropped from the trial for futility. The Data Monitoring and Ethics Committee (DMEC) will make recommendations to the TMG who will make the decision to drop the corresponding arm.

2.5 Design considerations

The EXPERTS-ALS protocol describes an overarching trial design to evaluate the effect of candidate drugs on blood NFL levels in patients with ALS receiving usual standard of care. The protocol is deliberately flexible, allowing:

- as broad a range of ALS patients to be recruited;
- participant randomisation between only those treatment arms that are not believed by the enrolling doctor to be contraindicated (e.g. by particular co-morbid conditions or concomitant medications); and
- treatment arms to be added or removed according to the emerging evidence from within the trial.

EXPERTS-ALS' NFL-based Bayesian model design has been led by an internationally respected innovator in clinical trial design and statistics, Professor Peter Jüni and his team, in collaboration with Dr Ruben van Eijk, an opinion leader on the specific challenges of ALS trial design. This Bayesian drug prioritisation platform design can significantly reduce the total sample size of the trial (11). This will allow us to more rapidly identify drugs that are promising and should be prioritised for investigation in a future Phase III placebo-controlled randomised trial with clinical outcomes. Drugs that are likely ineffective can be dropped early from further investigation in this Phase II trial due to futility and receive lower priority for further investigation. The approach requires a lower number of participants (estimated at <50 per drug) than conventional Phase II trials and thus reaches conclusions faster, which are key advantages for the advancement of ALS therapeutics.

2.6 Benefit-risk assessment

The benefit-risk assessment will be revisited periodically throughout the trial.

Benefits

EXPERTS-ALS is an innovative programme for the development of a UK multicentre platform for the rapid assessment of ALS drug candidates arising from pre-clinical models, based on change in biomarkers that predict human benefit. While EXPERTS-ALS does not assess clinical benefit, only biomarker response, this approach will uniquely prioritise the choice of drugs going forward in what are costly and ethically challenging placebo-controlled Phase III studies that have had a more than 99% failure rate to date in terms of UK licensed disease-modifying drugs. EXPERTS ALS completes a bench to bedside ALS drug pipeline, enabling prioritisation of the many candidates arising from University and industry-based preclinical models, for onward Phase III platforms e.g. the UK's MND-SMART and the pan-European TRICALS consortium.

The platform addresses key unmet needs identified by those living with ALS as well as clinicians involved in their care and industrial partners, namely that:

- The majority of those diagnosed with ALS are not currently offered participation in any drug study. Those that are, rarely participate in more than one in their shortened remaining lifetime, and there is a lack of geographical equity of access to such studies.

- A major rate-limiting step in therapeutic advancement is the limited capacity to deliver Phase III trials at pace. Using the current outcome measures of survival or significant slowing of disability accrual, Phase III trials in ALS necessitate large (300-600 participants), lengthy (12-18 months), and so are extremely costly (£10s of millions) studies.
- Given the overwhelming failure rate of Phase III studies to date, the use of a placebo arm without any prior attempt to look for strong human signals of likely clinical benefit in a candidate drug, is an ethical concern and an increasingly unacceptable proposition for many living a drastically shortened lifespan with ALS.

Risks

The study will be conducted in accordance with the protocol, Good Clinical Practice (GCP) and the Medicines for Human Use (Clinical Trials) Regulations 2004. The platform will initially use repurposed drugs but as the study progresses, more novel drugs may be considered for inclusion. The adverse effect profiles of the repurposed drugs are well documented and will be considered prior to inclusion in the study, paying particular attention to those that may be unacceptable to people with ALS. In the case that more novel drugs are considered for inclusion, the risk assessment will be revisited and the working group responsible for identifying new IMPs will consider the toxicity profile before a drug is recommended for the study. Adverse events will be monitored closely throughout the study and a detailed risk assessment will be completed prior to initiation. The risk assessment will be routinely re-reviewed with the introduction of every new arm. The trial design ensures safety assessments will be completed throughout a participant's involvement in the trial with the local investigator being responsible for their care.

Regular futility assessments will be undertaken throughout the trial which will require NFL analyses to be completed, data to be entered and cleaned, statistical analyses undertaken and Data Monitoring and Ethics Committee (DMEC) review. It will be essential for these processes to run smoothly in order to successfully implement the platform design. Furthermore, new drugs will be added to the trial based on the recommendations of the working group requiring regular substantial amendments to gain approvals for new drugs. Additional resources have been allocated to the trial to account for the workload associated with the platform design. The Trial Management Group (TMG) will monitor progress regularly and may implement changes as necessary.

3. Aims and objectives

3.1 Aims

To evaluate, in a multi-centre open label experimental medicine trial, the ability of candidate drugs to lower blood NFL levels to a relevant extent as the basis for prioritising formal testing in a Phase III RCT.

3.2 Objectives

Primary objectives

To determine:

1. Whether a candidate drug is associated with a relevant decrease from baseline in mean group NFL levels.
2. How a candidate drug ranks compared with concurrently or previously randomised competitor drugs on its effect on mean NFL levels.

Secondary objectives

1. To evaluate the safety and tolerability of candidate drugs in patients with ALS.
2. To assess the effect of candidate drugs on standard clinical measures of daily functioning (e.g. ALS revised functional rating scale ALSFRS-R) and clinical (King's) stage.
3. To create an ALS sample bioresource for further research.

Exploratory objectives

1. To explore survival at 12 months without non-invasive ventilation >22 hr/day or invasive ventilation, and compare it with the median prediction of survival without non-invasive ventilation >22 hr/day or invasive ventilation from the European Network for the Cure of ALS (ENCALS) survival prediction model.
2. To explore the effect of candidate drugs on disability and quality of life.
3. To explore respiratory function assessments and determine the feasibility and validity of remote, unsupervised respiratory function assessment as compared with supervised assessments.
4. To explore participant and site staff (Principal Investigators, Research Nurses) understanding and experience of the EXPERTS-ALS platform trial design including barriers and enablers for recruitment and retention.

4. Trial Design

A multi-centre, randomised, open-label, multi-arm platform trial that enables comparisons between drugs. Figure 1 illustrates the analyses and adaptations at trial arm level. Figure 2 illustrates potential adaptations to the trial arms following the planned futility analyses for the example of three concurrently evaluated drugs. Both Figures will be further explained in Sections 11.1 and 11.2. These procedures are not fixed and are provided as representative examples. Changes to these procedures during the trial will be discussed with and approved by the independent Data Monitoring and Ethics Committee prior to implementation.

Figure 1: Illustration of analyses and adaptations at trial arm level

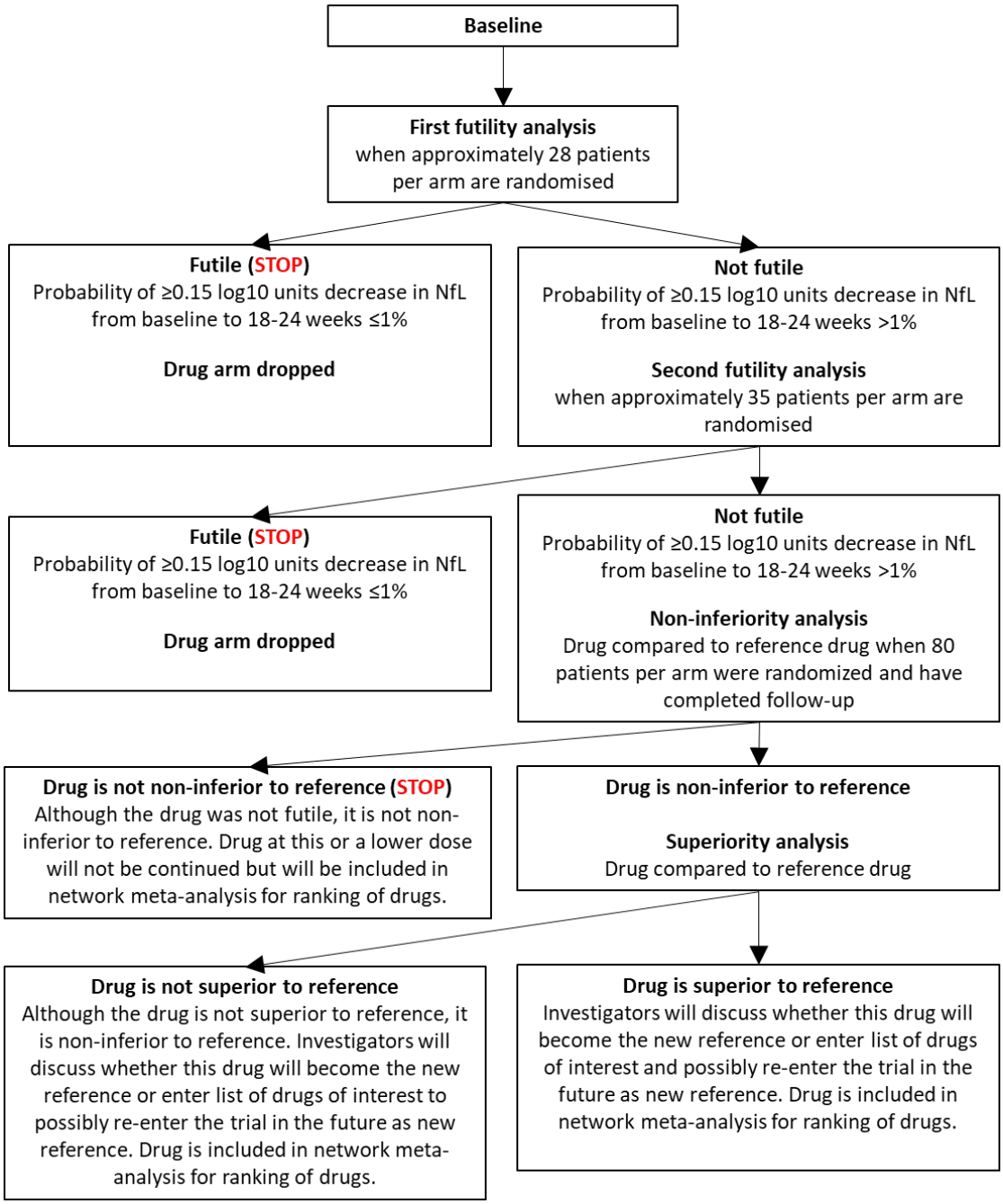
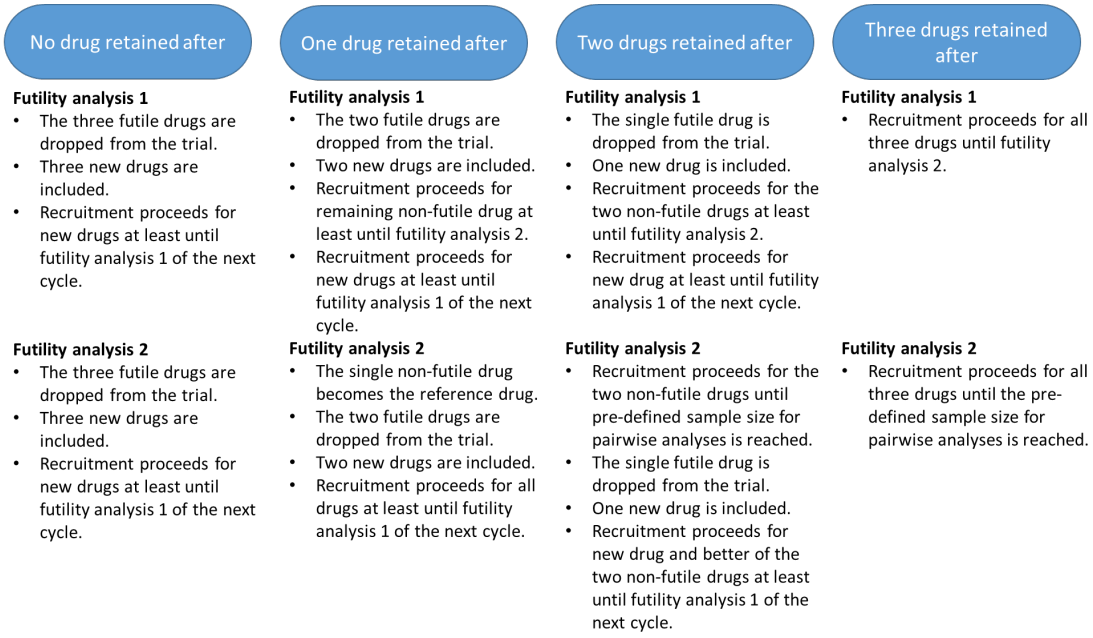


Figure 2: Illustration of potential adaptations at trial level following futility analyses.



The trial will be conducted in patients with ALS meeting the Gold Coast criteria (12). Participants must be able to provide informed consent. Data will be collected from participants on age, sex, gender identity, socioeconomic status and ethnicity and if there are concerns during the trial that certain groups are not adequately represented, advice will be sought on how to maximise opportunities for these groups.

Selection of trial participants will use a validated prognostic model, the ENCALS survival model, based on clinical profiles of 11,475 patients, to optimise patient selection and maximise inclusion rates simultaneously (based on (13), see www.encalssurvivalmodel.org). The selection parameters of the mathematical model are designed to influence eligibility by:

- Excluding patients at high immediate risk of death because candidate drugs will need up to 6 months before an NFL endpoint can be detected.
- Excluding very slowly progressing individuals.

Within the ENCALS model, these criteria correspond to:

- Score > -2.0 [High Risk]
- Score < -6.0 [Low Risk]

Applying these criteria will exclude approximately 25% of the patients, which compares favourably with the ~90% exclusion rate of more traditional criteria. The design is optimised to provide early and reliable evidence of futility of candidate drugs within approximately 30 weeks of the start of their evaluation and to establish non-inferiority or superiority of potentially effective candidate drugs in decreasing NFL levels within approximately one year of the start of their evaluation.

Setting

The study will be a UK multi-centre, academic-led study involving 11 centres (see Section 1.1) of excellence in ALS care and research.

4.1 Blinding

The NFL assessor in the EXPERTS-ALS Oxford Laboratory will be blinded to IMP allocation. The TMG and site study teams will only be notified of results of the NFL analyses if a change to the protocol is required, e.g. dropping an arm or if an arm is identified as the new "reference standard". Otherwise, the results will be kept confidential within the DMEC, unblinded trial statistician(s) and other relevant members of the central trials unit team until the final analysis on an arm is completed. Full details will be documented in a blinding planner. Assessor bias is unlikely given that the primary outcome measure is objective.

4.2 Unblinding

N/A

5. Selection of participants

5.1 Inclusion criteria

1. Diagnosis of ALS according to Gold Coast criteria.
2. Age at least 18 at the time of consent.
3. ENCALS prognosis risk score of -6.0 to -2.0 as calculated from the results of the screening visit. See study-specific Research Manual for more details.
4. Those taking riluzole must be on a stable dose for at least 30 days prior to the baseline visit or must have chosen not to take it for the study duration.
5. Must be able to be randomised to at least two of the open arms after reviewing contraindications, current medication and the IMP-specific eligibility criteria as detailed in the IMP-specific appendices.
6. Fertile persons must use adequate contraception if required by the IMPs (see Section 5.8 and IMP-specific appendices for details).
7. Persons of childbearing potential must have a negative pregnancy test prior to randomisation.

5.2 Exclusion criteria

1. Clinically significant history of unstable or severe cardiac, oncological, hepatic or renal disease or other medically significant illness which, in the opinion of the local investigator[a], is a contraindication to participation.
2. Presence of an active disorder (other than ALS) or currently taking a drug which is known to independently alter NFL levels[b].
3. Treatment with IMP in any other investigational drug trial within 30 days prior to screening.
4. Pre-existing use of current EXPERTS-ALS IMPs or drugs in the same class as current EXPERTS-ALS IMPs that would result in the patient not being able to be randomised between a minimum of two arms.
5. Contraindications to IMPs that would result in the patient not being able to be randomised between a minimum of two arms. Refer to IMP-specific appendices for details.
6. Use of non-invasive ventilation >22 hr/day or invasive ventilation.
7. Pregnant or breastfeeding.
8. Unable to comply with trial procedures.

[a]In the event of any uncertainty, local investigators may contact the central team to discuss.
[b]E.g. Concern has been raised about Minocycline but please contact the central team to discuss.

5.3 Participant identification

Site PIs and their delegates will identify potential participants from the local population of patients with ALS. Potential patients will be provided with a copy of the participant information sheet (PIS), either in person or via post or their preferred email address. A member of the local research team may follow up with a telephone call to answer any initial questions, complete a pre-screen and determine if the patient is interested. If the patient indicates that they prefer to be contacted via email, the research team may use email for further communication. Interested patients will be invited for a screening visit. Non-EXPERTS sites and national registries will also be used to raise awareness of the study. Participant Identification Centres (PICs) may also be set up to identify potential participants. Potential participants identified and those who self-refer will be put in touch with their nearest EXPERTS-ALS site.

All patients who are considered for the study will be included on a pre-screening log and assigned a study ID number, regardless of whether they go on to join the study or not. Patients who do go on to be randomised will keep this number throughout the study. Information on the reasons for non-recruitment will be recorded on the log where possible. The pre-screening log will also capture basic demographic data (sex and age) but will not contain any direct identifiers. More details are provided in the study-specific Research Manual.

Pre-screening

Part of the initial contact by the local research team can include a pre-screen to ensure a patient is likely to fulfil the general requirements of the trial, avoid unnecessary travel to appointments and manage patient expectations. If possible, the local research team will confirm the following:

- Patient is at least 18, has a diagnosis of ALS, is not pregnant or breastfeeding and is not taking part in any other investigational drug trial.
- Whether there are at least two treatment arms available to which the patient could be randomised to, based on current and previous drug and allergy history.
- Whether the patient is established on riluzole for at least 30 days or has chosen not to take it for the duration of the study.
- Whether the patient has a clinically significant history of unstable or severe cardiac, oncological, hepatic or renal disease or other medically significant illness.

Members of the clinical care team can review patient records to pre-screen. Information discussed or reviewed during the pre-screen will not be recorded for the trial, except for the primary reason for non-recruitment. All trial data should be formally collected and recorded in the Case Report Form (CRF) after informed consent, this includes confirming the eligibility of the patient.

5.4 Informed consent process

Potential participants will receive an approved PIS. They will be given sufficient time to read and understand the information provided to them and ask further questions as required. They will be advised that they are free to withdraw from the study at any time, without obligation, with no impact on subsequent clinical care. They will also be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for study purposes by authorised individuals other than the treating physicians. No study related procedures will occur before the approved consent form is signed, other than initial case note review by the referring clinician or pre-screen by the clinical care team. As the study is a Clinical Trial of an Investigational Medicinal Product (CTIMP) a medically qualified

individual (site PI or other co-investigator who has been delegated this responsibility) will confirm eligibility and provide clinical oversight for the consent process. Consent will be taken by GCP accredited, appropriately trained, suitably qualified and delegated individuals. Where the PI wishes to delegate the task of consent to members of the team who are not medically qualified doctors, it is expected that the staff member has a significant level of specialist clinical knowledge in the disease area. Consent may be taken remotely in accordance with the procedures detailed in the study-specific Research Manual, where permitted locally. The consent process will be documented in the medical notes.

If there are language barriers preventing a patient from providing informed consent, the potential for a translated version of the PIS and consent form will be explored as appropriate. Interpreters may be provided via the site's usual processes or arranged specifically for the trial if required. If an interpreter is used, patients should still give their own written consent unless they are unable to do so. If a patient is unable to give written consent due to physical disability or due to being unable to read/write, they can give verbal consent in front of a witness who will sign the consent form. The witness should initial (using their own initials) and sign the consent form upon verbal confirmation of consent by the patient. The witness must be independent of the research team (not on the delegation log). Patients who are unable to give informed consent will not be included in the study.

Participants will be given the opportunity to consent for the following optional aspects of the study:

- Receiving information about the trial e.g. results/newsletters
- Being approached about further research

Consent for these aspects of the study is optional and will not affect participation in the main study.

For each participant, the original copies of the signed consent forms will be retained by the Investigator in the Site File including printed copies of remotely obtained consent. Participants will also receive a copy (either electronically or physically) of the PIS and their signed consent form to keep, and a copy will be filed in their medical notes. Consent will be reconfirmed at each study visit.

5.5 Screening and baseline procedures

A complete list of screening and baseline assessments can be found in the Study Assessments Schedule in section 9.1. The screening procedures will include an eligibility review where a medically qualified investigator who has been delegated this task will confirm that the patient meets all the inclusion criteria and none of the exclusion criteria. If any assessments cannot be completed at the screening visit, they can be completed at a later date provided they are within the screening period defined in the study assessments schedule (section 9.1). Eligibility must be reconfirmed at the baseline visit, prior to randomisation, when the results of all screening assessments are available. If the exact required screening tests have been performed for clinical reasons prior to the date of consent, these results can be used for the study database provided they are within the visit window specified in the study assessments schedule (section 9.1).

Demographic information will be collected including date of birth, sex, gender identity and ethnicity (it is recommended that, where relevant, the patient's medical records are updated during the visit to include the ethnicity data provided by the participant). Participants' geographical location (postcode) will be collected to map to the Index of Multiple

Deprivation. Health literacy will be assessed using the Brief Health Literacy Screening Tool (14). Medical information will be gathered including current and past medical history, ALS-specific history (including date of symptom onset, date of diagnosis, site of symptom onset, upper and lower motor neuron signs, relevant family history or known genetic cause), and current and relevant past medication use. Some of the information required may come from the participant's MND care team or be confirmed by them. The participant will consent to them being contacted as part of the consent for the trial.

5.6 Co-enrolment guidelines

Concurrent participation in any other clinical study of an investigational medicinal product is not allowed while a participant is in treatment or follow up for EXPERTS-ALS. Participation in other interventional studies may be acceptable in accordance with local guidelines and with agreement from the Chief Investigator or delegate of EXPERTS-ALS.

5.7 Re-enrolment guidelines

Participants who have previously been randomised into EXPERTS-ALS will not be permitted to re-enrol, unless the drug to which they were allocated is dropped from the study for futility prior to the participant receiving any study treatment, in which case they may be re-enrolled subject to discussion with the central team.

Re-screening of participants who fail screening is permissible.

5.8 Contraception/ Lifestyle Guidelines

Persons of childbearing potential (defined below) and fertile persons (post puberty unless permanently sterile by bilateral orchidectomy) whose partner is of childbearing potential must be willing to use a highly effective method of contraception (defined below) if required by the IMP (as per the SmPC). Contraceptive methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods (as defined by the Clinical Trial Facilitation Group, CTFG (15)) include:

- Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - Oral
    - Intravaginal
    - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation
    - Oral
    - Injectable
    - Implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised partner (if the sole sexual partner and the vasectomised partner has received medical assessment of the surgical success)
- Sexual abstinence (in the context of this guidance, this is defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant)

Refer to the IMP-specific appendices for IMPs specific requirements.

For the purposes of this trial, a person is considered of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level or a low anti-Müllerian hormone (AMH) level in the postmenopausal range may be used to confirm a post-menopausal state in persons not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, an FSH or AMH measurement is insufficient.

Participants must not be breastfeeding.

6. Trial treatment

6.1 IMP details

The investigational medicinal products (IMPs) for this study, where licensed drugs, will be sourced from local hospital stock within the participating centres.

6.2 Treatment details

Refer to the IMP-specific appendices for details.

6.3 Concomitant treatments

Participants may remain on a stable dose of riluzole, refer to section 4, (as a NICE standard of care) throughout the duration of the trial but are encouraged not to initiate or stop riluzole for the duration of the trial. In the event that changes are made to riluzole treatment during the trial, this will be documented in the eCRF.

The following medications are contraindicated with study treatment:

- Use of the allocated EXPERTS-ALS study drug, either for their licenced indications or off-label, or drug in the same class.
- Use of any medications post-randomisation that are contraindicated with the allocated study drug (refer to IMP-specific appendices).

In the event that a contraindicated medication is required by a participant, a medical assessment should be completed urgently and the study drug withheld. If a patient requires the ongoing use of a contraindicated medication the study drug should be discontinued, however every effort should be made to follow up the participant as per protocol. If the contraindicated drug is only required for a short period then the patient may re-commence the study drug once the contraindicated medicine is stopped according to the investigator's discretion.

There may also be medications which should only be used with caution as detailed in SmPC section 4.5. If a participant requires the use of any of these medications they may continue the study drug at the investigators discretion with additional monitoring as decided by the site PI as necessary.

6.4 Dispensing

IMPs will be dispensed from local hospital stock and the study does not mandate the use of a specific brand of each IMP. Trial-specific dispensing and labelling will be required. Participants will be dispensed a sufficient supply of medication to last until their next

scheduled study visit. Prescribing and dispensing may be completed in advance of a study visit if required provided the study team has contacted the participant in advance of writing the prescription to determine the appropriate dose and quantity required. Further details are provided in the Pharmacy Manual and Research Manual. Where necessary, and in accordance with local policies, study drugs may be delivered to the participant by the research team or couriered to participant homes. Unused IMP and used, unused and part-used packaging will be returned at the next study visit to allow compliance and accountability checks to be completed. Local destruction policies will be followed. Full dispensing details will be provided in a study-specific pharmacy manual.

6.5 Accountability

Master accountability logs will not be mandated and ring-fencing is not required. However, sites may choose to do this locally to manage supplies. Participant-level IMP accountability documentation will be maintained by clinical trials pharmacy. Local records and procedures can be used provided these allow patient level batch numbers and quantities to be matched to participants and archived. Otherwise, additional trial-specific records will be required where local processes are not sufficient. Full details will be provided in a study-specific pharmacy manual.

6.6 Adherence

Participants will be asked about adherence at each study visit and their responses recorded in the eCRF. Participants will also be asked to return all used, unused and part-used packaging to allow adherence to be assessed where possible. Refer to the study-specific Research Manual and Pharmacy Manual for more details.

6.7 Dose Modification and interruptions

In the case of adverse events felt to be clinically significant and related to study treatment by the local investigator, the IMP may be withheld, interrupted or discontinued or the dose may be reduced at the investigator's discretion in the interests of the participant. The adverse event(s) and dose modification / interruption will be documented in the study records. Refer to section 9.10 for more details on early discontinuation of study treatment.

Refer to the IMP-specific appendices for guidance on missed doses, and treatment interruptions.

6.8 Overdose

Participants will be counselled on the importance of taking the study medications as prescribed. An overdose is defined as taking double the normal medication/day for one day or more. In the event that an overdose of study medication occurs, the participant will contact the local EXPERTS-ALS study team as soon as possible to receive appropriate advice. Participants will be provided with an out of hours contact number but will be advised to attend A&E in the case of an emergency. Participants will then be managed on a case-by-case basis and toxicity will be managed according to standard practice. An overdose leading to an SAE should be managed clinically and the procedures in Section 10 should also be followed. Overdoses will be documented.

7. Randomisation and enrolment

Prior to randomisation, all screening investigations will be reviewed by the local medically qualified investigator to confirm eligibility. The investigator will complete and sign the "Confirmation of Eligibility" form as documentation of this review. The investigator will be

responsible for indicating which of the treatment arms the patient is eligible for as this information will be required for randomisation. A patient must be eligible for a minimum of two treatment arms.

Once eligibility has been confirmed and baseline data recorded, the participant will be randomly allocated to one of the current treatment options for which they are eligible. A member of the local study team will perform the randomisation by accessing a web-based randomisation system provided by the Sheffield CTRU (SCRAM). Patient details (ID, age, eligibility details) will be entered and the treatment allocation will be returned. We will use probabilistic minimisation to balance site of onset (bulbar vs spinal) and groups of trial sites based on patient volume (high (Oxford, Sheffield, King's College) vs medium (Salford, University College London, Newcastle, Liverpool) vs low (Cambridge, Edinburgh, South Wales, Exeter)).

Following randomisation, all patients must be given a patient contact card. Site on-call contact details for 24-hour medical care must be added to this card, and participants advised to carry this with them at all times whilst participating in the trial. Where licenced products, 24-hour medical care will be provided via routine out of hours services i.e. trial-specific out of hours cover will not be required. Where non-licenced products, please refer to the IMP-specific appendices for more information.

8. Outcomes

8.1 Primary outcome/endpoint

Change in blood NFL levels from baseline to weeks 18 and 24.

8.2 Secondary outcomes/endpoints

- Change in ALSFRS-R score from baseline to weeks 12 and 24
- Progression in King's Stage from baseline to week 24 by 1 stage or more
- Adverse events and serious adverse events during the trial (definitions in Section 10).

8.3 Exploratory outcomes/endpoints

- Survival at 12 months without non-invasive ventilation >22 hr/day or invasive ventilation, compared with the ENCALS median prediction of survival without non-invasive ventilation >22 hr/day or invasive ventilation (16,17).
- Change in WHO Disability Assessment Schedule (WHODAS 2.0) and Quality of Life (WHOQOL-Bref) at 24 weeks (or early discontinuation of treatment) against a natural history cohort.
- In-person forced vital capacity (FVC) and peak cough flow (PCF), compared with remote FVC (rFVC) and remote PCF (rPCF) where readings are available within +/- 7 days of each other.

8.4 Feasibility outcomes

The trial will include an internal pilot. After approximately 8 months of start of recruitment, Sheffield CTRU will aggregate study data to assess the feasibility of the research based on the following feasibility outcomes:

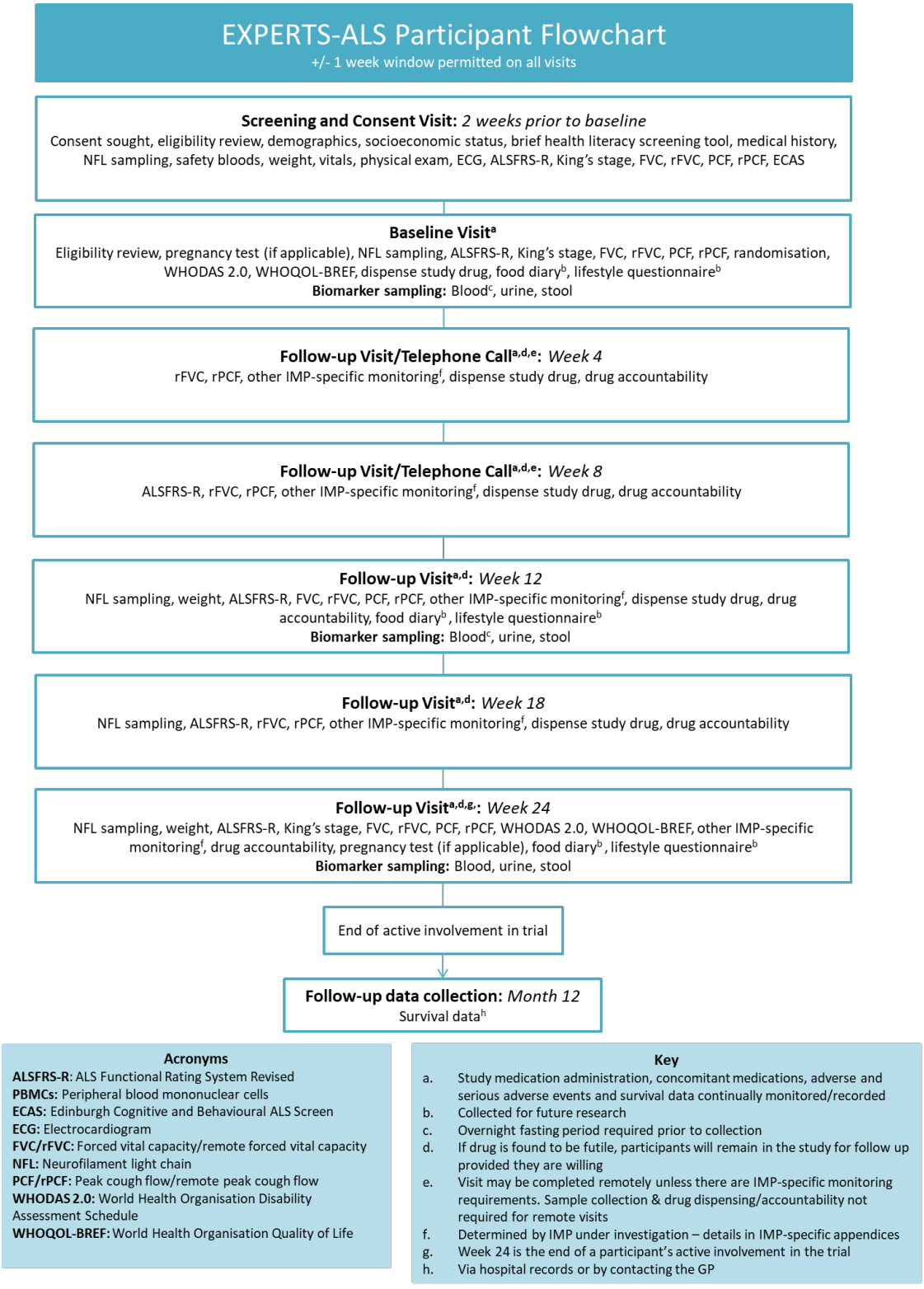
Table 1: Feasibility outcomes

Outcome	**Red***	**Amber****	**Green*****
Site set up (number of centres set up and recruited their first participant)	<6 centres (<50%)	6-10 centres (50-91%)	11 centres (100%)
Participant recruitment	<60%	60-99%	100%
Proportion of NFL results (primary outcome) useable/verified	<80%	80-90%	>90%

* Trial may be stopped if adaptations deemed unlikely to result in necessary improvement
** Trial proceeds but adaptations may be required
***Trial proceeds

9. Assessments and procedures

Figure 3. EXPERTS-ALS flowchart.



Acronyms

ALSFRS-R: ALS Functional Rating System Revised
PBMCs: Peripheral blood mononuclear cells
ECAS: Edinburgh Cognitive and Behavioural ALS Screen
ECG: Electrocardiogram
FVC/rFVC: Forced vital capacity/remote forced vital capacity
NFL: Neurofilament light chain
PCF/rPCF: Peak cough flow/remote peak cough flow
WHODAS 2.0: World Health Organisation Disability Assessment Schedule
WHOQOL-BREF: World Health Organisation Quality of Life

Key

a. Study medication administration, concomitant medications, adverse and serious adverse events and survival data continually monitored/recorded
b. Collected for future research
c. Overnight fasting period required prior to collection
d. If drug is found to be futile, participants will remain in the study for follow up provided they are willing
e. Visit may be completed remotely unless there are IMP-specific monitoring requirements. Sample collection & drug dispensing/accountability not required for remote visits
f. Determined by IMP under investigation – details in IMP-specific appendices
g. Week 24 is the end of a participant's active involvement in the trial
h. Via hospital records or by contacting the GP

9.1 Study assessments schedule

Table 2: Study Assessments Table

Assessments	**Week -2**	**Week 0**[a] (Baseline)	**Week 4**[b]	**Week 8**[b]	**Week 12**	**Week 18**	**Week 24**	**EDoT visit**[c]	**Month 12**
Visit window	**-/+ 1 wk**		**+/- 1 wk**	**+/- 1 wk**	**+/- 1 wk**	**+/- 1 wk**	**+/- 1 wk**		**+/- 1 wk**
Informed consent	X								
Eligibility review[d]	X	X							
Demographics[d]	X								
Socioeconomic status[d]	X								
Brief health literacy screening tool	X								
Medical history[d]	X								
Pregnancy test[e]		X					X	X	
NFL sampling	X	X			X	X	X		
Safety bloods[f]	X								
Weight	X				X		X		
Vital signs	X								
Physical examination	X								
ECG[p]	X								
Other IMP-specific monitoring[g]			X	X	X	X	X	X	
ALSFRS-R	X	X		X	X	X	X		
King's Stage	X	X					X		
FVC	X	X			X		X		
Remote FVC[h]	X[i]	X[i,j]	X[k]	X	X	X	X[j]		
Peak cough flow	X	X			X		X		
Remote peak cough flow[h]	X[i]	X[i,j]	X[k]	X	X	X	X[j]		
ECAS	X								
Randomisation		X							
WHODAS 2.0		X					X	X	

Assessments	**Week -2**	**Week 0**[a] (Baseline)	**Week 4**[b]	**Week 8**[b]	**Week 12**	**Week 18**	**Week 24**	**EDoT visit**[c]	**Month 12**
Visit window	**-/+ 1 wk**		**+/- 1 wk**	**+/- 1 wk**	**+/- 1 wk**	**+/- 1 wk**	**+/- 1 wk**		**+/- 1 wk**
WHOQOL-BREF		X					X	X	
Dispense study drug		X	X	X	X	X			
Drug accountability			X	X	X	X	X	X	
Study medication administration		Continually recorded							
Concomitant medications	Continually recorded								
Adverse events	Continually monitored and documented								
Serious adverse events	Continually monitored and documented								
Survival data		Continually recorded							X
Sample collection for future research									
Blood sample		X[l]			X[l]		X	X	
Urine sample		X			X		X		
Stool sample[q]		X			X		X	X	
Data collection for future research									
Lifestyle questionnaire		X			X		X	X	
Food diary[m,o,q]		X			X		X	X	
FVC PDF reports[n, o]	X	X			X	X	X	X	

a. Refer to IMP specific appendices for drug titration requirements. Note that additional remote contact (for example, telephone calls) and/or visits may be required in order to complete the drug titration.
b. Week 4 and week 8 visits may be completed remotely unless there are IMP specific monitoring requirements as detailed in the IMP specific appendices. Study drug dispensing and accountability are not required for remote visits.
c. An early discontinuation of treatment (EDoT) visit should be completed for participants stopping study treatment early. This may be completed at the same time as another scheduled visit or as a separate visit at the discretion of the local investigator. If a participant stops study treatment early but remains in the study for follow-up, the following assessments do not need to be repeated at week 24 if they are completed at EDoT: pregnancy test, WHODAS 2.0 and WHOQOL-BREF.
d. Refer to section 5.5 for details.

e. Persons of childbearing potential must have a negative pregnancy test prior to randomisation (at the baseline visit or within 7 days prior to baseline) and at treatment discontinuation or at the next study visit (see Section 5.8 for definitions). Additional testing may be required for individual IMPs, refer to the IMP specific appendices for details.
f. As per section 9.6 the following parameters will be measured: Full blood count including haemoglobin, white blood count, lymphocytes, neutrophils and platelets; liver function tests including ALT, AST, ALP, bilirubin and GGT; renal function tests including sodium, potassium and eGFR.
g. Determined by IMP under investigation – refer to the IMP-specific appendix for details.
h. Test can be completed +/- 7 days around appointment date.
i. Face-to-face training provided for participants at screening and baseline visits.
j. Conducted at same time as standard FVC/peak cough flow.
k. Remote training provided for participants at week 4.
l. An overnight fasting period is required for the blood samples collected at the baseline and week 12 visits.
m. A food diary will be completed by the participant over the three days leading up to the stool sample collection. The local study team will record in the database whether the diary has been completed or not but the data will not be entered into the trial database. Paper copies of the diary will be stored securely by the participating site.
n. The study team will download PDF reports from home spirometers at each study visit where possible, the procedure is detailed with the FVC / PCF procedure document. The local study team will record in the database whether the reports have been downloaded but, other than FVC and peak flow values recorded within the app, the data will not be entered into the trial database. PDF copies of the reports will be stored securely by the participating site prior to being securely transferred to the University of Sheffield for analysis.
o. Non-database items.
p. ECG only required if salbutamol is a potential outcome of randomisation.
q. Stool sample kits and food diaries to be given to participants at screening, baseline and week 12.

9.2 Study Assessments

Study assessments will be completed as per Section 9.1. Randomisation will occur within 2 weeks (+/- 1 week) after screening. All other visits will be scheduled from the date of randomisation or from the day of initiation of the study drug if the initiation of the study drug is delayed for more than 7 days for drug-specific logistical reasons (e.g. vaccination requirements before the initiation of a study drug).

If it is not possible to complete some of the study assessments at a visit, for example due to ill health, then results obtained as part of routine clinical care can be used, if collected during the appointment window as defined in Section 9.1. The values obtained from the medical records should be entered in the CRF with the date they were collected.

At 12 months, a review of survival status will be completed and participants are informed of this in the PIS. Ideally this will be confirmed without requiring further contact with the participant (refer to study-specific research manual for more details). Survival status may be confirmed by reviewing hospital records or by contacting the participant's GP to review their records.

9.3 Unscheduled visits

An unscheduled visit or video/telephone call may be arranged if an IMP is found to be futile and is dropped from the study in order to discuss the next steps with the participant. Refer to section 9.10 for details.

Other unscheduled visits or video/telephone calls may be arranged at the discretion of the local study team, for example if the participant contacts the team with a medical concern about the study.

9.4 Procedures for assessing efficacy

NFL

As described in Section 8.1, the primary outcome is blood NFL levels as a surrogate outcome for biological efficacy. Blood samples will be collected, processed and stored at site before being shipped in batches to EXPERTS-ALS Oxford Laboratory, for analysis. The sample handling procedures will be fully described in a study-specific Sample Collection SOP.

9.5 Procedures for clinical assessments

ENCALS Risk Score

The ENCALS risk score (13) must be calculated at screening and is used to determine eligibility. Details of how to access the online calculator and document the risk score are provided in the study-specific research manual. The following clinical variables are required for risk estimation: date of birth, date of ALS diagnosis, date of ALS symptom onset, date of screening, ALSFRS-R total score at screening, FVC % predicted at screening (according to GLI-2012), site of ALS symptom onset, El Escorial diagnostic criteria category and presence of ALS-FTD. If a patient is unable to generate a FVC measurement, Slow vital capacity (SVC) can be measured instead, and SVC % predicted at screening can be used to calculate the risk estimation instead of FVC % predicted. The risk profile is based on the ENCALS survival model and can be conceptualised as a relative summary of prognostic information. The risk profile indicates how participants compare to each other (i.e., who is faster or slower

progressing than average) without estimating the absolute survival time or probability.

ALS Functional Rating Scale Revised (ALSFRS-R)

The ALS functional rating scale revised (ALSFRS-R) (18) score is an investigator-administered function-based symptom questionnaire that can be used as an indicator of disease progression. It comprises 12 questions examining lower limb, upper limb, bulbar and respiratory function. Each question scores between 0 and 4 points with a maximum overall score of 48 (higher scores indicate better function). Staff training will be provided and the full procedure is detailed in the study-specific research manual.

Forced Vital Capacity (FVC)

Forced vital capacity (FVC) is the measurement of the total volume of air exhaled following full inspiration and is used to measure the strength of the respiratory muscles. Seated FVC will be assessed. Participants will be asked to inhale as far as possible then exhale quickly into a spirometer using a mask held firmly over the nose by the assessor (rather than a mouthpiece to overcome issues with lip seal due to bulbar dysfunction) until all air is exhaled. A minimum of three and a maximum of five trials will be completed and the best will be recorded. The measurement is adjusted for height and age. Staff training will be provided and the full procedure is detailed in the study-specific research manual.

Peak cough flow (PCF)

Peak cough flow (PCF) will be measured using the spirometer used to measure in-clinic FVC or a Wright's peak flow meter. A facemask will be held firmly over the participants nose and mouth by the assessor. Participants will be instructed to inhale to a maximum capacity and then forcibly cough through the oronasal facemask in a seated position. Three to five measurements will be taken. The maximum score will be recorded in litres per minute (L/min). A score of less than 60 is recorded as 0 L/min if using a Wright Peak FLow Meter and a score of greater than 880 L/min, recorded as 881L/min (19).

King's Stage

Disease staging will be completed using the King's staging system (20,21). It describes several key steps in the disease progression of MND including functional involvement of one, two or three CNS regions and need for gastrostomy or non-invasive ventilation. The stages are defined as follows:

- Stage 1: Symptom onset (involvement of first region)
- Stage 2: Involvement of a second region
- Stage 3: Involvement of a third region
- Stage 4A: Need for gastrostomy
- Stage 4B: Need for respiratory support (non-invasive ventilation)

Assigning participants to a stage can be done from assessment of the medical records or using standard questions and neurological examination. Staff training will be provided and the full procedure is detailed in the study-specific research manual.

Edinburgh Cognitive and Behavioural ALS Screen (ECAS)

The Edinburgh cognitive and behavioural ALS screen (ECAS) is a 130-point cognitive screening tool that is adapted for use in people with difficulty communicating or writing due to muscle weakness. It takes 15-20 minutes to complete. The ECAS will be administered face-to-face by a delegate trained in its use. Part of the ECAS is a behavioural screen which

involves a semi-structured interview with a relative/carer or friend of the participant completed independently of the participant. Ideally the behavioural screen will be completed face-to-face but it can be completed by telephone if necessary. The behavioural screen should be completed within 2 weeks of the participant ECAS. This part of the assessment will only be completed if consent has been provided by the participant and the relative/carer.

The ALS-specific score is out of 100 and the non-ALS-specific score is out of 36. An ECAS total score is produced by summing these scores together to give a maximum score of 136. The thresholds for 'normal' scores can be found in the guidelines (22). In the UK, the threshold for ECAS total is 105 and a score at, or below, 105 suggests potential cognitive impairment.

WHODAS 2.0

The WHODAS 2.0 is a generic self-assessment instrument for health and disability covering 6 domains of functioning (cognition, mobility, self-care, getting along, life activities and participation). Each item scores between 1 and 5 with higher scores indicating greater disability. The 36-item self-administered version of the questionnaire will be used (or 32-item if the participant is not working), as this is suggested to be the optimum amount of information (23).

9.6 Procedures for assessing safety

Adverse events will be recorded in the medical notes and case report form. Refer to Section 10 for full details. If there are any clinical concerns about a participant, identified through any of the research procedures or assessments, these will be referred to the appropriate clinical team for further investigation. This includes abnormal blood results, responses to questionnaires that cause concern about the participant's wellbeing, and any other concerns aside from the expected course of ALS.

The safety assessments listed below will be completed as per the study assessments schedule in Section 9.1. The assessments may be completed at additional timepoints if clinically indicated. Where additional IMP-specific monitoring is required, this will be detailed in the IMP-specific appendices.

Safety bloods

Blood samples will be taken as per the timings in the Study Assessments Schedule in 9.1. The samples will be analysed locally and the following parameters measured:

- Full blood count (FBC) including Haemoglobin (Hb), white blood count (WBC), lymphocytes, neutrophils and platelets
- Liver function tests (LFTs) including ALT, AST, ALP, bilirubin and GGT
- Renal function including sodium, potassium, eGFR

Where additional IMP-specific monitoring is required, this will be detailed in the IMP-specific appendices.

Vital signs

Blood pressure, heart rate, weight, respiratory rate and height (screening only) will be measured. Where additional IMP-specific monitoring is required, this will be detailed in the IMP-specific appendices.

Physical examination

A physical examination will be completed and non-ALS abnormalities will be recorded.

9.7 Procedures for assessing quality of life

Questionnaires will be provided in print to the participant for self-completion. Data from the paper questionnaires will be entered onto the study database by the local research team. At the time of completion, questions may be clarified for the participant if the question is not understood, but the researcher will not provide any bias towards any of the answer options.

WHOQOL-bref

Quality of life (QoL) will be assessed via the WHOQOL-bref (24) which is a self-administered questionnaire comprising 26 questions on the individual's perceptions of their health and wellbeing over the previous two weeks. The responses to questions are on a 1-5 Likert scale and it produces four domain scores (physical, psychosocial, social relationships and environment. Higher domain scores indicate higher quality of life.

9.8 Procedures for sample and data collection for future research

Whole blood, plasma, serum, urine and stool samples will be collected from all participants as per the study assessments schedule. An overnight fasting period is required for the blood samples collected at baseline and week 12. Stool sample collection kits will be provided to participants at the screening, baseline and week 12 visits and participants will be asked to return a sample to the EXPERTS-ALS UCL Laboratory via a pre-paid envelope prior to baseline, week 12 and week 24 (or early discontinuation of treatment). The stool sample should be completed the day before the visit. Participants will complete a food diary over the three days leading up to each stool sample collection. At the screening, week 12 and week 24 (or early discontinuation of treatment) visits, participants will be asked to complete a lifestyle questionnaire. Samples will be processed and stored locally prior to shipping in accordance with the study-specific sample collection SOP. Samples will be shipped in batches to EXPERTS-ALS Oxford Laboratory and EXPERTS-ALS UCL Laboratory, and stored for future research. Access to samples for future research will be subject to a review by the EXPERTS-ALS WS3 committee in accordance with the relevant study specific SOP.

Future studies will include whole genome sequencing, completed at King's College London, on an anonymised basis, without individual feedback of genotype, for which there is a separate clinical pathway. Stool samples and the associated food diaries and lifestyle questionnaires will be used in future research to understand how the microbiome affects IMP response. Participants are informed of this in the PIS.

The maximum quantity of blood to be taken within a 24 hour period is 90 ml.

9.9 Procedures for remote respiratory function assessments

Currently the primary measures of respiratory function (FVC and PCF) require in-person measurements. This is burdensome on patients and clinical trials. These measures are volitional and rely on good technique which is often difficult for people with MND due to bulbar and limb dysfunction. They may be affected by the fatigue associated with travel to trial visits. Conversely, problems with technique may affect unsupervised assessments. At-home measures of FVC can be undertaken using handheld spirometers such as the Spirobank smart which can record FVC and provide qualitative data using a flow volume loop. These have been used in small case studies but are not currently validated for either

supervised or unsupervised use and therefore are not currently acceptable trial outcome measures. There are no at-home PCF devices but the Mini-Wright Standard Peak Flow Meter provides a basic measure of peak expiratory flow volume and may be an appropriate surrogate marker of PCF.

Remote Forced Vital Capacity (rFVC)

Those participants able to generate an FVC in clinic and who have a smartphone will be provided with a spirometer to allow FVC to be measured remotely (rFVC). They do not require access to the internet to complete the assessments. They will conduct a maximum of three measurements of unsupervised seated rFVC on each assessment.

The MIR Spirobank Oxi spirometer with a mask and filter will be used. The Spirobank Oxi connects using bluetooth to the participant's smartphone (no internet connection is required). Participants will be provided with diaries in which to log their results which will be collected at each visit. The results and flow volume loops are stored within the app on the phone and downloaded at each clinic visit.

Participants will be trained to use the Spirobank Oxi in person. Instructional videos and paper guides will show the participants the correct technique. During training sessions they will complete up to three supervised attempts. The instructor will then leave the room and the participant will complete a further three attempts. All scores will be recorded. Participants will be trained face to face at screening and again at baseline. At week 4 the study team will contact the patient by telephone or video and collect the remote scores. If the patient's week 4 scores are not within 150mls of their baseline FVC, further coaching and review of the flow-volume loops will be given by video or telephone.

In the event the participant is unable to generate any acceptable FVC, rFVC, PCF or rPCF (typically due to bulbar dysfunction) they will not be given a device. Site staff will record reason(s) why patients are not given a spirometer or PCF machine.

Participants will complete rFVC as per the schedule. Participants will be asked to conduct rFVC within a seven day window before or after their follow up visit (remote or in person).

Remote Peak cough flow (rPCF)

Participants able to provide at least three PCFs will be provided with a Wright Peak Flow Meter and mask. The same training and testing schedule as rFVC will be used. The participants will record the results in a diary as the devices do not use a smartphone.

Data collection

Patients will record the results for rFVC and rPCF in a diary. The rFVC data is collected by the Spirobank app and stored on the phone using the participant's study ID and date of birth only. Each recording result will be saved as a PDF by the participant during a study visit with assistance from the local study team as needed. The PDFs will be transferred to the study site via email (or via bluetooth transfer, if required) and the local study team will assist the participant to do this during a study visit. PDFs will be stored locally at site before being securely transferred to The University of Sheffield for analysis.

9.10 Participant withdrawals

Early discontinuation of treatment
Participants may wish to discontinue study treatment, the treatment arm may be dropped from the study for futility, or there may be a clinical need to discontinue it. If this occurs, it will be documented on an intervention withdrawal form and in the patient notes. If applicable, a pregnancy test will be completed at treatment discontinuation or at the next study visit as per Section 9.1. The study assessments schedule in Section 9.1 provides details of other assessments to be completed at treatment discontinuation (or at the next study visit). Early discontinuation of treatment does not constitute withdrawal. Participants discontinuing treatment early should continue in the study as normal for follow up if they are willing, apart from intervention administration. Follow up would include scheduled study visits up to week 24 (as per the study assessment schedule) and allowing the study team to access their medical records and any relevant hospital data that is recorded as part of routine care.

Withdrawal from study
Participants may withdraw their consent for the study at any time, without providing a reason for this. If this occurs, this will be documented on a study completion/ discontinuation form and the patient notes. Although the participant is not required to give a reason for discontinuing their study treatment, a reasonable effort will be made to establish this reason while fully respecting the participants' rights. Any data collected up to the point of the participant's withdrawal will be retained, and used in the final analysis, and this is made clear to the patient at the time of consent. Any samples collected up to the point of the participant's withdrawal will be retained, and used in the final analysis, unless the participant requests otherwise, and this is also made clear to the patient at the time of consent.

Excessive participant withdrawal from follow-up has a negative impact on a study. Centres will explain the importance of remaining on study follow-up to participants, and that changes to planned treatment need not imply withdrawal from the study. Nevertheless, if participants do not wish to remain in the study their decision must be respected. If the participant explicitly states their wish not to contribute further data to the study, this will be recorded on the study completion/discontinuation form and in the patient notes. Withdrawn participants will not be replaced. For those participants who do not want to actively participate in follow up the local study team will continue to collect data from medical notes and other available healthcare sources unless the participant specifically refuses permission for this. Remote follow up e.g., via telephone calls may also be used if the participant does not wish to attend study visits in person.

9.11 Loss to follow-up
Participants will be defined as lost to follow up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the site. Reasonable attempts should be made to contact the participant where possible, before they are considered lost to follow-up. Data from hospital records may still be collected if possible and this is explained in the PIS. If a participant is lost to follow up, this will be recorded in the CRF using the study completion/discontinuation form.

9.12 Ethnicity data
In addition to collecting ethnicity data for EXPERTS-ALS participants, all staff on site delegation logs will be asked to complete an optional question on their ethnicity. The purpose of

collecting this information is to look at the demographics of our trial workforce as this may be a contributing factor in the diversity of participants recruited for the trial. Anonymised data may be aggregated with that from other studies to inform future research. CTRU will send a link to an online questionnaire to all members of staff listed on site delegation logs. The first page of the questionnaire will provide information about the data we are collecting and why. Names and email addresses will not be collected.

10. Safety Reporting

ICH-GCP requires that both investigators and sponsors follow specific procedures when reporting adverse events/reactions in clinical studies. These procedures are described in this section. IMP-specific reporting may be required for some IMPs, in which case the details will be included in the IMP-specific appendices. Additional guidance is provided in a study-specific SOP.

10.1 Definitions

Table 3: Safety reporting definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a study participant. Refer to Section 10.2 for study-specific exemptions.
Serious Adverse Event (SAE)	An AE which is serious, defined as any untoward medical occurrence or effect that: ● Results in death ● Is life-threatening* ● Requires hospitalisation or prolongation of existing hospitalisation** ● Results in persistent or significant disability or incapacity ● Congenital anomaly/birth defect ● Other important medical event ***
Adverse Reaction (AR) or Serious Adverse Reaction (SAR)	Any AE or SAE that is judged, in the opinion of the PI, to be related to an investigational medicinal product.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A SAR, the nature or severity of which is not consistent with the reference safety information for the IMP.

*The term life-threatening in the definition of a serious event refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe, for example, a silent myocardial infarction.

**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, that has not worsened or for an elective procedure for a condition which has not worsened do not constitute an SAE.

***Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when, based upon appropriate medical judgement, they may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

10.2 Study specific exemptions

Events that are expected due to the participant's ALS (even if they meet the definition of Serious as defined in section 10.1) should **not** be recorded or reported as adverse events.

Due to the heterogeneity of disease progression in ALS the Principal Investigator, or delegate, is required to assess whether the event is consistent with expected disease progression in the participant. Events consistent with disease progression should be recorded in the participant's medical notes only, with the exception of hospitalisation due to disease progression which should be recorded on the ALS Progression Hospitalisations form and death which should be recorded on the Study completion/discontinuation form in the CRF. The study team will inform the patient's local ALS care team (nurse/consultant) or GP in the event of disease progression occurring so that appropriate management can be initiated.

If the event is related to ALS but judged to be an unexpected worsening of the condition and/or possibly related to participation in the trial/ trial medication it should be treated as an adverse event, recorded in the participant's medical notes and recorded/reported as an AE. The seriousness of the AE should be assessed as per section 10.1 and if it meets the definition of serious then it should be reported as per section 10.5.

Exemptions may include, but are not limited, to:

- Symptoms and signs due to ALS and its expected progression e.g. minor cramps, fasciculations, sialorrhea, mild musculoskeletal discomfort, breathlessness.
- Hospitalisation:
    - for gastrostomy insertion
    - due to falls
    - due to choking and panic attacks (pharyngeal spasm)
    - for secretion management
    - due to aspiration pneumonia
    - associated with complications of NIV use (including titration of NIV pressure)
    - for weaning of ventilation for end of life care
    - for end of life care, particularly during the last 24-48hrs of life
    - due to carer burden
    - due to inability to manage activities of daily living and lack of social support
- Death
    - caused by type 2 respiratory failure

Where there are any modifications to AE reporting for individual IMPs, these are detailed in the appendix for that IMP.

10.3 Identification and assessment at site

Identification
AEs/SAEs which are not exempt (as per Section 10.2) will be recorded in the eCRF from consent until the participant has completed their involvement in the trial, up to week 24.

Participants will be asked about AEs/SAEs at every study visit with open-ended and non-leading verbal questioning. Participants will also be asked if they have been admitted to hospital or had any accidents. AE data may also be identified via information in the medical records.

Seriousness
AEs must be assessed by the investigator for seriousness in order to determine if the event is an SAE. Assessments must be based on the definitions provided in Section 10.1. The notification procedure for SAEs is detailed in Section 10.5.

Causality (relatedness)
The relatedness of all AEs will be assessed by the site Principal Investigator or delegate and recorded on the AE form. The relatedness to the IMP will be categorised as follows:

- Reasonable probability of being related – where the nature of the event, the underlying medical condition, concomitant medication or temporal relationship make it possible that the AE has a causal relationship to the study drug.
- No reasonable probability of being related – where an event is not considered to be related to the IMP.
- Not assessable – where there is insufficient information to assess relatedness. Follow up reports for any events categorised as 'not assessable' should be submitted as soon as possible to update the causality assessment when more information is available.

For the purposes of regulatory reporting, if a causality assessment is not provided by the site, or is recorded as not assessable, SAEs will be deemed to be related until the site Principal Investigator or delegate confirms otherwise.

Severity (intensity)
The severity of all SUSARs will be assessed by the investigator as follows:

- Mild – an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with routine activities.
- Moderate – an event that is sufficiently discomforting to interfere with routine activities.
- Severe – an event that prevents routine activities.

The worst severity grade for each SUSAR will be recorded in the Prospect database.

10.4 Recording and reporting

AEs and ARs will be recorded from the time of consent for trial entry until the participant has completed their involvement in the trial, up to week 24.

AEs and ARs except those exempt as per section 10.2 will be recorded on the adverse event report form, within the study database, including those that fulfil the criteria for being serious (see section 10.1). Sites are asked to enter all available information onto the study database as soon as possible after the site becomes aware of the event.

Out of range lab values will only be recorded as an AE if they are considered clinically significant and require intervention to treat.

SAEs, SARs and SUSARs will require more detailed information to be recorded. In such cases, the event must also be reported to the Sheffield CTRU within 24 hours of the site becoming aware of the event. The CTRU will notify the Sponsor of each of these events in accordance with the Agreement between Sheffield Teaching Hospitals and University of Sheffield.

10.5 SAE notification procedure

Site staff must notify CTRU of all SAEs within 24 hours of becoming aware of the event, with the exception of the events listed in Section 10.2. All SAEs must be reported on the Serious Adverse Event (SAE) reporting form and sent to CTRU by email: ctru-saes-group@sheffield.ac.uk within the reporting timelines.

The SAE form must be completed by the investigator (a clinician named on the delegation log who is responsible for the participant's care). In the absence of the investigator the form will be completed by a member of the study team and emailed as appropriate. The responsible investigator will subsequently check the SAE form, make changes as appropriate, sign and re-send the form to CTRU as soon as possible.

Receipt of the initial report should be confirmed by CTRU within one working day. The site research team should contact the study team at CTRU if confirmation of receipt is not received within one working day.

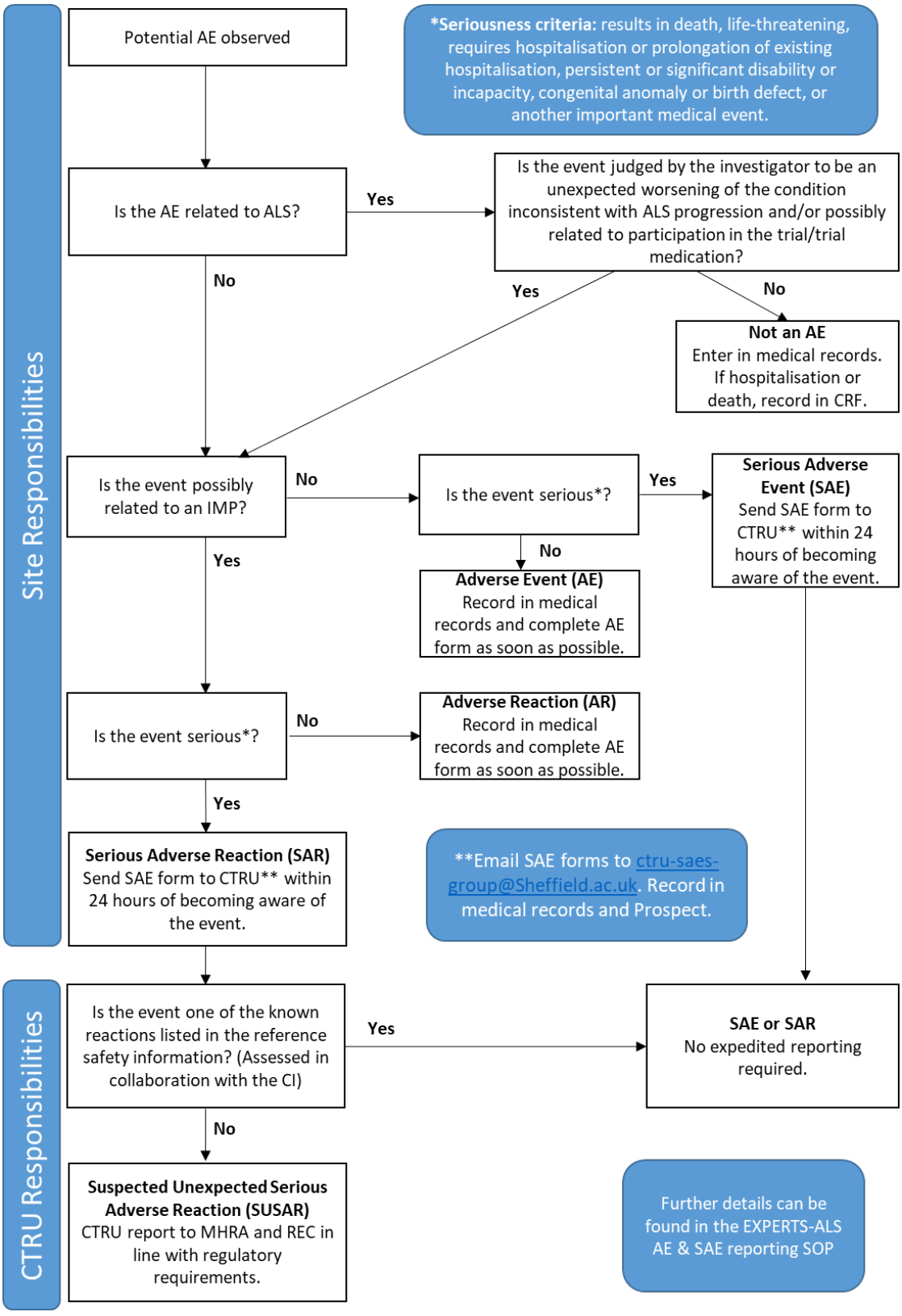
Concomitant medications are recorded throughout the study and will not be collected on SAE forms as standard. However for any event classified as a SAR or SUSAR CTRU may request additional information on concomitant treatments to facilitate onward reporting.

Follow up
Initial SAE reports must be followed by detailed reports when further information becomes available.

SAEs must be followed up until clinical recovery is complete and laboratory results have returned to normal or baseline, or until the event has stabilised. Follow up information will be provided on an SAE form marked as such. This may continue beyond a participant's involvement in the trial and this is specified in the PIS. Follow up of unresolved SAEs (SAEs that have not resolved or stabilised, or where causality and/or expectedness assessments are incomplete) will continue until database lock for the arm to which they were randomised.

Further clarification on the reporting process can be seen in Figure 4.

Figure 4: AE and SAE reporting process



10.6 Pregnancy Reporting

All pregnancies within the trial should be reported using the Pregnancy Reporting Form within 24 hours of notification. The Chief Investigator and the TMG will be informed, so that a discussion can take place regarding the participant's continuation in the study. Any such discussions will be documented, and recommendations for continuation or discontinuation in the study will be made according to clinical judgement.

Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/foetus. If the outcome meets the criteria for seriousness, this would be considered an SAE. Any participant who becomes pregnant whilst taking IMP will be asked to consent to follow up of the pregnancy, irrespective of any treatment withdrawal or changes. Follow up will be recorded on the pregnancy follow-up form. Pregnancy reporting requirements for partners of participants are provided in the IMP-specific appendices.

The DMEC and the Programme Steering Committee (PSC) will be advised at each meeting, of any pregnancies reported since their previous meeting.

10.7 CTRU responsibilities

CTRU will assess all SARs for expectedness in collaboration with the CI. An unexpected adverse reaction is one which is not previously reported in the Reference Safety Information (RSI) used in the study, or one that is more frequent or more severe than reported in the RSI. If a SAR is assessed as 'unexpected', it is classified as a SUSAR.

The RSI to be used in the study will be section 4.8 of the SmPC for the relevant IMP in the version which has been submitted to and approved by the MHRA for this trial.

The Sponsor has delegated CTRU responsibility for the reporting of SUSARs and other SARs to the regulatory authorities and the research ethics committee as appropriate. CTRU will also keep all investigators informed of any safety issues that arise during the course of the study. CTRU will report all SAEs to the Sponsor as documented in the delegation of duties agreement.

The DMEC and TMG will also receive information on all AEs and SAEs, at a frequency agreed with each committee and documented in the appropriate charter/terms of reference.

10.8 SUSARs

The CTRU will be responsible for reporting SUSARs to the MHRA and REC in line with regulatory requirements. Fatal or life-threatening SUSARs will be reported no later than 7 calendar days of CTRU being aware of the event. All other SUSARs will be reported no later than 15 calendar days of CTRU being aware of the event. Each site will be informed of SUSARs occurring across the study.

11. Statistics

11.1 Statistical Analysis

There are six possible conclusions for a given candidate drug:

1. Potential effectiveness of a candidate drug: the predictive probability of a reduction in NFL levels at 18 to 24 weeks is >97.5%

2. Futility: the predictive probability of reaching a mean reduction in NFL levels of 0.15 log10 units or more is <1%
3. Non-inferiority compared with current reference drug: the posterior probability of being inferior to the reference drug by 0.10 log10 units or more is <=2.5%.
4. Superiority over current reference drug: the posterior probability of being superior to the reference drug by 0.10 log10 units or more is >=97.5%.
5. No established non-inferiority compared with the current reference drug: the posterior probability of being inferior to the reference drug by 0.10 log10 units or more is >2.5%.
6. No established superiority compared with the current reference drug: the posterior probability of being superior to the reference drug by 0.10 log10 units or more is <97.5%.

Primary outcome analysis

We will use a Bayesian linear model with minimally informative priors that allows for repeated NFL levels assessed at 18 and 24 weeks, with inclusion of baseline NFL levels assessed at the screening visit at -2 weeks and before randomization at week 0. NFL levels originally measured in pg/mL will be log10 transformed to achieve more symmetrical distributions. The primary outcome analysis will follow the intention-to-treat principle, where all patients will be analysed as randomised.

A multivariable Bayesian prediction model that incorporates baseline characteristics and NFL levels pre-randomization and intermediate NFL levels ascertained at 12 weeks as covariates will be used to estimate predictive probabilities of futility and potential effectiveness based on all patients randomised to a trial arm at the time of an interim analysis despite incomplete follow-up. The model can account for all additional data that will accumulate until all patients have completed final follow-up, and appropriately incorporate all sources of uncertainty. Arm-specific Bayesian predictive probabilities for early identification of drugs that are unlikely to be associated with a relevant decrease in NFL levels from baseline will be estimated, declaring futility as described above after at least 16 patients (in case of futility analysis 1) and 20 patients (in case of futility analysis 2) have reached 18 weeks of follow-up. If a trial arm is declared futile, the DMEC will make a recommendation to the TMG who can decide to drop the drug from the trial. A previously dropped candidate drug may re-enter the trial at a higher dose if considered clinically justifiable. The cut-offs used to declare futility, potential effectiveness, non-inferiority or superiority, and decisions on timing and frequency of analyses are based on extensive simulations. A total of 2000 trials were simulated under various scenarios, each trial using 5000 iterations after a burn-in period of 1000 iterations.

If a concurrently randomised candidate drug was not declared futile based on arm-specific Bayesian predictive probabilities obtained in futility analyses 1 and 2, we will estimate pairwise between-group mean differences in NFL levels at 18 to 24 weeks with 95% credible intervals and Bayesian posterior probabilities of non-inferiority, and, if reached, superiority to the reference drug after 80 patients per arm reached 24 weeks of follow-up. Drugs that were dropped due to futility after futility analysis 1 or 2 will not be included in non-inferiority or superiority analyses.

Irrespective of which conclusion was reached for a drug, we will estimate arm-specific mean changes from baseline with 95% credible intervals with final posterior probabilities to reach a reduction from baseline. Using Bayesian network meta-analysis, which fully maintains

concurrently randomised comparisons, we will then rank all candidate drugs by their effectiveness in decreasing NFL levels and calculate the posterior probability that each candidate drug has the highest or lowest NFL decrease from baseline.

Candidate drugs associated with a decrease in NFL levels will become candidates for investigation in a Phase III trial, particularly if they were considered non-inferior or superior to effective reference drugs as described above. Candidate drugs that ranked lower than reference drugs but were associated with a decrease in NFL levels can be considered for investigation in a Phase III trial based on other possible advantages, such as better safety profile and/or lower costs.

The first candidate drug that is retained after futility analyses 1 and 2 and associated with >97.5% probability of a reduction in mean group NFL levels different from zero at 18 to 24 weeks after 80 patients per arm reached 24 weeks of follow-up will be considered the first reference drug. As the trial continues, patients will continue to be randomised to this reference drug as long as DMEC and/or TMG do not consider another candidate drug as reference. Figure 2 (above) illustrates potential adaptations to trial arms following the planned futility analyses for the example of three concurrently evaluated drugs.

Candidate drugs should be considered as the potential new reference drug by the DMEC and/or TMG under two scenarios:

1. Superiority to current reference drug: If a candidate drug has demonstrated superiority over the current reference drug, it warrants consideration as a new reference drug. This evaluation should adhere to the predefined criteria established in the protocol.

2. Non-inferiority to current reference drug: A candidate drug may also be considered as the new reference drug if it has been shown to be non-inferior to the current reference drug following the criteria established in the protocol. This consideration may be triggered by factors such as improved tolerability or when the DMEC believes that sufficient data have been accumulated for the current reference drug within the context of the platform trial so that a change to a new reference drug is warranted.

Further details of the primary outcome analysis will be pre-specified in the statistical analysis plan. In the event that a candidate drug has a prolonged titration phase to reach the target dose, the statistical analysis plan may be amended to account for this.

Analysis of secondary and exploratory outcomes

Secondary and exploratory outcomes will be analysed only after enrolment for an arm is complete and all enrolled patients have finished follow-up or have been definitively classified as lost to follow-up. Survival at 12 months without non-invasive ventilation >22 hr/day or invasive ventilation will be analysed using restricted mean survival time. ALSFRS-R scores, WHODAS 2.0, WHOQOL-Bref, FVC and PCF will be analysed using linear models adjusted for baseline values of the respective outcome. Progression in King's stage by one stage, adverse events and serious adverse events will be analysed using Poisson regression. All models will be Bayesian, using minimally informative priors to derive both within arm estimates and between-arm comparisons for concurrently randomised arms.

The face to face and remote measurements of respiratory function analyses will be compared where readings are available within +/-7 days of each other. The correlation between pairs will be calculated using the Pearson correlation coefficient and graphical means will be used to examine trends and outliers. The number of completed assessments and reasons for non-completion will be reported. Observed survival at 12 months without non-invasive ventilation >22 hr/day or invasive ventilation will be compared with the median ENCALS prediction of survival without non-invasive ventilation >22 hr/day or invasive ventilation, and graphical means will be used to examine trends and outliers. Further details on the analysis of secondary and exploratory outcomes will be pre-specified in the statistical analysis plan.

Dealing with missing outcome data

The Bayesian linear model will implicitly account for missing outcome data if a patient has at least one of the two NFL levels at 18 or 24 weeks ascertained. If more than 10% of patients in an arm have both NFL levels at 18 and 24 weeks missing, we will use a multivariable Bayesian prediction model that incorporates baseline characteristics, NFL levels pre-randomisation, intermediate NFL levels ascertained at 12 weeks, available NFL levels observed at 18 and 24 weeks and clinical outcomes to derive posterior predictive distributions that allow estimation of pairwise between-group mean differences in NFL levels at 18 to 24 weeks with 95% credible intervals and Bayesian posterior probabilities of non-inferiority or superiority and arm-specific mean changes from baseline with 95% credible intervals and posterior probabilities to reach a reduction from baseline.

11.2 Sample size

In a dataset with repeated NFL levels provided by the Clinical Research in ALS and Related Disorders for Therapeutic Development (CreATe) Consortium, the correlation between repeated measures of log10 transformed NFL levels (pg/mL), obtained within 2 to 8 months, was ≥ 0.85 (5). The typical standard deviation at any given measurement time point was 0.35 log10 units.

Figure 1 (above) illustrates the analyses and adaptations at trial arm level. The first futility analysis will be conducted when at least 23 randomised patients per candidate drug reached 12 weeks and at least 16 patients reached 18 weeks of follow-up, which will occur when approximately 28 patients per arm were randomised. This will result in >85% power to detect an average decrease in NFL levels from baseline of 0.15 log10 units and >80% power to declare futility of the candidate drug, assuming a correlation between baseline and follow-up of 0.80. The second futility analysis will be conducted when at least 29 randomised patients per candidate drug reached 12 weeks of follow-up and at least 20 patients reached 18 weeks of follow-up, which will occur when approximately 35 patients per arm were randomised (Figure 1). This will result in >90% power to detect an average decrease in NFL levels from baseline of 0.15 log10 units or declare futility of the candidate drug, assuming a correlation between baseline and follow-up of 0.80. A decrease in NFL levels of 0.15 log10 units, for example, corresponds to a 30% decrease in the geometric mean from 60 pg/mL at baseline to 42 pg/mL at 18 to 24 weeks of follow-up. Of note, since recruitment is accelerating at the beginning of the platform trial, the number of patients randomised will be somewhat higher when futility analyses 1 and 2 will be performed during the first phase of the platform trial.

Potential effectiveness in decreasing NFL levels will be declared if the Bayesian predictive probability of a candidate drug to reach any reduction from baseline at 18 to 24 weeks of follow-up is 97.5% or more. Futility or potential harm will be declared if the posterior predictive probability of a candidate drug to reach a reduction of at least 0.15 log10 units at 18 to 24 weeks of follow-up is 1% or less.

To achieve >80% power for both non-inferiority and superiority analyses, the target sample size is set at 80 patients per candidate drug who will be randomised and followed-up until 18 to 24 weeks. This sample size will result in >80% power to declare non-inferiority to the concurrently randomised reference drug based on a non-inferiority margin of 0.10 log10 units or to declare superiority over the reference drug provided that the true mean reduction in NFL levels associated with the candidate drug is 0.10 log10 units greater than the reduction seen with the reference drug. Non-inferiority will be declared if the Bayesian posterior probability of having a decrease from baseline at 18 to 24 weeks of follow-up that is 0.10 log10 units smaller than the decrease of NFL levels of the reference drug is 2.5% or less. If non-inferiority is reached, we will test for superiority. Superiority will be declared if the posterior probability of having a decrease from baseline larger than the competitor drug is 97.5% or more. To ensure sufficient power of superiority analyses, we will estimate the predictive probability to detect superiority of a candidate drug given the observed data over the reference drug (analogous to conditional power) when 50 randomised patients per arm have reached 18 weeks of follow-up. If the predictive probability is above 60% but below 80%, we will consider increasing the target sample size to reach a predictive probability of 80%. If the predictive probability is below 60% or above 80%, we will adhere to a target sample size of 80 patients per candidate drug. Figure 1 (above) illustrates corresponding analyses and adaptations at trial arm level.

We aim to recruit approximately 700 people with ALS from 11 centres over 43 months and screen between 9 and 20 candidate drugs, depending on the number of drugs that are retained after futility analyses.

12. Ancillary sub-studies

Participants will be asked to provide consent to additional future research using their data and/or samples. The appropriate approvals will be obtained prior to any additional research being undertaken.

12.1 Qualitative sub-study

Background

Critical to ensuring EXPERTS-ALS is a success, is understanding how trial participants view and experience taking part in an innovative trial design in ALS. Although PPI has informed the trial design, it is important to understand how participants experience the trial, especially if there are modifications we can make to the design or trial processes that improve participation and attrition.

EXPERTS-ALS is innovative in design in a few ways. Firstly, its use of a surrogate marker as an endpoint. Secondly, participation for people with ALS (PwALS) is time-limited and a maximum of 6 months, which is significantly shorter than the usual 2 year involvement in an ALS trial investigating the clinical benefit of treatments. Thirdly, EXPERTS-ALS is an adaptive trial that allows drugs to be identified as futile and immediately dropped from the platform as early as possible. Historically, MND trials have experienced attrition rates, which has been

as high as over 20% (25, 26), and this is associated with a high risk of bias (27). It is unknown how a trial with these innovative design features may affect attrition.

Factors influencing trial participation are also important to understand. Age has been identified as an influencing factor, with older participants being less likely to take part in MND trials (28). However, other social and demographic characteristics are yet to be explored. Understanding potential barriers and enablers to recruitment will ensure the EXPERTS-ALS study processes and procedures can be revised as necessary to be inclusive, and to ensure they do not exclude certain groups so that study findings are generalisable.

As well as understanding pwALS experience of EXPERTS-ALS, the views of multidisciplinary staff implementing platform studies at sites is not well understood. Literature exists which describe the practical considerations for Clinical Trials Unit staff in running platform studies, as well as the resources (29, 30). However, as far as we know, the experience and practical considerations for site staff such as Principal Investigators (PIs)or Research Nurses (RNs) have not been explored. Understanding site staffs' experience of implementing a platform trial will allow us to understand challenges encountered, and if necessary, inform revisions of study procedures and documents for future IMPs in the platform.

We want to explore how the expectations and experience of participants influence the decision to participate and remain in EXPERTS. We will explore trial participant and decliner decision making for participation in EXPERTS including barriers and enablers to recruitment. We will explore participant experience in the trial, exploring views on design elements such as use of a surrogate marker and time-limited participation, and how key events such as study arm dropping and randomisation outcome are experienced. We will explore if these influence the decision to remain in the study. By evaluating site staff experience of the EXPERTS-ALS platform study, we will identify challenges or barriers to implementation as well as study procedures which work well, in comparison to traditional fixed study designs.

Rationale for the qualitative sub-study
To our knowledge, the perspectives and experience of participants whose trial arm has been stopped due to limited treatment effectiveness, and how these may relate to participation and attrition, have not yet been explored. Similarly, the experience and perspectives of PwALS taking part in a trial for a fixed six-month period and using a surrogate endpoint have not yet been explored. Similarly, social and demographic characteristics are yet to be explored. Key findings from the qualitative sub-study will be reported to the TMG to revision of the EXPERTS-ALS study processes and procedures if appropriate. The benefits being to maximise recruitment to the trial, and to ensure trial recruitment is equitable and inclusive.

Aims and objectives

<u>Research questions</u>

1. What are the perspectives and experiences of trial participants and site staff taking part in the EXPERTS trial platform?
2. What are the barriers and enablers for recruitment and retention in the EXPERTS-ALS trial platform?

Aim

There are two aims to the qualitative sub study:

1. To explore participant and site staff (PIs, RNs) understanding and experience of the EXPERTS-ALS platform trial design, with the aim to improve trial procedures and documents, to maximise recruitment 2. To explore barriers and enablers for recruitment and retention to EXPERTS-ALS, with the aim of ensuring trial procedures promote equitable participation and continued involvement in the trial.

Objectives

People with ALS:

- Evaluate the reasons why people with ALS choose to take part (or not take part) in EXPERTS-ALS, including whether taking part in EXPERTS-ALS affects taking part in other ALS trials (or alternatively if other ALS trials affect participation in EXPERTS-ALS)
- Evaluate barriers to taking part in EXPERTS-ALS, explore if social and demographic characteristics of potential participants are associated with the decision to participate in EXPERTS-ALS, and if any groups may be underrepresented
- Evaluate understanding, experience and attitudes of trial participants to study arm dropping both shortly after consent and on completion of their involvement in EXPERTS-ALS (i.e. for participants who complete six months and <6 months of treatment administered)
- Evaluate the reasons for various forms of participant discontinuation (withdrawal from treatment only (continued in the study for follow-up visits); withdrawal from follow-up and did/did not give continued consent for data to be collected from medical records)
- Evaluate understanding of the purpose of the EXPERTS-ALS platform and its relationship with other MND trials (in particular phase III)

Site staff: Principal Investigators and Research Nurses

- Evaluate experience and attitudes of trial staff implementing the EXPERTS-ALS trial at sites, and in comparison with their experience of 'traditional fixed trial design' i.e. no adaptive element
- Evaluate confidence and experience of trial staff in explaining the trial design to PwALS
- Evaluate their experience of the reasons PwALS take part (or do not take part) in the study, including any observation of barriers to taking part
- Evaluate their experience of the reasons participants give for withdrawing from study treatment/follow-up and participants' decision making on the level of being involved in the study
- Evaluate experience of implementing trial decisions and any impact on site staff and trial participants such as randomisation or study arm dropping
- Evaluate understanding of the purpose of EXPERTS-ALS and its relationship with other MND trials (in particular phase III)

Sampling

Sampling will be purposive to include a diverse range of participants. We will aim to recruit up to 37 PwALS, comprising up to 17 patients who decline to take part in EXPERTS and up to 20 EXPERTS trial participants. Caregivers will also be invited to take part to support the person with ALS as appropriate. We will aim to recruit up to 17 site staff. Code saturation should be reached within 9-17 interviews, according to Hennick and Kaiser, 2022 (31).

For PwALS participants, we will purposefully select participants to reflect the range of possible intervention arm outcomes (e.g. continued to full superiority analysis, allocated to an arm dropped for futility) and varying length of time receiving study treatment/taking part in the trial (6 months on study treatment or <6 months study treatment).

We will develop a sampling matrix and review this regularly to ensure that our PwALS sample is purposively recruited to be representative of a range of views and experiences. This may include characteristics such as age, gender, ethnicity and socioeconomic status. In order to ensure a representative sample, we will aim for approximately 20% of pwALS to be from a minority ethnic background. This means that not all those who consent to be contacted about the interviews will be selected and interviewed.

We will aim to identify trial staff participants from all study sites if possible, or we will ensure a purposeful selection of a range of study sites. Purposeful selection will consider years' experience working with PwALS, and experience level in conducting trials. We will aim to recruit the PI and a RN or equivalent from each site. Again, we will develop a sampling matrix and review this regularly, however the diversity of our sample will be dependent on the individuals working within these roles.

Eligibility

People with ALS

The qualitative study will be available at all trial sites and all PwALS who are being considered for inclusion in EXPERTS-ALS will be eligible. Each person who consents to take part in EXPERTS will be asked to consent (optionally) to be contacted by a qualitative researcher to take part in the qualitative study. Participants will be provided with the participant information sheet (PIS) detailing the qualitative study either before or at the EXPERTS-ALS screening appointment.

The qualitative study will also be available to people who are offered the opportunity to take part in EXPERTS-ALS but who decline. A separate consent to be contacted form will be available for participants who do not wish to take part in EXPERTS-ALS but who agree to be contacted about the qualitative study.

PwALS can take part with a family member, friend or caregiver if they wish but this is not mandatory. Where relevant, this person will also be provided with a PIS. This person can join the interview(s) for support only or they can choose to actively participate in the interview by sharing their views too.

EXPERTS-ALS site staff

PIs and RNs involved in the running of EXPERTS-ALS at study centres will be purposefully selected to include a range of sites and experience level in conducting trials.

Approaching PwALS who have declined EXPERTS

PwALS who have declined to take part in EXPERTS will ideally be approached to take part in the qualitative study straight after making their decision to decline. Site staff will briefly explain the purpose of the qualitative study, provide the PIS detailing the qualitative study and seek consent to pass contact details to the qualitative researchers who can explain the qualitative study in more detail. Site staff may also contact the PwALS by phone should more time be required as to whether contact details can be passed on. If it is not possible to discuss the qualitative study straight after the decision to decline taking part in EXPERTS, a member of the pwALS's clinical team will phone them a few days after to discuss the study. If the pwALS expresses interest in taking part in the sub-study, the PIS will be sent to them via email/post and consent to pass their contact details on to the qualitative researchers will then be sought.

The consent to pass on contact details may be obtained in person. If this is not possible, two options for digital consent will be offered via a digital copy of the consent form sent via email to the patient or an individualised online consent form via Qualtrics. Full details regarding the consent to contact process are provided in the study-specific research manual.

Interview scheduling

Individuals will be approached by a member of the qualitative research team at the University of Sheffield via their preferred method of contact (email or telephone) to invite them to take part in the interview. If they are contacted via email and do not respond after 2 weeks, they will be contacted once more to see if they are interested in taking part. If they do not respond following the second contact, the study team will assume that they are not interested in taking part in the interview and they will not be contacted again. Contact via telephone will be attempted a maximum of two times.

Consent

Potential participants will receive an approved PIS. They will be given sufficient time to read and understand the information provided to them and ask further questions as required.

On the day of the interview, the researcher(s) will explain the study to the participants again, allow time for any questions they may have and confirm verbal consent. Verbal consent will be recorded on an encrypted dictaphone on a separate recording to the interview recording. The researcher will complete the qualitative interview audio consent form and then share a copy with the participant after the interview for their records.

Participants will also be given the option to give written consent if required.

If a family member/friend/caregiver chooses to actively participate in the interview by sharing their views, they will also be required to confirm verbal consent (the same process as outlined above).

The researcher(s) will explain to potential participants that entry into the study is entirely voluntary and that they can withdraw at any time. In the event of their withdrawal, it will be explained that their data collected so far cannot be erased and will be used in the final analyses.

Interview timing

We will interview participants who decline to take part in EXPERTS-ALS once soon after they have been approached to take part in the study.

We will interview EXPERTS-ALS participants at least twice; once soon after agreeing to take part in the trial and once soon after their involvement in the trial has ended. We will include an optional interview for participants who complete 6 months treatment within EXPERTS, and then subsequently the arm they were allocated to is dropped for futility.

We will interview EXPERTS-ALS site staff once. This may be approximately 2-3 months after the site has opened to recruitment or following an IMP being dropped for futility. The exact date will be determined based on recruitment and screening activity and IMP futility outcomes on the study.

Data collection

Review of demographic data

Demographic data such as ethnicity and socioeconomic status will be collected from trial participants, and if possible, for participants who declined to take part in EXPERTS. Where possible, reasons for not taking part in the trial will be captured. Ethnicity for staff members on the study delegation log will also be captured.

Interviews

Interested participants will be contacted to arrange a suitable time and method of interview. It is anticipated that most interviews will be conducted remotely by telephone or on the online media platforms Google Meet, Microsoft Teams or ZOOM. Interviews may also be conducted over email if this is preferred by the participant, and the secure sth.expertsqual@nhs.net nhs.net email address will be used by the study team to conduct email interviews.

Qualitative interviews will be audio recorded before being transcribed. The audio recorder will be encrypted and stored securely when not in use. Recordings will be removed from the device as soon as possible and stored in an access restricted folder on the University of Sheffield network drive. Recordings will be transcribed by support staff at the University of Sheffield who have completed research data protection training and signed a confidentiality agreement. Identifiable information such as name and date of birth will not be included in the transcripts. The interview transcripts are classed as source data and will be retained as part of the project archive. Analysis will be carried out on the transcript, as detailed in the 'Data analysis' section below. Once analysis has been completed, the consent and interview audio recordings will be destroyed.

Before each interview, the interviewer will familiarise themselves with the participant's experience on EXPERTS so far including whether they have experienced an intervention outcome; this will be used to guide the interview.

A topic guide will be used to ensure key areas are covered, however with a view to keeping the interview process open and flexible to allow participants to raise issues that are personally relevant. The topic guide may be refined in response to early data collection and analysis. If these changes are substantial these will be submitted to REC for approval, minor modifications will not be submitted.

PwALS will have the opportunity to be interviewed as a dyad, with their family member/friend/caregiver, or individually. The researchers will ask each participant about their preferences for interview and work to support these (i.e. presence of another person, time of day).

Data analysis

Descriptive statistics will be used to analyse demographic data being collected within the trial, and reasons for not taking part in the trial. We will review these data to determine if some groups are underrepresented within the trial.

Interview data will be analysed using framework analysis, a form of thematic analysis that integrates both inductive and deductive approaches. Analysis will be conducted concurrently with data collection, to monitor data quality and inform subsequent data collection. Members of the PPI group will be invited to participate in the data analysis process through coding of anonymised transcript excerpts and discussing these with the research team in group sessions.

Data management

Personal data

Personal data for EXPERTS-ALS participants will be stored and accessed in accordance with the main trial protocol (via the Clinical data management system, Prospect).

Personal data for pwALS who decline EXPERTS-ALS and family/friends/caregivers will be stored in an access restricted folder on the University of Sheffield network drive.
Interview transcripts and consent forms for all participants will be destroyed 10 years after completion of the qualitative sub-study.

Data controller

Sheffield Teaching Hospitals NHS Foundation Trust and The University of Sheffield are joint data controllers.

Sub-study management and funding

All interviews will be conducted by University of Sheffield staff, overseen by Sheffield CTRU Assistant Director, Diana Papaioannou. Alys Griffiths (Senior Research Fellow, University of Sheffield) will provide expert advice during the project and has over 10 years of experience in qualitative research, with specific expertise in conducting qualitative research with people with communication and cognition difficulties.

The qualitative sub-study is funded by Sheffield BRC, project reference NEU Y2.Q1.1.
Interviewer staff costs are funded by the EME Programme (NIHR158515).

PwALS who participate in the qualitative sub-study will receive a £20 voucher per interview to thank them for their time. If a family member/friend/caregiver takes part in an interview, they will also receive a £20 voucher, regardless of whether they take part to offer support only or actively participate by sharing their own experiences and views. We anticipate that most

interviews will be conducted remotely but participants will be reimbursed for travel costs where necessary.

13. Trial supervision

13.1 Programme Steering Committee (PSC)

The PSC will consist of an independent Chair, two independent clinicians and a PPI representative. The role of the PSC is to oversee the entire EXPERTS-ALS programme, including the process for IMP identification, drug prioritisation platform, biomarker development studies. The PSC is a high-level oversight committee giving an independent view of the progress of the whole programme commenting on quality, progress against milestones, deliverability and value for money. The PSC will not be responsible for providing day to day advice, reviewing futility criteria or providing approvals for protocol amendments. The PSC will report to the funder. The PSC will meet at regular intervals, as defined in the PSC terms of reference.

13.2 Data Monitoring and Ethics Committee (DMEC)

The DMEC will consist of an independent Chair, an independent clinician and an independent statistician. The DMEC will review reports provided by the CTRU to assess the progress of the study, the safety data and the critical endpoint data as required. The DMEC will regularly review the accumulating data, including the results of the planned interim analyses and safety data. Based on these data, the DMEC will make recommendations to the Trial Management Group (TMG) including recommendations to amend or stop one or more of the study arms if applicable. A DMEC charter will document time points and details of all interim analyses including stopping rules for futility and safety data to be reviewed. The DMEC will be able to recommend changes to the study including study closure to the TMG / funder on safety or feasibility grounds.

13.3 Trial Management Group (TMG)

The TMG consists of the CI and co-CI, collaborators and staff from CTRU. The CI or Co-CI will chair regular (approximately monthly) meetings to discuss the day-to-day running of the study, including any implementation issues, as well as monitoring recruitment and retention. Further details are provided in the TMG terms of reference.

14. Data handling and record keeping

Participant confidentiality will be respected at all times and the principles of the General Data Protection Regulation (GDPR) will be followed.

Data management will be provided by the University of Sheffield Clinical Trials Research Unit (CTRU) who adhere to their own Standard Operating Procedures (SOPs) relating to all aspects of data management, including data protection and archiving. A separate data management plan (DMP) will detail data management activities for the study in accordance with SOP (Shef/CTRU/DM009).

The investigator or delegate at each site will maintain comprehensive and accurate source documents to record all relevant study information regarding each participant. A source data agreement will be completed by each site prior to activation to clarify the location of the source data for each form. The CTRU will provide worksheets (shadow CRFs) to allow the

site staff to check what is required for a visit to ensure all data required for the eCRF can be collected appropriately.

If a participant consents to being sent information about the study, such as being informed of the results of the study, their name and email address and/or postal address will be collected and stored locally by the study team. NHS numbers (of participants at English and Welsh sites) and Community Health Index (CHI) numbers (of participants at Scottish sites) will be collected and shared with The University of Sheffield to allow data linkage with data from other studies in the future. Directly identifiable data will be collected in a separate eCRF so that access can be restricted. All other eCRFs will only identify the participant by their study ID number. All participants will be assigned a unique study ID number at screening that will link all of the clinical information collected for them on the study database. It will also be used in all correspondence between CTRU and participating centres.

Laboratory specimens to be preserved or stored will be labelled without the use of patient identifiable information. Labels will contain study ID, type of sample, and the date the sample was taken, and will be cryo-labels to withstand freezing of the sample.

14.1 Archiving

Study records, including source data, will be stored for 25 years after the completion of the study by participating sites, before being destroyed. Each investigator is responsible for ensuring records are retained and securely archived during the retention period and information supplied to the Chief Investigator and Sponsor. Where trial related information is documented in the medical records, those records will be retained for at least 25 years after completion of the study. Access will be restricted to authorised individuals.

Data held by the CTRU will be stored in accordance with the archiving Standard Operating Procedure (CTRU SOP PM012) for 25 years following completion. Archived documents will be logged on a register which will also record items retrieved, by named individuals, from the archive. Electronic data will be stored in an 'archive' area of the secure UoS server for a minimum of 25 years to ensure that access is future-proofed against changes in technology. Electronic data may also be stored (e.g. on a compact disc or USB flash drive) with the paper files.

15 Data access and quality assurance

The study will use the CTRU's in-house data management system (Prospect) for the capture and storage of study specific participant data. Access to Prospect is controlled by usernames and encrypted passwords, and a comprehensive access management feature will be used to ensure that users have access to only the minimum amount of data required to complete tasks relevant to their study role. This feature can also be used to restrict access to personal identifiable data.

The study team at each site will enter data into the study specific Prospect database. Data checks are applied at the point of entry and after data have been entered; post entry data checks are applied to the database on a regular basis; discrepancies are tracked and resolved through the Prospect database. All entries and corrections are logged with the person, date and time captured within the electronic audit trail.

Participant confidentiality will be respected at all times. All research data will only be identifiable by the participant's study ID number. No direct identifiers will be transferred from the database to the statistician.

Participating investigators shall agree to allow study-related monitoring, including audits, ethics committee review and regulatory inspections by providing direct access to source data and documents as required. Participants' consent for this will be obtained as part of the consent process.

15.1 Site assessment

Throughout this protocol, the trial 'site' refers to the hospital at which trial-related activities are conducted. Participating sites must be able to comply with:

- Trial treatments, clinical care, follow up schedules and all requirements of the trial protocol
- Requirements of the UK Policy Framework for Health and Social Care Research and the Medicines for Human Use (clinical trials) Act (SI 2004/1031 and all amendments)
- Data collection requirements

All site staff, including research staff, must be appropriately qualified by education, training and experience to perform the trial related duties allocated to them, which must be recorded on the site delegation log. CVs for all staff must be kept up to date, and copies held in the Investigator Site File (ISF). Staff should also have completed GCP training within the last three years, ensure this is renewed every three years, and copies of the GCP certificate are held within the ISF.

Before each site is activated, capability to conduct the trial will be assessed and documented using a site assessment form. The CTRU will arrange a site initiation with each site, which may be carried out face-to-face or remotely. Site staff will be trained in the day-to-day management of the trial and essential documentation required for the trial will be checked. Once all the required documentation is in order and site staff have been trained, CTRU will formally activate the site to start recruitment. Sites should not open to recruitment until CTRU have provided this confirmation of activation.

15.2 Risk Assessment

A risk assessment has been performed by the CTRU, in accordance with Sheffield CTRU Standard Operating Procedures. The study has been categorised as Type B = somewhat higher than the risk of standard medical care. The level of risk has been agreed with the Sponsor.

Central and/or on-site monitoring (including Pharmacy) will be undertaken at a level appropriate to the detailed risk assessment, and will be documented in the Site Monitoring Plan (SMP). The risk assessment will be reassessed for each new trial arm and the monitoring processes will be amended as necessary.

15.3 Reporting serious breaches and non-compliances

A "serious breach" is a breach of either: the conditions and principles of GCP in connection with the trial or; the protocol relating to the trial; which is likely to effect to a significant degree:

- the safety or physical or mental integrity of the participants of the trial; or
- the scientific value of the trial

All serious breaches and protocol non-compliances should be reported to CTRU within 24 hours of site staff becoming aware.

The sponsor will be notified immediately of any case where the above definition may apply during the trial conduct phase. The sponsor has delegated CTRU responsibility for notifying the REC and MHRA in writing within 7 days of becoming aware of a serious breach.

Additional information is provided in a study-specific SOP.

15.4 On-site and remote monitoring

On-site or remote monitoring will be performed according to the monitoring plan and in line with the Sheffield CTRU Site Monitoring SOP (*SOP QA001 Site Monitoring).*

Regular site monitoring visits will occur throughout the study as specified in the Site Monitoring Plan and additional visits will be undertaken where required. At these visits, the Monitor will review activity to verify that the:

1. Data are authentic, accurate and complete.
2. Safety and rights of the patient are being protected and
3. Study is conducted in accordance with the approved protocol and study agreements, GCP and all applicable regulatory requirements.

Accurate and reliable data collection will be assured by verification and cross-check of the eCRF against Investigator's records by the Study Monitor (source document verification) (see section 14 for further details on data collection). The Study Monitor will contact and visit sites regularly to inspect Investigator's records throughout the study, to verify adherence to the protocol and completeness, consistency and accuracy of the data being entered on the eCRFs. Monitoring visits will also include a pharmacy visit to review processes, documentation and accountability of study drug.

A close-out visit will be performed, either on site or remotely after the last patient last visit at each site. Further close-out activities may be carried out remotely after this time, up to database freeze.

15.5 Central monitoring

CTRU staff will review entered data for possible errors and missing data points. A central review of consent forms will also be completed, and sites will be requested to share consent forms with CTRU via a study-specific NHS.net account on an ongoing basis. This will be made clear to the participant prior to their consent to the trial. CTRU will review pharmacy dispensing logs centrally to allow drug accountability checks to be completed. Details will be included in the Pharmacy manual.

15.6 Lab audits

On-site and remote audits of the Oxford lab will be completed by CTRU and the Sponsor. Further details will be provided in the study-specific monitoring plan.

15.7 Regulatory information

As a CTIMP, the trial will be conducted in accordance with ICH GCP and the Clinical Trials and Medicine for Human Use (Clinical Trials) Regulations 2004. A site agreement between the Sponsor and the participating sites outlines responsibilities of all parties and is to be signed prior to commencement of recruitment at sites. All clinicians responsible for recruiting patients to the trial will be required to complete training in International Conference on

Harmonisation of Technical Requirements for Registration of Pharmaceutical/s for Human Use (ICH) Good Clinical Practice (GCP).

16. Publication

A major concern expressed by our PPI co-applicants was how trial progress has been historically communicated poorly to participants. EXPERTS-ALS will prioritise the relationship with study participants. Our PPI co-applicants and Programme Manager will lead our communication strategy, coordinating with the UK ALS Charities. We will utilise accessible formats including podcasts, talking heads and a dedicated website, linked with the UK MNDRI and updated monthly with study progress. We will announce our results as they become known, first to our participants, followed by the wider ALS community. Dissemination to a scientific audience will be via national and international ALS and other neurology scientific meetings and via peer-reviewed manuscript publication as well as submission of a final report to the funder, which will be made available online.

The results will be published on a freely accessible database within one year of completion of the trial.

Full details, including guidance on authorship, are documented in the Publication and Dissemination Plan.

17. Finance

This project (NIHR158515) is jointly funded by the Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership, and Biomedical Research Centre Capacity Funding. Additional funds have been secured from MND associations and My Name'5 Doddie Foundation.

Full details of the funding are included in a separate agreement. Payments for research activity at participating centres including participant travel costs will be detailed in the site agreements.

18. Ethics approval

Before initiation of the study at participating sites, the protocol, informed consent forms and information materials to be given to the participants will be submitted to an NHS Research Ethics Committee for approval. Any amendments will also be submitted for approval.

The study will be submitted to local participating Trusts to confirm Capacity and Capability before any research activity takes place.

In addition, the study will be submitted for HRA review and approval. Recruitment of study participants will not commence until the letter of approval has been received from the HRA.

19. Regulatory Compliance

To demonstrate that the trial will comply with regulations, the trial will also not commence until a Clinical Trial Authorisation (CTA) is obtained from the MHRA and Favourable REC opinion. The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

20. Sponsor and site approval

Before initiation of the study at participating sites, the protocol, informed consent forms, and information materials to be given to the participants will require sponsor approval.

A site agreement between the Sponsor and participating sites outlines responsibilities of all parties and is to be signed prior to commencement of recruitment at sites.

Recruitment of study participants will not commence at a site until a letter of local R&D Confirmation of Capacity and Capability (CCC) has been issued and until CTRU has issued green light authorisation for the site to begin recruitment.

21. Trial Organisation and Responsibilities

21.1 Principal Investigators

Each site will have a local Principal Investigator (PI) who will be delegated responsibility for the conduct of research at their centre and must sign a declaration to acknowledge these responsibilities. The local PI should ensure that all relevant staff involved are well informed about the trial and trained in study procedures, including obtaining informed consent and conduct of the trial according to GCP. The local PI will liaise with the Trial Manager on logistic and administrative matters connected with the trial.

21.2 Sheffield Clinical Trials Research Unit (CTRU)

The Sheffield CTRU at Sheffield University will provide set-up and monitoring of the trial conduct to CTRU SOPs and the GCP conditions and principles as detailed in the UK Policy Framework for Health and Social Care Research 2017. CTRU responsibilities include randomisation design and service, database development and provision, protocol development, CRF design, trial design, source data verification and monitoring schedule for the trial. In addition, the CTRU will support the main REC, HRA and site-specific submissions, clinical set-up, on-going management including training, monitoring reports and promotion of the trial.

The CTRU trial manager will be responsible for supplying investigator site files to each collaborating centre after relevant ethics committee approval and local R&D Confirmation of Capacity and Capability approval has been obtained. The CTRU will be responsible for the day-to-day running of the trial including trial administration, database administrative functions, data management, safety reporting and all statistical analyses. The CTRU will develop the site monitoring plan and data management plan and will assist the CI to resolve any local problems that may be encountered during the trial including any issues of noncompliance.

21.3 University of Oxford

Statisticians at the University of Oxford will be responsible for completing the statistical analysis for the trial. The EXPERTS-ALS Oxford Laboratory, at University of Oxford will be responsible for the NFL sample analysis providing the primary endpoint data, using the SIMOA HDX instrument (Quanterix) which has been used in many international studies for this purpose (4-10). The Oxford laboratory team are working with the QA Manager to complete a pre-trial validation of the SIMOA NFL assay method. This validation process will confirm that this assay will meet the required sensitivity and accuracy for the analysis of trial samples. The lab will also coordinate the preparation of the sample collection kits to be provided to participating sites.

The Oxford Laboratory team will work with a Quality Assurance (QA) manager consultant to ensure the NFL sample receipt, storage, analysis and results reporting is conducted in compliance with Good Clinical Laboratory Practice (GCLP) and applicable regulatory requirements. The Oxford project manager will oversee all operational aspects of the study at the Oxford site including adherence to regulatory requirements, chairing regular meetings with the laboratory team including the QA manager consultant as applicable. The Sponsor/CTRU will audit the Oxford laboratory prior to issuing Green Light for the EXPERTS-ALS trial to commence.

22. Patient & Public Involvement & Engagement (PPIE)

Two PPI representatives were co-applicants on the grant and are members of the TMG. There is also an independent PPI representative on the PSC. Additional PPI support will come from the Sheffield Motor Neuron Disorders Research Advisory Group (SMNDRAG). Set up in 2008 the SMNDRAG is a well-established group with a diverse range of patients and carers who meet regularly to give PPIE input into the MND research programmes at the University of Sheffield and further afield.

PPI members of the TMG will provide PPIE input to the governance of the trial, commenting on design amendments when they impact trial participants and helping develop trial patient facing materials.Our PPI co-applicants and Programme Manager will lead our communication strategy, coordinating with the UK ALS Charities. A key role will be to support our planned innovative communication approach for informing participants about study progress and results. We will utilise accessible formats including podcasts, talking heads and a dedicated web site, linked with the UK MNDRI and updated monthly with study progress. We will update participants every month with study progress. We will announce our results as we know them first to our participants, then to the wider MND community, and then through traditional dissemination routes.

23. Indemnity / Compensation / Insurance

The University of Sheffield has in place clinical trials insurance against liabilities for which it may be legally liable, and this cover includes any such liabilities arising out of this clinical study.

The University of Oxford has all relevant insurances in place to cover research activities being undertaken within its premises.

Standard NHS indemnity operates in respect of the clinical treatment which is provided and the trial Sponsor.

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Appendices

Appendix 1: IMP selection criteria

ESSENTIAL CRITERIA (substantial evidence must be available for all three categories)

1. **Biological rationale:** the drug targets a clear disease relevant pathway, with substantial evidence from the ALS scientific literature (or from other neurodegenerative diseases) for the targeted pathway to operate in the pathophysiology of ALS, or neurodegenerative disease pathways more widely.
1. **CNS penetration:** Given the widely distributed nature of pathology in ALS, and the related condition TDP43-FTD (fronto-temporal dementia) in the CNS, it is essential that there is pre-clinical pharmacodynamic evidence of blood brain barrier (BBB) penetration. This can vary widely even within a class of drugs, and therefore requires direct evidence for each drug.
2. **Risk analysis:** a clear toxicity profile, with data from clinical trials or post-marketing surveillance in the target ALS age group (50-75) should be available for the drug. This is essential, since the single arm, open-label nature of the study design does not allow a primary characterisation of adverse effects in comparison to placebo.

DESIRABLE CRITERIA (significant evidence to support a drug is likely to be available in many or most cases, but may be incomplete)

1. **Target engagement:** while recognising that repurposed drugs in particular may have non-canonical targets, drugs will be prioritised when: i) the putative target is known; ii) there is evidence in pre-clinical models for target engagement; iii) this can be measured in the human experimental study in WS2.
2. **Phenotypic improvement** across multiple models (multiple types of cellular model, different model organisms) will allow selection of drugs, limiting the risk that phenotypic effects are an isolated feature of a single pre-clinical model.
3. **Applicability to all types of ALS regardless of genotype:** a demonstrable effect across multiple genotypes and in putative models of sporadic ALS will ensure that the pathway is more likely to be a general feature of ALS pathophysiology, and applicable to ‘sporadic’ ALS which represents 90-95% of ALS cases.

SUPPORTIVE CRITERIA (evidence will not be available in all cases, but if present can be used to support prioritisation)

1. **Therapeutic tractability:** there is evidence that the target pathway is in a stage of pathophysiology which is likely to maintain function, e.g. avoiding late phase disease phenomena defined by cell death pathways, which are less likely to be therapeutically tractable.
2. **Collateral evidence:** from *in silico* techniques including genomics, population prescribing registries, effects in related neurodegenerative diseases (*e.g.* PD, AD etc).

Appendix 2: Metformin

SmPC

Metformin hydrochloride 500mg prolonged-release tablets, Strides Pharma UK Ltd (formulation-specific SmPCs are available as needed)

Justification of IMP selection

Pre-clinical data

Metformin is associated in multiple pre-clinical ALS model systems with prolonged lifespan, which is supported by a systematic review concluding that metformin may extend both healthspan and lifespan independent of its actions as an anti-diabetic drug and is therefore a credible geroprotective agent (1). Metformin has been shown to have a specific effect on *C9orf72* mediated RAN translation, reducing dipeptide repeat protein levels and improving the phenotype of a C9-mouse model (2).

Metformin crosses the blood-brain barrier, although the levels in the cerebrospinal fluid that have been reported are only about one-tenth of basal plasma levels at about 100 ng/ml (3). Metformin has a wide range of putative mechanisms of action, including effects on promoting mitochondrial bioenergetics, anti-inflammatory and inhibition of cellular senescence pathways (eg; mTOR signalling; NK-kB mediated proinflammatory cytokine expression). It reduces ROS and β-amyloid production in models of Alzheimer's disease. How it might act in ALS is currently uncertain, but there are a range of markers that can be assessed.

Phase I, II and III data

To our knowledge, there are no clinical trial data for metformin in patients with ALS.

Other available data

Epidemiological evidence suggests that taking metformin is associated with a significant reduction in the incidence of ALS (OR: 0.83) (4).

Adverse events

Metformin, as the drug of first choice for Type 2 diabetes, is one of the commonest prescribed medicines in the world. It has proved to be safe for long-term use, with a low risk of lactic acidosis in patients without liver disease or severely reduced kidney function. The most common side effects are dose-related gastrointestinal (nausea, vomiting, bloating and diarrhoea) and with minimal problems with patient compliance estimated at only 5% (5). It promotes weight loss, a median of 2.5kg in the UK Prevention Programs Diabetes Study (5). This suggests that enhanced nutritional monitoring should be performed in ALS patients taking metformin.

Dosing in ALS (including titration requirements)

Prolonged-release tablets

Where possible, prolonged release tablets should be used. Starting dose is 500mg once daily, taken with the evening meal. After 14 days the dose should be increased to 1000mg once daily.

Immediate-release tablets

If a participant is unable to use prolonged-release tablets, for example due to swallowing difficulties or PEG insertion, immediate-release tablets may be used (6). Tablets are commonly

crushed and mixed with water in practice, although an oral solution which is licensed for administration via enteral feeding tubes may be used if available. Starting dose is 500mg once daily for at least one week, dose to be taken with breakfast. Then increase to 500mg twice daily, dose to be taken with breakfast and evening meal.

Dose modifications and interruptions in ALS

If a participant experiences undesirable effects that they cannot tolerate, the dose can be reduced to 500mg at the discretion of the investigator.

Participants may be switched from prolonged-release to immediate-release tablets if required at the discretion of the local investigator.

Dose modifications can be done between scheduled visits if required. Further details are provided in the Research Manual and Pharmacy Manual.

Drug withdrawal

No specific requirements.

Monitoring requirements for ALS

Participants over the age of 65 years and/or with impaired renal function (<60mL/min) at screening must have an assessment of renal function at the Week 12 visit.

No other specific requirements beyond those specified in Section 9.

Exclusion criteria

Pre-existing diabetes is an exclusion for the metformin arm in this study.

Other exclusions are as per the SmPC:

- Hypersensitivity to metformin hydrochloride or to any of the excipients
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)
- Diabetic pre-coma
- Severe renal failure (eGFR <30 mL/min)
- Acute conditions with the potential to alter renal function, such as dehydration, severe infection, shock
- Disease which may cause tissue hypoxia (especially acute disease, or worsening chronic disease) such as decompensated heart failure, respiratory failure, recent myocardial infarction, shock
- Hepatic insufficiency, acute alcohol intoxication, alcoholism

AE reporting requirements

No specific requirements beyond those specified in Section 10.

Contraceptive requirements

Participants of childbearing potential must use a highly effective method of contraception while taking IMP and it is recommended to continue contraception for 30 days after the last dose of IMP. See Section 5.8 for details.

There are no specific contraceptive requirements for fertile participants with partners of childbearing potential.

Appendix 3: Nifedipine

SmPC

Coracten XL 30 mg capsules TEOPHARMA S.R.L (formulation-specific SmPCs are available as needed)

Justification of IMP selection

Pre-clinical data
Nifedipine is a dihydropyridine calcium-channel blocker (CCB). There is recent evidence for CCBs to increase autophagy in the brain, via an mTOR-independent pathway (7). Since there are multiple potential pathways through which nifedipine might act in ALS, therapeutic tractability remains unclear, but enhancing autophagy is a potential mechanism at all stages of ALS.

Phase I, II and III data
To our knowledge, there are no clinical trial data for nifedipine in patients with ALS.

Other available data
A recent Mendelian randomisation study suggested that reducing blood pressure, with an independent enhanced effect of calcium channel blockers, was associated with reduced ALS risk (8). The King's drug prediction tool independently identified this class of drugs as potentially having therapeutic benefits for ALS (9). A drug screen for neuroprotection using a library of FDA approved compounds in an ES-motor neuron TDP-43 model in Oxford, identified multiple CCBs as neuroprotective.

Adverse events
Nifedipine has well understood side effects, and a good safety profile with the most common side effects being constipation, malaise, oedema and vasodilation. It has clear stopping criteria for people with persistent symptomatic postural hypotension associated with a systolic blood pressure drop of 20mmHg or more on change in posture. Many other drugs, including antihypertensives, work synergistically with nifedipine and therefore increase the risk of hypotension.

Dosing in ALS (including titration requirements)

Coracten is the preferred brand of nifedipine as this is suitable for use with enteral feeding tubes. Participants with enteral feeding tubes must be prescribed the Coracten brand. Coracten is available as 30mg XL capsules (once daily dosing) or 10mg SR capsules (twice daily dosing). The modified-release capsules can be opened and the contents flushed down enteral feeding tubes for administration. The capsule contents should not be crushed as this will destroy their modified-release properties. Enteral tubes should be flushed well after administration.

LA/XL versions of nifedipine formulated for once daily dosing will be used where possible. Starting and target dose is 30mg LA/XL once daily. As a precaution against potential hypotension, it is recommended that the dose is taken at bedtime.

In the case of supply issues where 30mg tablets are unavailable, a twice daily dose can be provided using 10mg SR tablets as follows: one 10mg SR tablet in the morning and two 10mg SR tablets in the evening.

Dose modifications and interruptions in ALS

If a participant experiences persistent symptomatic postural hypotension, or an undesirable effect that they cannot tolerate, the dose may be reduced to 10mg SR twice daily at the discretion of the local investigator.

Dose modifications can be done between scheduled visits if required. Further details are provided in the Research Manual and Pharmacy Manual.

Drug withdrawal

No specific requirements. Sudden withdrawal may be associated with the exacerbation of pre-existing myocardial ischaemia. The local investigator may choose to taper the dose in these participants at their discretion.

Monitoring requirements for ALS

No specific requirements beyond those specified in Section 9.

Exclusion criteria

There is no data regarding nifedipine administration in swallowing difficulties. Patients who are unable to swallow and cannot have medications via gastrostomy or equivalent will not be eligible for the nifedipine arm of this study.

Other exclusion criteria are as per the SmPC:

- Known hypersensitivity to nifedipine, other dihydropyridines because of the theoretical risk of cross reactivity or to any of the excipients
- Nursing individuals or those who are or may become pregnant
- Patients with clinically significant aortic stenosis, cardiogenic shock, unstable angina, or during or within one month of a myocardial infarction
- Inflammatory bowel disease, Crohn's disease or with a history of gastrointestinal obstruction, oesophageal obstruction or with decreased diameter of the gastrointestinal lumen
- Hepatic impairment
- Malignant hypertension
- Patients with a Kock pouch (ileostomy after proctocolectomy)
- Concomitant treatment with rifampicin
- Acute porphyria

AE reporting requirements

No specific requirements beyond those specified in Section 10.

Contraceptive requirements

Participants of childbearing potential must use a highly effective method of contraception while taking IMP and it is recommended to continue contraception for 30 days after the last dose of IMP. See Section 5.8 for details.

There are no specific contraceptive requirements for fertile participants with partners of childbearing potential.

Appendix 4: Ropinirole

SmPC

Ropinirole KRKA 2mg prolonged-release tablets, KrKa UK Ltd (formulation-specific SmPCs are available as needed)

Justification of IMP selection

Pre-clinical data

Dopamine agonists (DA), as a drug class, have been associated with neuroprotection in multiple pre-clinical models of ALS (bromocriptine in SOD mice; ropinirole in human iPSC MN models (10)), and in other neurodegenerative diseases. Ropinirole is an agonist of the post-synaptic dopamine D2 receptor and is routinely used as a dopamine agonist treatment in patients with Parkinson's disease.

In in vitro model systems ropinirole has been shown to alleviate mitochondrial dysfunction (11,12), to support antioxidant responses (13,14) and exert neurotrophic effects (15). Okano et al, using human ALS iPSC derived model systems showed that ropinirole suppressed oxidative stress, inhibited TDP-43 and FUS aggregation, improved mitochondrial function and reduced neurite retraction and cell death (16). One study showed that ropinirole may affect mitochondrial function by blockade of the mitochondrial permeability transition pore triggered by Ca++ (12). Another study provided evidence that ropinirole increases the synthesis of glutathione (GSH) a major anti-oxidant system in the CNS (14). A drug screen for neuroprotection using a library of FDA approved compounds in an ES-motor neuron TDP-43 model at Oxford University, identified multiple DA agonists, including bromocriptine and pramipexole.

Whether DA agonists exert their potential effect through the DA receptor or through a non-canonical target is unclear, but evidence from an iPSC-based drug screen suggests that it exerts a protective effect by preventing mitochondrial damage, but also that it might have specific effects on reducing aggregation of misfolded TDP-43 (10).

Across multiple pre-clinical models; the related dopamine receptor agonist bromocriptine has shown efficacy in SOD1 mouse models, ropinirole in iPSC models and other DA agonists in ES-MN models. Although the evidence is incomplete, if the main effect is on mitochondrial protection, this is likely to be downstream of pathways at disease initiation.

Dopamine has been shown to promote regeneration of adult motor neurons (17).

Phase I, II and II data

To our knowledge, only one clinical trial has been completed with ropinirole in patients with ALS to date – an exploratory study in Japan. The primary outcome was safety (n=13 treated) and the trial demonstrated that ropinirole can be used safely in patients with ALS (18). Further details are provided in Section 4.4.

Other available data

Ropinirole has excellent blood-brain barrier penetration and is routinely used in Parkinson's disease. The usual clinical dose of 2-16mg/day will achieve concentrations of approximately 2-16ng/ml in the brain.

Adverse events
Ropinirole is in routine clinical use for Parkinson's disease and restless legs syndrome and the side effect profile is well established in these indications. In an exploratory study in ALS, no participants discontinued treatment due to adverse events (AEs) and the incidence of AEs was similar across both groups. The most common ropinirole-related AEs were constipation, nausea, somnolence and headache (18).

Dosing in ALS (including titration requirements)

Prolonged-release tablets

Where possible, prolonged-release tablets should be used. Ropinirole HCl extended release in a starting dose of 2mg once per day and building up by 2mg per day at weekly intervals to a dose of 16mg per day. This dosing regime is routinely used and is generally well tolerated in patients with Parkinson's disease.

Participants will be provided with instructions regarding dose titration and advised to contact the study team if they have any questions.

Immediate-release tablets

If a participant is unable to use prolonged-release tablets, for example due to swallowing difficulties or PEG insertion, immediate-release tablets may be used (6). The tablets can be crushed and mixed with soft food for patients with swallowing difficulties. The tablets can be crushed and mixed with water for administration via enteral feeding tubes. The conversion chart below will be used to calculate the dose:

Ropinirole prolonged release	**Ropinirole immediate release**
2mg od	0.75mg TDS (using 0.5mg tablets-can be divided into equal halves)
4mg od	1mg tds
6mg od	2mg tds
8mg od	3mg tds
10mg od	3.5mg tds
12mg od	4mg tds
14mg od	4.5mg tds
16mg od	6mg tds

Dose modifications and interruptions in ALS

If a participant experiences undesirable effects that they cannot tolerate, the dose can be reduced to a previously tolerated dose at the discretion of the local investigator.

If treatment is interrupted for one day or more, re-initiation by dose titration should be considered as above at the discretion of the local investigator.

Dose modifications can be done between scheduled visits if required. Further details are provided in the Research Manual and Pharmacy Manual.

Drug withdrawal

As a precautionary step, due to the risk of dopamine agonist withdrawal syndrome (DAWS), treatment should be discontinued slowly by reducing the daily dose gradually. The recommended schedule is to reduce the dose gradually over the course of one week. An additional dispensing may be required at week 24 to cover the withdrawal period. Further details are included in the Pharmacy Manual and Research Manual.

Monitoring requirements for ALS

No specific requirements beyond those specified in Section 9.

Exclusion criteria

Presence or history of any psychotic disorder is an exclusion for the ropinirole arm in this study.

Other exclusion criteria are as per SmPC:

- Hypersensitivity to the active substance or to any of the excipients
- Severe renal impairment (creatinine clearance* <30ml/min) without regular haemodialysis
- Hepatic impairment

* eGFR will be used to assess renal function in EXPERTS-ALS

AE reporting requirements

No specific requirements beyond those specified in Section 10.

Contraceptive requirements

Participants of childbearing potential must use a highly effective method of contraception while taking IMP and it is recommended to continue contraception for 30 days after the last dose of IMP. See Section 5.8 for details.

There are no specific contraceptive requirements for fertile participants with partners of childbearing potential.

Appendix 5: Salbutamol (also known as albuterol)

SmPC

Ventolin Syrup, Salbutamol Sulphate, GlaxoSmithKlineUK

Justification of IMP selection

The rationale for use of β2 receptor agonists in ALS is largely based on positive effects of this drug class in other muscle-wasting, neuromuscular, and neurodegenerative diseases. Stimulation of β2-adrenoceptors activates many signalling pathways in different tissues and cell types that can maintain or enhance cell viability under conditions of physical stress, many of which may be relevant to ALS (see figure in appendix). In vivo, β2 agonists have been shown to have an anabolic effect on muscle fibres and increase muscle strength and mass, improve neuromuscular transmission, reverse muscle wasting, and delay the onset of motor deficits in a range of animal models of muscle degeneration. Animal studies have also indicated they may exert neuroprotective effects and promote neural repair following different insults, although the precise mechanism is not clear.

The clinical efficacy of β2-agonists has been tested in a variety of neuromuscular diseases of different types (e.g., those with a primary neurologic pathology, as in ALS, those characterised by degeneration and dysfunction of the NMJ, and those with a primary myopathology), with a range of effects reported, including improved muscle strength and mass (19). Some positive clinical results of β2-agonists on motor function and immunologic responses have been reported in multiple sclerosis (20,21) and a press release from a Phase II trial in Parkinson's disease and mild cognitive impairment claimed rapid improvements in cognition and mood (22).

BBB penetrance: Studies on rats found salbutamol reached brain concentrations amounting to ~5% of plasma concentrations. In structures outside the BBB (pineal and pituitary glands found in concentrations >100x those in whole brain (23).

Preclinical

Very few preclinical studies have investigated the effects of β2-agonists in ALS models. Those identified are shown below. Overall, evidence for a beneficial effect is limited and appears to vary with the model used, assay and outcome measure.

- Linares et al. (2023) (24) performed a phenotypic screen of a small molecule library of approved drugs for the ability to increase ALS/FTD induced motor neuron (iMN) survival. iMNs carrying C9orf72 expansions were first used. Candidates found to improve survival were then tested on a wider panel of C9orf72 lines (3 independent lines) and a sporadic ALS (sALS) iMN panel (8 lines in total). This screen included several β2-agonists (see below). Only bambuterol was found to be effective in C9orf72 iMNs and sALS lines (note: other drugs not tested in sALS lines).

Drug	Effect on C9ORF72 iMNs	Effect on sALS iMNs
Albuterol	Improved survival, but not significantly.	N/A
Bambuterol	Significantly improved survival	Significantly improved survival of 6/8 iMN lines
Terbutaline	Did not affect survival	N/A
Clenbuterol	Did not affect survival	N/A
Fenoterol	Did not affect survival	N/A
Ritodrine	Did not affect survival	N/A

Clinical data

Salbutamol (Albuterol)

- Brooks et al. (2014) (25) performed a retrospective clinical audit of systemic albuterol use in non-invasive ventilation-supported ALS patients and found it was well-tolerated. ALSFRS-R respiratory-, but not bulbar-sub-score was significantly decreased in treated patients. Vital capacity remained unchanged at 3 months but declined at 6 months.
- Brooks et al. (2000) (26) evaluated effect on neck flexion (NF) strength in ALS patients (unclear RoA/dose). Treated patients showed delayed decline in NF due to sustained improvement in neck muscle strength.
- A Phase II monocentric, randomised, controlled, pilot study (not yet recruiting) is planned to evaluate effect of salbutamol on walking capacity in 36 ambulatory ALS patients (NCT05860244) (27). The study will also measure target engagement, as well as safety and tolerability. Exploratory objectives include fatigue scales, muscle strength, respiratory function, motor unit count, muscle/spinal MRI parameters and blood biomarkers of muscle damage (CPK, LDH and creatinine serum levels).

Adverse events

Adverse events are not anticipated to be different from a non ALS population. Precautions are therefore as per SmPC.

Owing to the hypokalaemic effect of beta-agonists, concurrent administration of serum potassium depleting agents known to exacerbate the risk of hypokalaemia, such as diuretics, digoxin, methyl xanthines and corticosteroids, should be administered cautiously after careful evaluation of the benefits and risks with special regard to the increased risk of cardiac arrhythmias arising as a result of hypokalaemia.

Dosing in ALS (including titration requirements)

Salbutamol 2mg tds then one week later increase to 4mg tds.

Dose modifications and interruptions in ALS

If experiencing tolerability issues, dose can be reduced to 2mg tds and further reduced to 1mg tds if required. If 1mg tds is not tolerated then withdraw salbutamol.

If dose is interrupted, re-introduction should involve retitration.

Drug withdrawal

Can be stopped immediately if urgent medical need otherwise to be tapered withdrawal over 3 days.

Monitoring requirements for ALS

Screening ECG to screen for significant underlying severe heart disease.

Exclusion criteria

- Underlying severe heart disease (e.g. ischaemic heart disease, arrhythmia or severe heart failure).
- Diabetes
- Thyrotoxicosis
- Use of non-selective beta blocking drugs (e.g. propranolol)

AE reporting requirements

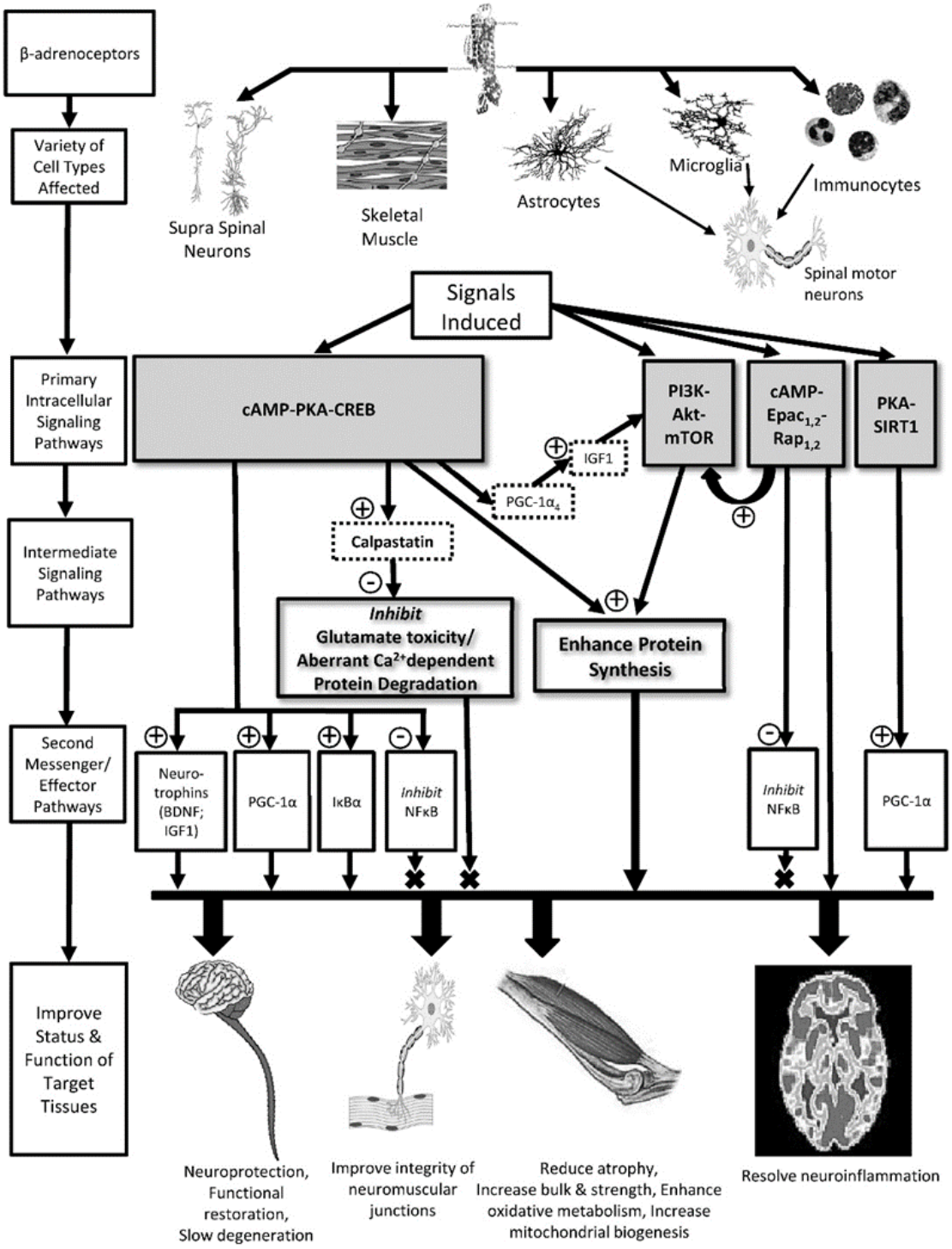
No specific reporting requirements

Contraceptive requirements

Participants of childbearing potential are required to use a highly effective method of contraception while taking IMP. It is recommended that this continues for 30 days after the last dose of IMP.

There are no specific contraceptive requirements for fertile participants with partners of childbearing potential.

Summary of signalling pathways of relevance to ALS that are modulated by β2-adrenoceptor agonists



(Taken from 19)

Appendix 6: Doxycycline

SmPC

Doxycycline 50mg capsules, Sovereign Medical (formulation-specific SmPCs are available as needed)

Justification of IMP selection

Multiple lines of evidence point to a complex deleterious pro-inflammatory mechanisms contributing to the neurodegeneration seen in ALS. A significant component is mediated through matrix metalloproteinase-9 (MMP9) which leads to MMP9-dependent microglial dysfunction (1-4).

MMP9 inhibition in human derived ALS iPSC cells ameliorated pro-inflammatory toxicity (1)

Doxycycline is a commonly used antibiotic. In addition to it's bactericidal properties Doxycycline has off target effects. Of note is the fact that doxycycline is a potent MMP9 inhibitor (32). Other potential beneficial off target effects of doxycycline include reactive oxygen species (ROS) scavenging, antiapoptotic effects, anti-inflammatory effects, protein anti aggregation activities, and protection against mitochondrial dysfunction (33).

Doxycycline has good CNS penetration (34).

Phase I, II and II data

No clinical trials of doxycycline have been conducted in ALS. A number of Phase 2 and 3 studies in other diseases have been conducted where the primary purpose has been to use doxycycline to reduce inflammation.

In studies in patients with multiple sclerosis 100mg od has been given for 4 months (n=16) and 6 months (n=60) (35, 36). In these studies doxycycline was well tolerated.

Higher doses of doxycycline (200mg per day) have an equally good side effect/safety profile over 30 weeks (215 patients with rheumatoid arthritis) and 3 months (43 patients with Alzheimer's disease) (37, 38).

In summary doxycycline is well tolerated at doses of 100-200mg per 24hrs taken up to 6 months in a range of disorders.

Other available data
Minocycline is another tetracycline which has previously been tested in clinical trials in ALS. In the phase 2 studies safety and tolerability was observed in doses up to 400mg/day (39).

In a phase 3 study of minocycline in escalating doses up to 400mg/day for 9 months, patients with ALS appeared to deteriorate faster. Evidence suggests that high levels minocycline may exhibit neurotoxicity (40). It is increasingly recognised that there is an important balance between the beneficial aspects of neuroinflammation and the negative aspects (41, 42). This has been demonstrated by the beneficial of Il-2 at a dose substantially lower than immunological therapy high dose used for renal cancer (43).

We therefore propose low dose doxycycline 50 mg od.

Adverse events

Adverse events are not anticipated to be different from a non ALS population. Precautions are therefore as per SmPC.

Dosing in ALS (including titration requirements)

Doxycycline 50mg capsule once per day.

If a participant has swallowing difficulties or a feeding tube, dispersible tablets may be used. The dose will be 50mg once per day. The dispersible tablets are available as 100mg but have a break line to allow 50mg to be used.

Dose modifications and interruptions in ALS

The requirement for dose modifications due to intolerance is unlikely. No dose reductions will be permitted.

If treatment is interrupted, the patient can be administered the 50mg dose with no titration required.

Drug withdrawal

No withdrawal requirements

Monitoring requirements for ALS

No additional monitoring requirements

Exclusion criteria

- Hypersensitivity to doxycycline or to any of the tetracyclines or to any of the excipients listed in the SmPC.

AE reporting requirements

No specific reporting requirements

Contraceptive requirements

Participants of childbearing potential are required to use a highly effective method of contraception while taking IMP. It is recommended that this continues for 30 days after the last dose of IMP.

There are no specific contraceptive requirements for fertile participants with partners of childbearing potential.

Appendix References

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