CLArithromycin for post-Stroke Pneumonia:

A prospective, randomised open-label blinded-endpoint (PROBE) phase 3 multicentre trial

CLASP

This protocol has regard for the HRA guidance.

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PROTOCOL VERSION

Version 1.0

Dated 12 December 2024

CO-SPONSORS

University of Glasgow

NHS Greater Glasgow and Clyde

SIGNATURE 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, the Sponsor's (and 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.

For and on behalf of the Trial Co-Sponsors:

Signature: Date:
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.....

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Position: Research Regulation & Compliance Manager

(University of Glasgow)

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Signature: Date:
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Position: Research Regulation & Compliance Manager

(NHS Greater Glasgow and Clyde)

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Chief Investigator:

Signature: Date:
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Name: (please print): Prof Craig J Smith

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Statistician:

Signature: Date:

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Name: (please print): Prof Alex McConnachie

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Position: Professor of Clinical Trial Biostatistics & Director of Biostatistics

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KEY TRIAL CONTACTS

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Funder	**National Institute for Health and Care Research (NIHR)**
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i. LIST of CONTENTS

ii. LIST OF ABBREVIATIONS

Define all unusual or 'technical' terms related to the trial. Add or delete as appropriate to your trial. Maintain alphabetical order for ease of reference.

A&E	Accident and Emergency
AE	Adverse Event
AR	Adverse Reaction
BIASP	British Irish Association of Stroke Physicians
BNF	British National Formulary
CAP	Community-acquired pneumonia
CHI	Community Health Index
CI	Chief Investigator
COFAC	Costs of Family Caregiving in Palliative Care
COPD	Chronic obstructive pulmonary disease
CRN	Clinical Research Network
CRP	C-Reactive Protein
CSRI	Client Service Resource Inventory
CTIMP	Clinical Trial of Investigational Medicinal Product
CV	Curriculum vitae
CXR	Chest x-ray
DOAC	Direct oral anticoagulant
DSUR	Development Safety Update Report
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
ESO	European Stroke Organisation
GCP	Good Clinical Practice
GCTU	Glasgow Clinical Trials Unit
H&C	Health and Care
HAP	Hospital-acquired pneumonia
HES	Hospital Episode Statistics
HRA	Health Research Authority
ICER	Incremental cost-effectiveness ratio
ICF	Informed Consent Form
ICSR	Individual Case Safety Report
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
INR	International Normalised Ratio

IRAS	Integrated Research Application System
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
IVOS(T)	Intravenous-to-oral switch (therapy)
MHRA	Medicines and Healthcare products Regulatory Agency
mRS	Modified Rankin Scale
NHS GG&C	National Health Service Greater Glasgow and Clyde
NICE	National Institute for Health and Care Excellence
NIHR HTA	National Institute for Health and Care Research Health Technology Assessment
NIHSS	National Institutes of Health Stroke Scale
NIMP	Non-Investigational Medicinal Product
ONS	Office for National Statistics
OR	Odds ratio
PI	Principal Investigator
PIS	Participant Information Sheet
PPIE	Patient and Public Involvement and Engagement
PROBE	Prospective, Randomised Open-label Blinded-Endpoint
PROMs	Patient-reported outcome measures
PSP	Post-Stroke Pneumonia
PV	Pharmacovigilance
QALYs	Quality-adjusted life years
R&I	Research & Innovation
RCB	Robertson Centre for Biostatistics
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RR	Respiratory Rate
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SDV	Source Data Verification

SIS	Stroke Impact Scale
SIV	Site Initiation Visit
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSNAP	Sentinel Stroke National Audit Programme
SUSAR	Suspected Unexpected Serious Adverse Reaction
SViR	Stroke Voices in Research
TMG	Trial Management Group
TSC	Trial Steering Committee
UKCRC	UK Clinical Research Collaboration
VAP	Ventilator associated pneumonia
WBC	White Blood Cell

iii. TRIAL SUMMARY

Trial Title	CLArithromycin for post-Stroke Pneumonia: A prospective, randomised open-label blinded-endpoint phase 3 multicentre trial	
Internal ref. no. (or short title)	CLASP	
Clinical Phase	Phase III	
Trial Design	Prospective, randomised open-label blinded-endpoint (PROBE)	
Trial Participants	People with Post-Stroke Pneumonia (PSP)	
Planned Sample Size	1166	
Treatment duration	5 days	
Follow up duration	90 days (+/-7 for local research staff follow-up, +/-14 for central follow-up)	
Planned Trial Period	60 months	
	Objectives	Outcome Measures
Primary	Determine whether 5 days of treatment with clarithromycin in addition to usual non-macrolide antibiotic treatment for PSP improves functional outcome at 90 days	Blinded modified Rankin Scale (mRS) at 90 days
Secondary	Determine whether clarithromycin in addition to usual non-macrolide antibiotic treatment for PSP: Reduces mortality at 90 days Increases home time by 90 days Reduces cardiovascular mortality at 90 days Reduces urgent or unplanned readmissions at 90 days Reduces recurrent stroke at 90 days Reduces major cardiovascular events at 90 days Improves quality of life at 90 days Improves stroke-related health status at 90 days Reduces caregiver burden at 90 days	All-cause mortality at 90 days Days spent in pre-admission usual place of residence at 90 days Cardiovascular mortality at 90 days Non-elective admissions by 90 days Stroke at 90 days Major cardiovascular events at 90 days EQ-5D-5L at 90 days Stroke Impact Scale (SIS) at 90 days Zarit Caregiver Burden (ZBI-12) interview

	Is safe Is cost-effective from the perspective of NHS England	*Clostridioides difficile* infection within 90 days Ventricular arrhythmia within 7 days Health and social care resource use up to 90 days
Investigational Medicinal Product(s)	Clarithromycin	
Formulation, Dose, Route of Administration	Clarithromycin 500 mg 12 hourly for 5 days, via IV or oral/enteral route as appropriate and in accordance with local IVOS policy	

iv. FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this trial)	**FINANCIAL AND NON-FINANCIAL SUPPORT GIVEN**
National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA)	£3,238,557.07

This project is funded by the NIHR HTA programme (NIHR158678). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

v. ROLE OF TRIAL SPONSOR

Prior to study initiation, a non-commercially funded clinical trial co-sponsorship agreement will be put in place between NHS Greater Glasgow and Clyde (NHS GG&C) and the University of Glasgow. The roles and liabilities each organisation will take under the Medicines for Human Use (Clinical Trials) Regulations, 2004 SI 2001:1031 are laid out in this agreement signed by both organisations.

The University of Glasgow shall be responsible for carrying out the obligations and responsibilities set out in the aforementioned agreement and shall be deemed “sponsor” for the purposes of Part 3 of the regulations in relation to the study.

NHS Greater Glasgow and Clyde shall be responsible for carrying out the responsibilities set out in the agreement, and shall be deemed “sponsor” for the purposes of Parts 4, 5, 6, and 7 of the regulations in relation to the study.

The Co-Sponsors will delegate specific roles to the Chief Investigator (CI), Glasgow Clinical Trials Unit (GCTU) and other third parties. These arrangements will be clearly documented in agreements and/or the Sponsor Delegated Roles and Responsibilities Matrix.

vi. ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

The overall delivery of the trial according to the scientific protocol, budget and time will be the responsibility of the Chief Investigator and communicated directly through regular written reports to the funder.

Trial Management Group (TMG)

The trial will be coordinated from the University of Glasgow and NHS GG&C by the CLASP Trial Management Group (TMG). The TMG includes those individuals responsible for the day-to-day management of the trial: the CI and Co-CI, trial managers and representatives from GCTU, NHS GG&C and the University of Glasgow. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

Trial Steering Committee (TSC)

The role of the Trial Steering Committee (TSC) is to provide overall supervision of the trial and ensure that it is being conducted in accordance with the principles of Good Clinical Practice (GCP) and the relevant regulations. The TSC should:

- Agree the trial protocol and any substantial amendments
- Provide advice to the investigators on all aspects of the trial
- Have members who are independent of the investigators, in particular an independent Chair, aligned with NIHR recommendations
- Have a formal Charter outlining the roles and responsibilities of its members.

Decisions about continuation or termination of the trial or substantial amendments to the protocol are usually the responsibility of the TSC who will advise the Co-Sponsors.

The TSC will meet at the start of the study and regularly thereafter. The Committee may invite other attendees from the trial team to present or participate in discussions on particular topics. These attendees will be non-voting members.

Independent Data Monitoring Committee (IDMC)

The role of the Independent Data Monitoring Committee (IDMC) is to review the accruing trial data and to assess whether there are any safety issues that should be brought to participants' attention or any reasons for the trial not to continue. The IDMC will:

- Be independent of the investigators, the funder and Co-Sponsors
- Make recommendations to the TSC and Co-Sponsors
- Receive unblinded reports on study safety data, progress and outcomes
- Have a formal Charter outlining the roles and responsibilities of its members.

The IDMC will meet at the start of the study and at least annually thereafter.

vii. PROTOCOL CONTRIBUTORS

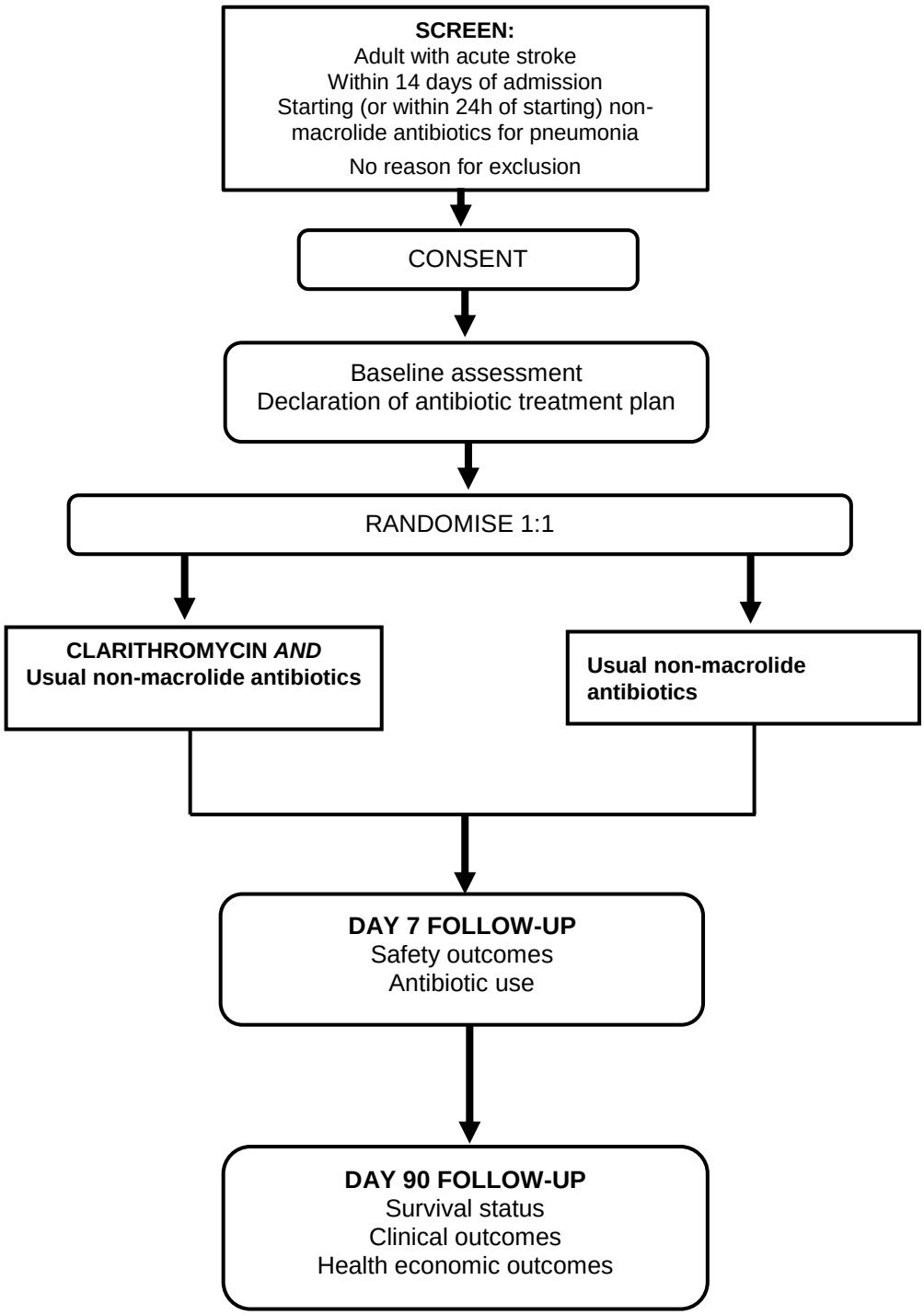
The protocol has been developed by a group with extensive clinical and research experience relevant to this study including the design and conduct of landmark trials. This includes specialists in stroke (Prof Craig Smith, Prof Jesse Dawson), microbiology (Dr Adam Jeans), respiratory and critical care (Prof Tim Felton), pharmacy (Dr Elizabeth Douglas), clinical trial design and biostatistics (Prof Alex McConnachie) and health economics (Prof Rachel Elliott).

Patient and Public Involvement and Engagement (PPIE) Group

A dedicated stroke survivor PPIE Lead and the Stroke Association's Stroke Voices in Research (SViR) Group were consulted to ensure that the trial design includes the priorities and views of stroke survivors. Key contributions to the trial design and delivery have included the appropriateness of the intervention and randomisation, eligibility criteria, approach to consent, outcome measures, widening participation, diversity and inclusion, 90-day follow-up processes and dissemination of findings to participants and their families. The PPIE Group is led by Wendy Westoby.

viii. KEY WORDS: Stroke, Post-Stroke Pneumonia, Cerebrovascular , Antibiotics, Macrolide, Clarithromycin, Microbiology

ix. TRIAL FLOW CHART



1 BACKGROUND

Stroke is a leading cause of death and disability worldwide. In the UK, there are around 100,000 new strokes each year [1]. Pneumonia (an infection in the lungs), is a serious complication of stroke which occurs most often in the first week after stroke onset and contributes significantly to worse clinical outcomes and healthcare costs. Overall, pneumonia occurs in around 14% of stroke admissions [2,3,4].

Post-Stroke Pneumonia (PSP), is considered a separate entity to pneumonia in other clinical settings, such as community-acquired pneumonia (CAP), hospital acquired pneumonia (HAP) or ventilator associated pneumonia (VAP), due to the specific clinical context [2,5]. Increasing age, worse stroke severity and swallowing impairment (dysphagia) are consistent risk factors for development of PSP [6]. Acute stroke also induces both activation and suppression of systemic inflammatory and immune responses [7], and a localised inflammatory response in the lungs [8,9]. It is thought that aspiration of naso-pharyngeal and oro-gastric material due to dysphagia, plus exposure to healthcare-associated bacteria, in the setting of impaired systemic innate and adaptive immunity are the key aetiological processes in PSP. PSP is associated most often with organisms seen in HAP, predominantly Gram-negative bacteria (e.g. *Klebsiella pneumoniae, Escherichia coli, Pseudomonas aeruginosa*) and *Staphylococcus aureus. Streptococcus pneumoniae*, a common cause of CAP, is identified infrequently in PSP (around 3.5%) [5]. Pulmonary inflammation in acute stroke is characterised by perivascular and peribronchial inflammation, with increased numbers of pulmonary neutrophils and plasma cells, and increased pro-inflammatory cytokine concentrations, which are augmented in the presence of pneumonia [8,9]. Systemic inflammation induced by stroke, for example measured by elevated plasma interleukin-6 or C-reactive protein (CRP) concentration, is enhanced in PSP and contributes to worse clinical outcomes [10].

PSP has a profound impact on people with stroke, their families and stroke services. In a recent study of UK stroke units in the Sentinel Stroke National Audit Programme (SSNAP), we found that in-hospital mortality in people with pneumonia occurring within 7 days of admission was 40% compared to 13% in those without pneumonia occurring within 7 days of admission (Figure 1) [4]. Patients with early PSP had an increased risk of longer length of hospital stay, increased odds of worse functional outcome at discharge and increased risk of in hospital mortality, despite adjustment for prognostic variables and modern stroke unit care (Table 1) [4]. In another UK study, PSP was associated with increased acute care costs and resulted in an adjusted incremental cost of £5817 (95% Confidence Interval £4945, £66890) per patient [11]. Furthermore, patients with post-stroke infections are also at an increased risk of any unscheduled re-admission, recurrent ischaemic stroke and post-stroke cognitive decline [12,13,14].

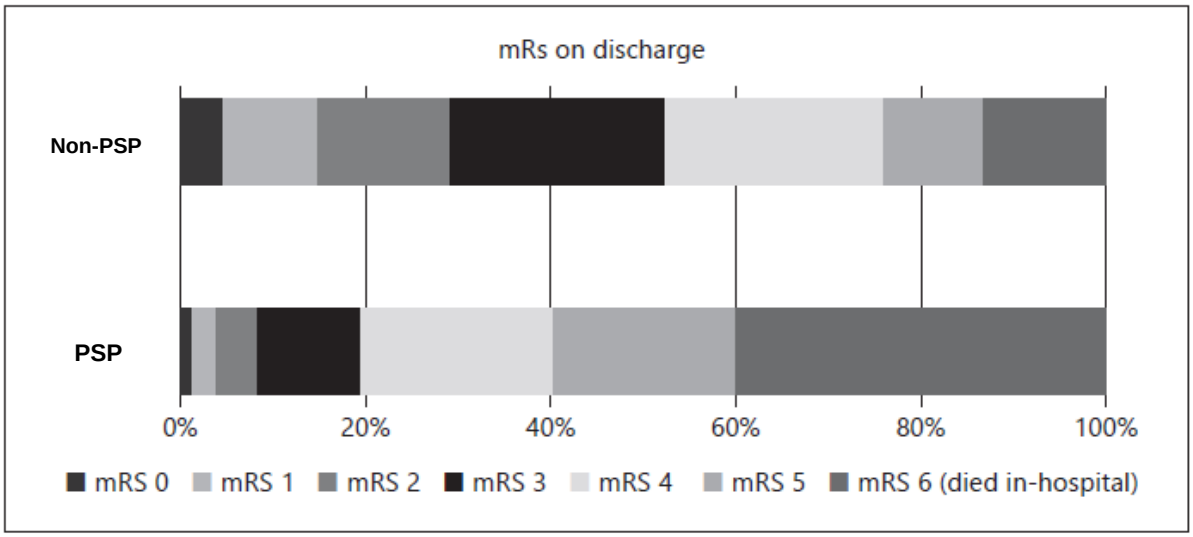


Figure 1: Stacked bar chart showing distribution of scores on the modified Rankin Scale (mRS) for patients with early PSP and those without early PSP. mRS of 6=died

Length of hospital stay, adjusted IRR (95% CI)	1.27 (1.25, 1.30)
mRS at discharge, adjusted OR (95% CI)	2.9 (2.9, 3.0)
In-hospital mortality, adjusted HR (95% CI)	1.78 (1.74, 1.82)

Table 1: Association between PSP and outcomes adjusted for prognostic variables and markers of good quality stroke unit care. IRR = incidence rate ratio. OR = odds ratio. HR = hazard ratio.

There are very limited strategies to prevent occurrence of PSP and trials of prophylactic antibiotics have failed to prevent PSP or improve clinical outcomes (see systematic search and individual participant data analysis [15]). Pneumonia as a complication of stroke is a top-10 research priority identified by the Stroke Association/James Lind Alliance priority setting partnership [16]. The importance of PSP has been recognised by the initiation of a European Stroke Organisation (ESO) guideline group to deliver best practice recommendations for clinical care.

2 RATIONALE

Antibiotics are the mainstay of treatment for PSP, however there is a lack of evidence to guide treatment compared to other types of pneumonia as identified in our recent systematic review [17], for example CAP [18]. The effectiveness of different antibiotic classes and the importance of potential immunomodulatory effect of some drug classes in PSP remains uncertain. This trial is a pragmatic randomised trial of immunomodulatory macrolide antibiotic therapy added to usual, non-macrolide antibiotic treatment for PSP, which could improve clinical outcomes for patients and their families and provide health economic benefits. Our results will directly inform national stroke treatment guidelines and clinical practice.

Macrolide antibiotics have powerful immunomodulatory properties and have been shown to reduce exacerbations in people with chronic obstructive pulmonary disease (COPD) and to improve lung function in people with cystic fibrosis [19]. Given the clear role of inflammation in PSP, macrolides are logical agents to assess to see whether their antimicrobial and immunomodulatory effects improve the poor outcomes in PSP. Whilst there may be differences in immunomodulatory effects between macrolide drugs, immunomodulation is generally accepted to be a class effect [20]. There is no

consistent difference in side effect profile between different macrolides [21]. Of the newer macrolides, clarithromycin and azithromycin are available as oral or intravenous (IV) formulations. In our recent survey of UK stroke units, IV and oral clarithromycin were available in 93% of responding units, whereas IV azithromycin was only available in 45% of units. This is important as the majority of patients with PSP have dysphagia and require IV antibiotics, at least until a consistent oral or enteral route is established. We have therefore chosen clarithromycin for this trial. We have opted for 5 days treatment with clarithromycin to align with current antibiotic recommendations for pneumonia and to reduce the risks of antimicrobial resistance [18,22]. Given their poor outcome, the presence of a usually severe stroke and possible dysphagia, participants would be considered seriously ill and requiring initial intravenous therapy (dose 500 mg twice daily). As soon as a reliable oral or enteral route is established, participants should switch to oral/enteral dosing at the dose for severe respiratory infection (500mg twice daily) in line with usual IVOS policies.

2.1 Assessment and management of risk

We have identified the following main areas of risk:

- Adverse reactions and drug interactions from clarithromycin use
- Potential risk from combination antibiotic therapy
- Inclusion of women of childbearing potential
- Changes to antibiotic therapy during the treatment phase of the study
- Potential risk of unblinding of outcome assessors

2.1.1 Potential for adverse reactions and drug interactions and mitigation of this risk

The most frequent adverse reactions of macrolides are gastrointestinal disturbances such as abdominal pain, diarrhoea, nausea and vomiting and taste disturbance. When given intravenously, injection site phlebitis and pain can also occur.

There is a risk of QT prolongation and ventricular arrhythmia when clarithromycin is used concomitantly with medicines such as domperidone and ivabridine in people with a history of QT prolongation or ventricular arrhythmia and in people with uncorrected hypokalaemia or hypomagnesaemia. There is an increased risk of myopathy and rhabdomyolysis when clarithromycin is used concomitantly with HMG-CoA reductase inhibitors (statins) that are extensively metabolised by CYP3A4 (including lovastatin, simvastatin and atorvastatin).

The SmPC advises caution in people with coronary artery disease, bradycardia and severe cardiac insufficiency. Participants will be randomised in acute stroke services and will be under regular monitoring as part of routine clinical care so people with these conditions can be included if they meet all other eligibility criteria.

The potential risks associated with clarithromycin will be minimised by avoiding use in people who are known to be intolerant (included as a trial exclusion criteria) and avoiding concomitant use with medicines which have known interactions or increase risk of QT prolongation. Concomitant use of medicines that are listed as contraindicated in the SmPC or as ‘manufacturer advises avoid’ in the BNF will not be permitted unless these can safely be stopped or temporarily withheld for the duration of clarithromycin treatment plus 3 days (72 hours) to allow >5 half-lives to elapse. In addition, we have excluded additional medications which could be associated with adverse reactions that could be difficult to detect or where clarithromycin levels could be significantly reduced. These are listed in Appendix 2. In addition, medications that can interact with clarithromycin but can be used with caution are listed in Appendix 3. The use of anticoagulant drugs is allowed after consideration of the risks and benefits. There is emerging evidence that DOACs pose little risk of bleeding complications in the early period after ischemic stroke and would not normally be use in people with intracerebral haemorrhage. Stroke physicians are well experienced in assessing these relative risks and benefits. The use of

calcium channel blockers, digoxin and drugs for diabetes mellitus is allowed as these can be readily monitored in routine practice and stroke physicians are experienced with these drugs. Corticosteroids, cilostazol and omeprazole use is allowed as the potential for significant adverse effects is low with a short duration of treatment. Omeprazole and cilostazol can usually be withheld for a short period or alternative agents can be used.

In addition, risk is mitigated by the fact participants will be randomised and initially treated in acute stroke services and by avoiding clarithromycin use in the following people:

- People with QT prolongation
- People with a history of long QT syndrome or ventricular arrhythmia or cardiac arrest.

People with these features will also be excluded from the trial. Hypokalaemia and hypomagnaesemia are also risk factors for QT prolongation. People with known hypokalaemia (defined as K+ < 3.5 mmol/l) or known hypomagnaesemia (defined as Mg2+ < 0.70 mmol/l) at the point of screening will be excluded from the trial. They can later be included if this is corrected and they remain eligible. People with hypokalaemia or hypomagnesaemia prior to screening that has already been corrected can also be included.

Clarithromycin is routinely used in clinical practice and information on clinically relevant interactions and contra-indications is well documented and easily accessible (e.g. SmPC and BNF), further minimising potential risks.

Clostridioides difficile infection is a documented risk from use of antibiotic therapy. There is uncertainty regarding any excess risk from clarithromycin use. An evidence summary published by NICE in 2015 [23] found that macrolides are likely to be associated with an increased risk of *C.difficile* infection but this risk is equivalent to use of penicillins and is likely less than antibiotics such as clindamycin, cephalosporins and tetracyclines [24].

Statins will be frequently used in this population. People prescribed statins can be randomised but suspension of statin therapy whilst receiving clarithromycin is required by the protocol [25]. There is no RCT evidence to support use of statins earlier than 7 days after stroke onset [26] and no evidence that delaying statin use for a short period will be detrimental.

2.1.2 Potential risk from combination antibiotic therapy and mitigation of this risk

This risk is related to the potential for drug interactions and adverse drug reactions, potential for increased risk of antibiotic resistance, and potential for increased risk of *C.difficile* infection. These risks are addressed as described above by avoiding drugs known to interact with clarithromycin, by excluding patients with specific risk factors for serious adverse effects and by reminding sites to follow their usual antibiotic policy.

2.1.3 Inclusion of women of childbearing potential and contraception requirements

The SmPC for clarithromycin advises against use in pregnancy without careful assessment of risks versus benefits as there is the potential for fetal harm but contraception use is not mandated. All women of childbearing potential will require a negative pregnancy test (urine or blood) before they can participate in the CLASP study.

It is anticipated that due to the severity of their condition, the vast majority of CLASP participants will remain inpatients for the duration of clarithromycin treatment. For women of childbearing potential, it may be clinically inappropriate to continue pre-stroke contraception methods such as combined oral contraception due to pro-thrombotic risks. It is also not practical to mandate the use of other contraception methods given the limited duration of systemic clarithromycin exposure and clinical context. The extent of stroke-induced injury may also mean that discussions around contraception methods could cause significant distress for some participants and may not be appropriate given the clinical condition of the participant. The extent to which contraception measures need to be discussed

at the point of enrolment will therefore be at the discretion of the Principal Investigator (or designee). Should the clinical condition of the participant be such that appropriate contraception advice is likely to be required prior to the end of the clarithromycin exposure period, the local site team must ensure appropriate advice is provided. This must be fully documented in the participant's medical records.

Where necessary, women of childbearing potential will be required to:

- Use highly effective methods of contraception, OR
- Other birth control methods with a failure rate of less than 1% OR
- Agree to abstain from sexual intercourse with a male partner (unless confirmed vasectomy) until at least 3 days (72 hours) after the last dose of clarithromycin.

Should a pregnancy occur, it will be reported in an expedited fashion in accordance with Adverse Event reporting requirements in the UK. Acceptable birth control methods are outlined in Appendix 1. This approach is felt to be pragmatic and justified given the severity of the clinical condition and limited period of exposure to clarithromycin.

2.1.4 Changes to antibiotic therapy during the treatment phase of the study

Clarithromycin is used in approximately 10% of people with PSP, although it will be used in people who are penicillin allergic and is routinely used for severe community acquired pneumonia in the hospital setting.

It is possible that participants will deteriorate, leading to clinical teams expanding antibiotic coverage, or develop other indications for antibiotic therapy. These decisions will be taken by clinical teams and, provided any additional drugs used do not have a known severe interaction with clarithromycin or appear on the list in the list of prohibited medicines in Appendix 2, treatment with clarithromycin can continue.

2.1.5 Potential risk of unblinding of outcome assessors

The participant follow-up at 90 days will be carried out by blinded central assessors who are not part of the clinical research team. There remains a risk of unblinding to treatment by the participant or caregiver during follow-up interviews. Central assessors will remind participants and caregivers that they should not mention any medication given to the participant unless directly questioned about medications at the time of interview.

With the above mitigations, the trial is categorised as:

• Type A = Risk no higher than the risk of standard medical care

3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

3.1 Primary objective

The primary objective of the trial is to determine whether 5 days of treatment with clarithromycin in addition to usual non-macrolide antibiotic treatment for PSP improves functional outcome at 90 days after stroke in comparison to usual non-macrolide antibiotic treatment.

3.2 Secondary objectives

This trial also seeks to determine whether 5 days of treatment with clarithromycin in addition to usual non-macrolide antibiotic treatment for PSP:

- Reduces mortality at 90 days
- Increases home time by 90 days

- Reduces cardiovascular mortality at 90 days
- Reduces urgent or unplanned readmissions at 90 days
- Reduces recurrent stroke at 90 days
- Reduces major cardiovascular events at 90 days
- Improves quality of life at 90 days
- Improves stroke-related health status at 90 days
- Reduces caregiver burden at 90 days
- Is safe
- Is cost-effective from the perspective of NHS England

3.3 Outcome measures/endpoints

Outcome measures were determined after discussions with PPIE collaborators and a search of the COMET Initiative database (terms “Neurology”, “Acute Stroke”, “Published”) for acute stroke trial core outcome sets. Two published recommendations were identified [29, 30] which incorporate survival, stroke recurrence, patient reported outcome measures (PROMs) across all domains including motor/non-motor problems, cognition, mood. However, whilst mRS is a standard outcome measure, there is no ubiquitous or agreed set of outcome/assessment scales used consistently in acute stroke trials. Outcome measures were chosen in partnership with the CLASP PPIE group and are aligned with the above recommendations to include survival, stroke recurrence and PROMs (quality of life and stroke-related health status). Caregiver burden was considered to be an important outcome measure by the PPIE group in view of the relatively poor prognosis of patients with PSP. The primary and secondary outcome measure scales (mRS [31], EQ-5D-5L [32], Home time [33], Stroke Impact Scale [34] and Zarit Caregiver Burden [35]) are well-established in stroke research and can be collected using telephone and postal assessments. The assessments will be centralised and undertaken by research staff blinded to treatment allocation. The timing of outcome assessments (described below) refers to time from randomisation.

3.3.1 Primary outcome

Modified Rankin Scale (mRS) score (a measure of functional outcome) at 90 days (+/-14 days) assessed by virtual online assessment or telephone using centralised, blinded, trained raters.

Postal questionnaires can be used only in the event that online or telephone assessment is not possible to avoid loss to follow-up.

3.3.2 Secondary outcomes

- All-cause mortality at 90 days
- Days spent in pre-admission usual place of residence at 90 days
- Cardiovascular mortality at 90 days
- Non-elective admissions by 90 days
- Stroke at 90 days
- Major cardiovascular events at 90 days
- EQ-5D-5L at 90 days
- Stroke Impact Scale at 90 days
- Zarit Caregiver Burden (ZBI-12) interview
- *Clostridioides difficile* infection within 90 days
- Ventricular arrhythmia within 7 days
- Health and social care resource use (index hospitalisation and post-discharge health and social care contact) up to 90 days to inform health economic analysis.

3.3.3 Exploratory outcomes

- Length of hospital stay (days) at 90 days
- Discharge destination (remains in hospital, home, care home) at 90 days
- Number of antibiotics doses received during first 7 days after randomisation
- Highest recorded CRP concentration (mg/L) during first 7 days after randomisation
- Highest recorded WBC count ($x10^9$/l) during first 7 days after randomisation
- Highest recorded respiratory rate (RR)/minute during first 7 days after randomisation
- Highest recorded temperature °C during first 7 days after randomisation
- Highest recorded NEWS-2 score during first 7 days after randomisation
- Lowest recorded lowest oxygen saturations (%) during first 7 days after randomisation
- Caregiver quality of life (EQ-5D-5L)

4 TRIAL DESIGN

CLASP is a prospective randomised open-label blinded-endpoint (PROBE) phase 3 trial.

- Population: Hospitalised adult patients within 14 days of admission for acute stroke when starting (or within 24 hours of starting) non-macrolide antibiotics for PSP.
- Intervention: Addition of clarithromycin 500mg bd (route of administration will be determined by local clinical team based on clinical condition and availability of route of administration in line with local IVOS policy) for 5 days in addition to usual non-macrolide antibiotic therapy.
- Comparator: Local guideline usual antibiotic therapy for PSP where macrolides are not indicated.
- Outcome: Primary outcome is blinded mRS score at 90 days.
- Time: Individual data will be collected over 90 days.

The CLASP study will include an 18-month internal pilot phase to confirm feasibility. During this phase, a target of 36 sites (80% of total sites) and 246 participants (21% of the total sample) at a rate of 0.55-0.7 participants/site/month during the first 6 months and 0.76 participants/site/month for the remaining 12 months will be set* (this will only apply to sites that have been opened for 3 months or more). Following the internal pilot phase, progression to the main recruitment phase will be based on a stop-go decision for both site and participant internal pilot targets (Table 2):

Progression criteria	Red	Amber	Green
% threshold	<75%	75-99%	≥100%
Number of sites open	<27	27-35	≥36
Recruitment/site/month	<0.54	0.54-0.71	0.72
Total number of participants recruited	<185	185-245	≥246
Proportion with primary outcome*	<80%	80-90%	>90%

Table 2: Internal pilot progression criteria

**Where the denominator is the number who have reached the 90-day period, undergone survival check and been contacted the maximum number of times in accordance with the trial protocol*

The progression criteria and actions are as follows:

- Green: ≥100%: continue seamlessly to main recruitment phase
- Amber: 75-99%: Discuss feasibility and develop improvement plan with the Trial Steering Committee (TSC) to present to Funder
- Red: <75%: Discuss closure options with the TSC and Funder

If there is inconsistency in the scoring of the progression criteria, then overall the trial will be categorised according to the criterion that is furthest from achieving the progression threshold (e.g. if four criteria are green but one is amber, the trial will be categorised as amber).

If criteria are met for progression, the main recruitment phase (27 months) will recruit the remaining additional 9 sites (during the first 6 months) and 920 participants. The trial will aim for a recruitment rate of 0.7 participants/site/month for the additional 9 sites during set-up and 0.8 participants/site/month otherwise.

5 TRIAL SETTING

CLASP is a multicentre trial and will take place across at least 45 NHS hyperacute and acute stroke units in the UK.

Sites will be identified through SSNAP/Scottish Stroke Care Audit, NIHR CRN, Northern Ireland Stroke Research Network, Welsh Stroke Research Network, Scottish Stroke Research Network and BIASP.

6 PARTICIPANT ELIGIBILITY CRITERIA

6.1 Inclusion criteria

- Age ≥18 years
- Acute stroke (ischaemic stroke or intracerebral haemorrhage [ICH]) within the past 14 days
- Starting (or within 24 hours of starting) non-macrolide antibiotics for a new diagnosis of PSP*
- Written informed consent from participant or from next of kin/designated representative or consultee or independent physician if participant lacks capacity (by phone if required)
- Women of childbearing potential must have a negative highly sensitive serum (beta-human chorionic gonadotropin [beta-hCG]) or urine test at screening (see Appendix 1 for further information)

*In the CLASP trial, PSP is defined as a clinician diagnosis of pneumonia within 14 days of stroke onset with or without supporting radiographic evidence. Participants can be included after non-macrolide antibiotics have been started for PSP provided they are randomised within 24 hours of the first dose. Clinical data will be collected to enable classification as probable or definite post-stroke pneumonia using published criteria [2].

Non-macrolide antibiotic use for disorders other than pneumonia is allowed at the point of randomisation.

6.2 Exclusion criteria

- Requirement for macrolide therapy as usual care
- Confirmed respiratory viral infection (e.g. COVID-19, influenza) at point of screening*
- Known antibiotic treatment for chest infection or pneumonia within the last two weeks (single doses or less than 3 days of treatment is allowed)
- Known toxin positive *C.difficile* infection in the past 12 weeks
- Contraindications or major cautions to macrolide antibiotic use:
    - Known hypersensitivity to clarithromycin, its excipients or other macrolide antibiotics
    - Established diagnosis of myasthenia gravis
    - Diagnosis of long QT syndrome
    - QTc interval >460ms on last ECG before screening†[36]
    - Known hypokalaemia (K+ < 3.5 mmol/l) which has not been corrected

  - Known hypomagnesaemia (Mg2+ < 0.70 mmol/l) which has not been corrected
  - History of ventricular tachycardia
  - History of cardiac arrest
  - Severe hepatic impairment defined as AST, ALT or bilirubin > 3 times ULN or known diagnosis of cirrhosis
  - Current use of medicine(s) known to increase risk of QT prolongation that in the opinion of the investigator cannot reasonably be withheld for the duration of study treatment plus 3 days (see Appendix 2)
  - Current use of medicine(s) that are contra-indicated in combination with clarithromycin that in the opinion of the investigator cannot reasonably be withheld for the duration of study treatment plus 3 days (see Appendix 2)
- Women of childbearing potential who are pregnant, breastfeeding or who are unwilling to use appropriate contraception or abstain from sexual intercourse for 3 days (72 hours) after the last dose of clarithromycin (see Appendix 1 for definitions and information on acceptable methods of contraception)
- Plan for imminent mechanical ventilation
- End-of-life care
- Previously randomised into the CLASP study

** A test for viral infection is not required by protocol, this is only if it is done for routine clinical care.*

†*Some ECG machines may provide different measures of QTc. For trial eligibility, the longer result should be used.*

Co-enrolment in other Clinical Trial of Investigational Medicinal Products (CTIMPs) is not permitted while participating in CLASP. Co-enrolment in observational studies, diagnostic studies or other research may be permitted subject to agreement of the Sponsors and Chief Investigators of both studies.

6.3 Caregiver eligibility

Caregivers completing burden and quality of life assessments will be aged 18 years or older and providing unpaid support to patients who are living in a private residence.

The main caregiver will be identified by the participant or next of kin but must be the person deemed most likely to be providing informal care to the participating patient.

7 TRIAL PROCEDURES

7.1 Recruitment

7.1.1 Participant identification

Potential participants will be identified by case note review by a member of the clinical team or by their attending doctor whilst in-patient in a stroke unit.

Eligibility will be confirmed by a medically qualified investigator.

7.1.2 Screening

Patients will be screened to determine if the following conditions are met:

1. Adult with acute stroke
2. Within 14 days of admission

3. Starting (or within 24 hours of starting) non-macrolide antibiotics according to local stroke unit policy
4. No other reason for exclusion

No additional procedures are required for screening.

7.1.3 Payment

There will be no payment to participants for participation.

7.2 Consent

7.2.1 Participant consent

Following identification of a potential participant by the clinical team and screening, potential participants will be approached in person and asked whether they would consider taking part in the trial. If the person approached lacks capacity, designated (e.g. relative) or professional (independent physician) consultees will be approached to discuss their participation. Consent may be obtained via telephone from a designated or professional consultee where no consultee is available in person. Participants or their representatives may decline to participate for any reason without explanation.

Those who are willing to hear more will be given a Participant Information Sheet (PIS) and a time will be arranged for further discussion with a member of the research team. Participants or their representatives will be permitted to consent at the initial visit, without 24-hour delay, as the population being studied will require the trial antibiotic treatment to start as quickly as possible upon diagnosis of PSP to maximise chances of success.

Potential participants or their representatives will be given an opportunity to ask any questions and those who wish to participate will be asked to sign an Informed Consent Form (ICF). Two copies will be signed (one each for the participant and the site file) and a copy of the signed consent form will be inserted into the patient's record. If a person has capacity to consent but is unable to write due to physical disability, an independent witness' signature will be used to confirm consent.

Consent will be taken by one of the designated investigators or by a delegated study research nurse (in which case it will be countersigned by an investigator).

Participants are free to withdraw consent for any aspect of the trial at any time and for any reason. They will be provided with contact details for local research staff via the PIS, which can be used should they wish to discontinue with the trial after discharge. If the participant wishes to withdraw from the study treatment, the reason(s) will be sought (but do not need to be given), and permission will be sought to continue with follow-up. If the participant wishes to withdraw from all study participation, the reason(s) will be sought (but do not need to be given). Unless the participant actively states that existing data, and/or future data from medical records may not be used, data will be used in accordance with the original signed ICF.

Participants who were consented by a representative and who are found to have regained capacity during the trial will be given a PIS outlining what their enrolment into the trial has entailed and, if they wish to continue in the trial, will be asked to complete an ICF to be stored in the participant's record and site file. If the participant has been discharged from hospital at the point capacity is regained, telephone or online re-consent is acceptable. If they do not consent to continuing in the study, they will be withdrawn. In this scenario, they will be asked to consent to use of their data. If this is not given, all of their data will be deleted.

A summary of who can give consent for the trial is shown in table below.

Summary hierarchy of informed consent for an incapacitated adult	
England, Wales and Northern Ireland	Scotland
Personal legal representative / consultee A person not connected with the conduct of the trial who is (a) suitable to act as the legal representative by virtue of their relationship with the adult, and (b) available and willing to do so. Professional legal representative.	Personal legal representative. 1A. Any guardian or welfare attorney who has power to consent the adult's participation in research. 1B. If there is no such person, the adult's nearest relative as defined in section 87(1) of the Adults with Incapacity (Scotland) Act 2000. Professional legal representative.

Table 3: Summary hierarchy of informed consent for an incapacitated adult

7.2.2 Additional consent provisions for collection and use of participant data

Participants will be invited to consent for longer-term follow-up (funding sought separately) via record linkage to routinely-collected healthcare data (e.g. 6-month mRS, recurrent stroke, recurrent PSP from the SSNAP registry/HES, longer-term survival (ONS) and dementia status).

7.2.3 Caregiver consent

Caregivers completing burden and quality of life assessments will be identified at the point of consent. Their eligibility will be checked (see section 6.3) and if suitable, they will be provided with a Caregiver Information Sheet and the opportunity to ask any questions. Those who wish to participate will be asked to sign a Caregiver Consent Form.

If consent is being given by a professional legal representative because a caregiver or other representative is not available, consent will only be obtained to approach a caregiver if and when a caregiver or other representative is identified.

Caregivers are free to withdraw from participating at any time for any reason. Unless the caregiver actively states that existing data may not be used, data will be used in accordance with the original signed Consent Form.

7.3 Randomisation

Patients will be randomised 1:1 to the following drug regimens:

- Intervention arm: Clarithromycin 500mg twice daily for 5 days total (route of administration will be determined by the local clinical team based on clinical condition and availability of route of administration in line with local IVOS policy) in addition to usual non-macrolide antibiotic treatment.
- Usual care: Local stroke unit usual non-macrolide antibiotic treatment.

A mixed minimisation/randomisation method designed to maintain balance with respect to baseline age (<80 v ≥80 years), stroke severity (National Institutes of Health Stroke Scale (NIHSS) score <12 v ≥12) and trial centre will be applied.

The randomisation list, the program that generated it and the random seed used will be stored in a secure network located within the Robertson Centre for Biostatistics (RCB), accessible only to those responsible for provision of the randomisation system.

7.3.1 Method of implementing the randomisation/allocation sequence

Consented participants that fulfil all screening criteria will be allocated to either the treatment arm or usual care in a 1:1 ratio, via a web-based interface integrated into the electronic Case Report Form (eCRF) designed and managed by RCB.

Investigators will be informed of the treatment arm allocation in the eCRF and will prescribe clarithromycin as appropriate.

7.4 Blinding

CLASP is an open-label study with no blinding of treatment to participants or care providers. Primary outcome assessors will be independent of the clinical research team, blinded to treatment and will not have access to patient records.

7.5 Baseline data

Baseline information will be collected from consented participants that meet all eligibility criteria. This includes but is not limited to:

- Baseline demographics:
  - Date of birth
  - Sex
  - Ethnicity
  - Pre-stroke mRS
  - Baseline EQ-5D-5L
- Time since symptom onset or last seen well to admission and randomisation
- Vascular risk factors:
  - Hypertension
  - Smoking history
  - Alcohol intake
  - Atrial fibrillation
  - Diabetes
  - Dyslipidaemia
  - Coronary artery disease
  - Peripheral vascular disease
  - Previous stroke
- Selected past medical history:
  - Chronic lung diseases
  - Cancer
  - Dementia
- Medications at baseline
- Stroke subtype:
  - Acute ischaemic stroke
  - Intracerebral haemorrhage
- Baseline stroke severity at admission (NIHSS score)
- Thrombolysis and/or thrombectomy treatment
- Current nutritional status:
  - Nil by mouth
  - Normal diet and fluids
  - Modified diet and fluids
  - Nasogastric tube feeding
  - Peripheral parenteral nutrition
- Previous treated infection earlier in this admission and/or 6 weeks prior to enrolment

- Highest recorded in the 72 hours preceding randomisation:
    - Plasma CRP concentration (mg/L)
    - White blood cell (WBC) count and neutrophil count
    - RR (/minute)
    - Temperature (°C)
    - NEWS-2 score
- Lowest oxygen saturations (%)
- Oxygen requirements
- Presence of unilateral or bilateral chest signs on examination
- Clinical chest X-ray (CXR) or other radiology findings
- Antibiotic treatment since admission including initial antibiotic treatment plan
- Health and social care resource use
- Caregiver quality of life (EQ-5D-5L)

7.6 Follow-up assessments

The trial will comprise of 4 visits: Screening, Randomisation, Day 7 and Day 90 follow-up.

The Day 7 (+3) visit will be carried out by research staff who will collect information such as the following from case notes:

- Information on safety outcomes - including *C.difficile* infection, and occurrence of defined SAEs (see section 9)
- Clarithromycin dose, doses administered and route(s) of administration (including reasons for any non-administered doses)
- Other antibiotics and doses received
- Highest CRP concentration (mg/L) to Day 7 (+3) visit
- Highest WBC count and neutrophil count ($x10^9$/l) to Day 7 (+3) visit
- Highest RR (/minute) to Day 7 (+3) visit
- Highest temperature (°C) recorded to Day 7 (+3) visit
- Highest NEWS-2 score to Day 7 (+3) visit
- Lowest oxygen saturations (%) to Day 7 (+3) visit
- Oxygen requirements
- Presence of unilateral or bilateral chest signs on examination
- Findings from clinical CXR or other chest radiology
- Contact details for follow-up (participant, consented caregiver, GP)

Participants and their caregivers/GP can be contacted by telephone, email or post between 1 week and 1 month prior to the due date of the Day 90 visit to confirm contact details and ongoing participation.

The Day 90 visit will involve local data collection by the research team and a centralised assessment (+/-7 for local research staff follow-up, +/-14 for central follow-up) by video or telephone.

Local research staff will collect the following data from the medical record at Day 90 (+/-7):

- Length of hospital stay (days)
- Mortality
- Discharge destination (remains in hospital, home, care home)
- Urgent or unplanned re-admissions
- Recurrent stroke or other vascular events

The centralised assessment will then be undertaken by appropriately trained University of Manchester staff blinded to treatment allocation. This will take place via video or telephone assessment after local research staff have carried out the mortality check. They will collect information such as the following measures:

- mRS
- Quality of Life (EQ-5D-5L)
- Stroke Impact Scale (SIS)
- Home time (number of days at usual place of residence [immediately prior to their admission] at day 90)
- Health and social care resource use (index hospitalisation and post-discharge health and social care contact up to 90 days)
- Caregiver quality of life (EQ-5D-5L)
- Zarit Caregiver Burden (ZBI-12)

The Day 90 visit marks the end of the study.

7.7 Longer-term follow-up

Participants will be invited to consent to storage of their NHS number (or CHI in Scotland/H&C number in Northern Ireland) for longer-term follow-up using routinely-collected healthcare data (6-month mRS, recurrent stroke, recurrent PSP from the SSNAP registry/HES, longer-term survival (ONS) and dementia status). This will only be performed if additional funding is obtained, in which case a separate protocol will be developed for this activity.

7.8 Qualitative assessments

Study drug adherence will be assessed at Day 7 (+3) and reasons for non-adherence will be documented in the eCRF.

7.9 Withdrawal criteria

7.9.1 Withdrawal from clarithromycin treatment (intervention arm)

Participants may be withdrawn from the study treatment by local clinical teams in the event of a Serious Adverse Reaction (SAR) and it is felt that it is in the best interest of the patient to discontinue treatment. Participants allocated to the intervention arm will also be withdrawn from clarithromycin treatment in the event:

- Treatment is initiated with a prohibited medicine, where the prohibited medicine has not been temporarily discontinued by the local PI (see Appendix 2)
- Requirement for macrolide therapy as part of evolving antibiotic use
- Known toxin positive *C.difficile* infection
- The participant deteriorates after enrolment and becomes for palliative care only
- Onset of contraindications or major cautions to macrolide antibiotic use:
    - Hypersensitivity to clarithromycin, its excipients or other macrolide antibiotics
    - Diagnosis of long QT syndrome
    - Any event of QTc prolongation of >20ms compared to the baseline value
    - Ventricular tachycardia
    - Cardiac arrest
    - Any occurrence of severe hepatic impairment defined as AST, ALT or bilirubin >3 times ULN

Discontinuation of treatment by local clinical teams does not require withdrawal of the participant from the study and follow-up can be continued.

7.9.2 Withdrawal from study

Participants can decide to withdraw from the clinical trial and further follow-up at any time without giving any reason.

The CI, Co-CI or site Principal and Co-investigators have the right to withdraw patients from the study if deemed in the best interests of the participant or in the event of SARs, protocol violations, administrative or other reasons.

Full details of withdrawal should be recorded on the eCRF. Participants who withdraw from the study can consent to their vital status being checked and follow-up via medical records if they wish. A withdrawal form will be completed and retained in site files.

7.10 End of trial

The CLASP trial will proceed with an internal pilot phase, in which over the course of the initial 18 months we will recruit 36 sites (80% of total sites) and 246 participants (21% of total sample).

If the trial does not achieve 75% of these thresholds as defined below, it will be reviewed by the funding body with the anticipation of the trial being stopped:

- ≥ 27 sites
- ≥ 185 participants recruited
  ≥ 0.54 Recruitment/Site/Month
  ≥ 80% Participants with primary outcome

If these targets are achieved, the trial will end when the TSC agrees that one or more of the following situations applies:

- The planned sample size has been achieved
- The (IDMC) has advised discontinuation, e.g. because of safety concerns about the trial, or a statistically significant difference in clinical outcomes is evident between the two treatments
- There is insufficient funding to support further recruitment, and no reasonable prospect of additional support being obtained
- Recruitment is so poor that completion of the trial cannot reasonably be anticipated.

The trial sponsor will notify the MHRA of the end of the trial within 90 days of its completion. This will be when the last participant has completed the Day 90 follow-up visit. Should the trial terminate early, the sponsor will notify the MHRA within 15 days.

Prior to database lock, all data collection activities must have stopped, trial monitoring must have been completed, all primary and secondary outcomes must have been derived, and all data queries must have been resolved as far as is reasonably possible. At this point, the study blind will be broken for the trial statistical team, and the final analysis results will be produced.

8 TRIAL TREATMENTS

8.1 Name and description of investigational medicinal product(s) (IMPs)

The IMP in the CLASP trial is the macrolide antibiotic clarithromycin. Clarithromycin is a widely used macrolide antibiotic with well-known effect and side-effect profile. The current license includes use in lower respiratory tract infections such as acute and chronic bronchitis and pneumonia. In practice, use

includes empirical combination antibiotic treatment in aspiration pneumonia in true penicillin allergy and CAP.

Macrolides are a class of broad-spectrum antibiotics have both antimicrobial and immunomodulatory effects, and include clarithromycin, azithromycin and erythromycin. All macrolides share a common mechanism of antibacterial action which results in similar antimicrobial activity against Gram-positive bacteria such as *Staphylococci* and *Streptococci* and exhibit a degree of activity against certain Gram-negative organisms such as *Haemophilus spp*.[37]. Clarithromycin selectively binds to the 50s ribosomal sub-unit of susceptible bacteria preventing translocation of activated amino acids, inhibiting the intracellular protein synthesis of susceptible bacteria inhibiting growth.

8.2 Regulatory status of the drug

There are a number of different presentations available with a Marketing Authorisation within the UK. The following presentations are permitted for use in the study:

- Oral presentations such as tablets, granules for oral suspension and oral suspension
- IV presentations including concentrate for solution for infusion and powder for solution for infusion

Any brand of clarithromycin preparation listed above may be used provided they have a UK Marketing Authorisation.

Prolonged release oral clarithromycin tablets are not permitted for use in the CLASP study.

8.3 Product characteristics

For clinical information on clarithromycin, please refer to the relevant manufacturer's SmPC for the presentation(s) used at site.

8.4 Drug storage and supply

All supplies for use in the CLASP study will be sourced from routine NHS hospital stocks and will not be reimbursed. There is no requirement to 'ring-fence' supplies for use. Clarithromycin supplies should be stored in accordance with the applicable SmPC and relevant local policies on the storage of medicines. There is no requirement by Sponsor for sites to conduct temperature monitoring on IMP supplies but sites should follow their local SOPs.

8.5 Preparation, administration and labelling of Investigational Medicinal Product

Preparation and administration of clarithromycin should be performed in near-patient clinical areas in line with current practice requirements, the relevant SmPC and local practice such as IV monographs. All IMPs must be labelled in accordance with local requirements. There is no requirement for study specific labelling to be applied.

8.6 Dosage schedules

Participants randomised to the intervention arm will receive treatment with clarithromycin 500mg administered every 12 hours for 5 days (10 doses in total). A reduced dose of clarithromycin 250mg will be given in the event of renal impairment with eGFR <30 mL/min/1.73 m^2. See section 8.7 dose modification for further information. Clarithromycin treatment should commence as soon as possible after randomisation and be prescribed by an investigator (or designee) delegated this responsibility on the site delegation log in line with local requirements. It should be clear from the prescription that clarithromycin being administered as part of the CLASP study protocol.

Clarithromycin should preferably be administered via the intravenous or oral route as per the relevant SmPC. Where the enteral route is available, this should only be used if this route is considered by the

investigator to be the most appropriate route of administration. Enteral routes of administration for clarithromycin are unlicensed and may lead to variable absorption and are not generally recommended. Local guidance and requirements for administration of medicines via the enteral route as well as specific information for clarithromycin must be followed.

During the treatment period, investigators (or designees) must maintain regular oversight of clarithromycin dosing to ensure doses are administered as intended, the route of administration is appropriate and that treatment withdrawal criteria are not met. This should be evident from the participant's medical records. In the event a route of administration ceases to be available (e.g. loss of oral route due to dysphagia) or in the investigator's opinion is no longer appropriate or in-line with local policies such as IVOS, an alternate route may be considered. There is no limit to the number of times the administration route and/or presentation of clarithromycin may be changed. Changes to the presentation and route of administration must be clearly documented in the participant's usual care records.

The clinical condition of people with stroke often fluctuates during their admission. Whilst the investigator is required to maintain regular oversight, the participant's usual care team are permitted to amend clarithromycin dose and route of administration if necessary in order to meet the changing clinical needs of the participant and ensure ongoing safety. Supervision of people receiving antibiotics is a normal part of care in stroke units. Clinical staff are not required to undertake study-specific training nor are they required to be on the site delegation log as this is within the scope of their usual practice. A Clinical Information Sheet with key information including permitted dose modifications and stopping criteria is provided for insertion into the medical notes for patients randomised to the intervention arm.

In the event a participant is discharged to home or other off-site long-term care facility such as a nursing home, any remaining oral clarithromycin doses should be provided at discharge where appropriate. In the event the oral route is not available, clarithromycin must be stopped at discharge. Clarithromycin treatment must be discontinued in the event participants are transferred to another hospital or site that is not participating in the CLASP trial.

If doses are missed and ongoing treatment is not contraindicated, study drug can be continued so a total of 10 doses are given over a maximum period of seven days.

8.7 Dosage modifications

The following dose modifications will apply:

- **At baseline or during treatment eGFR of <30 ml/min/1.73m^2:** Clarithromycin 250mg every 12 hours. Dose (re)escalation is permitted if eGFR improves within the treatment window.
- At investigator's discretion, the dose of clarithromycin may be reduced to 250 mg every 12 hours in the event of adverse effects.

Temporary stop to clarithromycin treatment

- Clarithromycin will be temporarily stopped if the participant is found to have hypokalaemia (defined as potassium <3.5 mmol/l) or hypomagnesemia (magnesium <0.70 mmol/l). At investigator's discretion, clarithromycin may be restarted once deficiency is corrected.

Criteria for permanent withdrawal of clarithromycin treatment are provided in section 7.9.1.

8.8 Known drug reactions and interaction with other therapies

Clarithromycin is a widely used macrolide antibiotic, with a known potent inhibitory effect on CYP34A. Drugs that are primarily metabolised by CYP34A may have elevated and prolonged therapeutic concentrations when administered concomitantly with clarithromycin and are prohibited. Conversely, drugs which are potent inducers of CYP3A may lower the plasma levels of clarithromycin and are

therefore also prohibited. The most likely relevant drug interactions in this population are use of statins and ticagrelor. However, a participant may still be enrolled if, in the local investigator's opinion and judgement, the prohibited medication can be temporarily stopped during the duration of the clarithromycin treatment (see section 8.9 below).

For detailed information on drug-drug interactions, please refer to the relevant SmPC or other local prescribing resources. Prohibited concomitant medicines are provided in Appendix 2. Please note this list is not exhaustive. Medicines with a known interaction which may be co-administered at investigator's discretion are provided in Appendix 3. See also information on permitted dose modifications in section 8.7.

8.9 Concomitant medication

A participant's concomitant medication should be checked by a medically qualified investigator before randomisation to ensure eligibility and to ensure appropriate action is taken regarding concomitant medication.

Participants prescribed or taking prohibited medicines as listed in Appendix 2 are ineligible for the study unless in the investigator's opinion the interacting medicine can safely and appropriately be withheld for the duration of clarithromycin treatment plus 3 days. Should an indication for these drugs develop during the study treatment period and treatment with a prohibited medicine commence, participants must be withdrawn from study clarithromycin treatment. Participants will also permanently stop trial clarithromycin treatment should clarithromycin (or other macrolide) become clinically indicated for antibiotic treatment as per local antimicrobial policies. Relevant data should continue to be collected on participants providing consent is still in place.

Participants prescribed or taking medication listed in Appendix 3 can be enrolled in the study at investigator discretion following consideration of advice contained in the protocol, the BNF and the SmPC.

8.10 Assessment of adherence with treatment

Administration of clarithromycin for all participants will be assessed from routine hospital medicine administration records. Sponsor does not require any additional records to be maintained over and above usual local practice for traceability purposes for those assigned to the intervention arm.

8.11 Name and description of each Non-Investigational Medicinal Product (NIMP)

The comparator for the CLASP study will be usual non-macrolide antibiotic care according to local hospital guidelines. Therefore, there will be no NIMPs in the study.

8.12 Usual care

Usual care will likely vary between sites but should not include macrolide antibiotics. All participants will receive antibiotics as part of usual care and this will often be a penicillin. If a participant in the usual care arm develops a clinical indication for macrolide antibiotics and these are needed for clinical reasons, they can continue in the study but this will be recorded.

9 PHARMACOVIGILANCE

9.1 Definitions

Term	Definition

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions. It is important to note that this is entirely separate to the known side effects listed in the SmPC. It is specifically a temporal relationship between taking the drug, the half-life, and the time of the event or any valid alternative aetiology that would explain the event.
Serious Adverse Event (SAE) Note: SAEs are further defined in section 9.2 in line with risk adaptation for this trial	A serious adverse event is any untoward medical occurrence that: • Results in death • Is life-threatening • Requires inpatient hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability/incapacity • Consists of a congenital anomaly or birth defect Other ‘important medical events’ may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences, e.g. emergency interventions within A&E departments that do not result in hospitalisation such as administration of glucagon/glucose in participants with hypoglycaemia. NB: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the reference safety information.

NB: To avoid confusion or misunderstanding of the difference between the terms “serious” and “severe,” the following note of clarification is provided: “Severe” is often used to describe intensity of a specific event, which may be of relatively minor medical significance. “Seriousness” is the regulatory definition supplied above.

9.2 Operational definitions for (S)AEs

Clarithromycin has been in clinical use for more than 30 years and is widely used for the treatment of respiratory tract infections, including community acquired infection. The IMP is generally well tolerated with the most common side effects being mild gastrointestinal adverse reactions. It has a well-defined safety profile obtained throughout the lifetime of the drug and therefore it is highly unlikely that this trial will identify any novel (serious) adverse reactions. Participants are anticipated to exhibit complications related to the index stroke, associated complications, and comorbidities resulting in prolongation of hospitalisation and high numbers of adverse events due to the short time frame between the index stroke and the commencement of treatment with IMP. In addition, participants may receive multiple treatments to manage stroke symptoms, and associated underlying medical conditions. Under these circumstances, participants may be subject to multiple ongoing adverse events and serious adverse events and it may be difficult for investigators to distinguish AEs and SAEs that are a consequence of disease processes and concomitant medications from those that have a causative relationship with the IMP(s) due to a high level of confounders. Taking the above into account, (S)AEs (except for those detailed below) will not be reported via the eCRF but must be recorded within participant medical records in accordance with GCP.

The principal risk associated in adding clarithromycin to the usual care pathway is the potential for prolongation of the QT and QTc interval resulting in cardiac arrythmias; primarily ventricular arrythmias. In addition, treatment with antimicrobial therapies, including macrolides, can be associated with an increased risk of developing infection with *C.difficule.* While cardiac arrythmias and *C.diff* infections may not necessarily always meet the regulatory definition of serious, they will almost certainly require intervention to prevent them from become so and are significant medical events.

Therefore, the following events will be subject to expedited reporting as serious adverse events from the point of randomisation until day 3 post cessation of trial IMP (generally, day 7 or earlier but could be up to day 10 after randomisation):

- Any suspected or confirmed infection with *C.difficile* irrespective of whether the event meets the regulatory definition of serious.
- Any incidence of sustained (>30s) ventricular arrythmias irrespective of whether the event meets the regulatory definition of serious.
- Any serious adverse event suspected to be directly related to the IMP that is considered unexpected by the local investigator.

Note: If an event occurs more than 72 hours after cessation of IMP that is considered related to IMP, it must be reported.

Hospitalisation, or prolongation of hospitalisation, related to the index stroke and associated complications, or other underlying medical conditions are excluded from reporting as a serious adverse event for the purpose of this trial. Such events should be recorded within the eCRF at visit 2 and visit 3 (day 90) as per routine data collection and will be used to inform trial endpoints. The IDMC will review event rates on a regular basis to ensure the frequency of these events is line with expectations.

The following are exempted from recording within the eCRF and reporting as SAEs:

- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- Treatment that is elective or pre-planned, for a pre-existing condition not associated with any deterioration in condition, e.g. pre-planned hip replacement operation which does not lead to further complications.
- Any admission to hospital or other institution for general care where there was no deterioration in condition.
- Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious as given above and not resulting in hospital admission.

9.3 Recording and reporting of Adverse Events

All AEs from the time of consent until 2 days post cessation of IMP that are observed by the Investigator or reported by the participant will be recorded in the participant's medical records.

In accordance with section 9.2, any confirmed or suspected *C.difficile* infections or ventricular arrythmia occurring from the point of consent until day 3 post cessation of trial IMP (generally, day 7 or earlier but could be up to day 10 after randomisation) must be reported in accordance with section 9.4.

9.4 Recording and Reporting of Serious Adverse Events (SAEs)

9.4.1 Initial reports

All SAEs as defined within section 9.2 must be recorded within the study eCRF from the point of informed consent until day 3 post cessation of trial IMP (generally, day 7 or earlier but could be up to day 10 after randomisation).

Protocol defined SAEs must be reported within the eCRF within 24 hours of investigator or study team awareness of the event.

Full details of these SAEs will be recorded in the eCRF. The following information will be collected at a minimum:

- Nature of the event
- Event duration (start and end dates, if applicable)
- Relationship to trial medication in the opinion of the investigator
- If related, whether the reaction would be considered expected or unexpected
- Action taken
- Outcome (if applicable)
- Seriousness criteria

All protocol defined SAEs will be subject to review by the local Principal Investigator, or their medically qualified designee(s), within 7 days of the site becoming aware of the event for fatal or life-threatening SAEs and within 15 days for all other SAEs.

Any change of condition or other follow-up information should be added to the eCRF as soon as it is Serious Adverse Events must be followed up until the event has resolved or a final outcome has been reached.

9.4.2 Review and follow up of SAEs

Where there is a change in causality, a worsening in the severity, increase in seriousness, or worsening in outcome of an event, then the local investigator is expected to re-review the event within the timelines detailed above. Significant changes in diagnosis, and any additions to the narrative that imply the need for further clinical review may also require re-review by all parties.

9.5 Assessment of Serious Adverse Events

All SAEs reported as per section 9.2 must be assessed for severity, causality and expectedness with reference to this protocol and the Reference Safety Information (RSI).

9.5.1 Assessment of seriousness

An adverse event will be considered serious if it:

- Results in death
- Is life threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Intervention is required to prevent one of the above

9.5.2 Assessment of severity

This should be assessed and described using the following categories:

- Mild - awareness of event but easily tolerated
- Moderate - discomfort enough to cause some interference with usual activity.
- Severe - inability to carry out usual activity

NB: “Severe” is often used to describe intensity of a specific event, which may be of relatively minor medical significance. “Seriousness” is the regulatory definition supplied above.

9.5.3 Assessment of causality

i.e. Does the event have a “reasonable causal relationship” with trial medication. A binary Yes/No decision will be used for the assessment of causality.

SAEs will be submitted with a provisional assessment of causality by the reporting investigator. Following this initial submission SAEs must be reviewed for causality by the Principal Investigator, or their medically qualified designee(s) as soon as possible and within 5 days of the site becoming aware of the event for fatal or life-threatening SAEs and 10 days for all other SAEs.

9.5.4 Assessment of expectedness

If the SAE is suspected to be related to IMP, an assessment should be made of the expectedness of the reaction, i.e. is the reaction a recognised adverse effect of the medication.

The Chief Investigator and/or the Sponsor PV Manager (or their delegates) are responsible for the assessment of expectedness of all SAEs deemed to be related to the IMP.

The expectedness of an adverse reaction is assessed against the Reference Safety Information (RSI), i.e. the information regarding expected reactions approved by the MHRA.

Expected events are those consistent with the relevant product information documented in the RSI, i.e. a Serious Adverse Reaction.

Unexpected events are those not consistent with the relevant product information documented in the RSI, i.e. a Suspected Unexpected Serious Adverse Reaction.

9.6 Reference Safety Information

The approved RSI for clarithroymycin in place at the time an SAE occurs will be used to assign expectedness of related events. This will be based on the SmPC for clarithromycin 500mg powder for solution for infusion vials (Bowmed Ibisqus Limited).

9.7 Recording and reporting of SAEs where eCRF web portal access is not possible

If recording in the eCRF is not possible, e.g. problems with the web portal, then a paper SAE form should be completed.

The SAE form is downloaded from https://www.glasgowctu.org/Home/00-safety-reporting/, printed, completed and signed. The form should be scanned and emailed to pharmacovig@glasgowctu.org. If this website is unavailable, a paper copy of the SAE form template is provided in the Investigator Site File.

9.8 Suspected Unexpected Serious Adverse Reactions (SUSARs)

Any SAE assigned as related by the local investigator, and determined to be unexpected by the CI or Sponsor, will be classified as a SUSAR and subject to expedited reporting to the Medicines and Healthcare products Regulatory Agency (MHRA) and the Research Ethics Committee (REC). If the CI disagrees with the PI's causality assessment, both opinions will be provided on the report.

The Sponsor PV Office will inform the MHRA and the REC of a notifiable SUSAR within the required timescales:

- Fatal or life threatening SUSARs: not later than 7 days after the sponsor had information that the case fulfilled the criteria for a fatal or life threatening SUSAR, and any follow up information within a further 8 days.
- All other SUSARs: not later than 15 days after the sponsor had information that the case fulfilled the criteria for a SUSAR.
- The sponsor will report SUSARs to the MHRA via the ICSR reporting system and to REC by email with accompanying CTIMP Safety Report Form.

9.9 COVID-19 vaccination and reporting

Where a deployed COVID-19 vaccine is suspected to be involved in the onset of a reported event, it should be recorded as a concomitant medication. A causal relationship between the vaccine and the event, including potential drug interactions should be assigned by the reporting investigator.

If a reported event is suspected to be due to a deployed COVID-19 vaccine alone, reporting investigators should ensure that standard Yellow Card reporting procedures are followed.

9.10 Notification of deaths

All deaths must be recorded within the eCRF. Where the death has a causative relationship with the IMP, it must also be reported as per section 9.2.

9.11 Reporting urgent safety measures

If any urgent safety measures are taken, the CI/Sponsor will phone the MHRA's Clinical Trials Unit on 020 3080 6456, ideally within 24 hours. This will be followed up no later than 3 days from the date the measures are taken, giving written notice to the MHRA (who will advise the format required) and the relevant REC of the measures taken and the circumstances giving rise to those measures. A substantial amendment must also be submitted to the MHRA.

9.12 Developmental Safety Update Reports

A Development Safety Update Report (DSUR) will be submitted once a year, or on request, to MHRA and REC until the trial is declared ended. The report will be submitted within 60 days of the anniversary of the issue of the Clinical Trials Authorisation for the trial. The DSUR will be prepared by the Sponsor in liaison with the CI,and submitted by the Sponsor.

9.13 Pregnancy

Pregnancy is an exclusion criterion for the CLASP trial. If a participant with an undetected pregnancy is enrolled, or in the event of a pregnancy occurring up to Day 90, these are to be reported to the Sponsor using the pregnancy form (https://www.glasgowctu.org/Home/00-safety-reporting/).

Pregnancy is not in itself considered to be an adverse event, unless a negative or consequential outcome is recorded for the mother or child/foetus and this would be considered an SAE and must be reported as per SAE reporting procedure above.

Any pregnancy occurring in a female trial participant or female partner of a male trial participant who becomes pregnant while participating in the trial will be reported by the PI (or designee) to the Chief Investigator and the sponsor using the pregnancy form within two weeks of the PI first becoming aware of the pregnancy.

The pregnancy will be followed up for outcome, and the outcome reported to the Sponsor.

9.14 Overdose

An overdose will be defined as any dose administered above the trial specific parameters.

An overdose can be identified from the participant's medication charts and will be recorded in the protocol deviation log.

Any overdose must be reported to the trial centre with or without associated adverse events using the serious adverse event forms according to the timelines detailed above and local guidelines.

9.15 Responsibilities

This section details the responsibilities for reporting and reviewing safety information arising from the trial.

9.15.1 Data Centre

The Data Centre will:

- Provide an eCRF for central data collection of ARs and SAEs
- Coding of events using MedDRA, where required
- Provide the Sponsor PV Office with read-only access to relevant data and reporting facilities in the study database
- Provide reports, including safety information, to the independent oversight committees identified for the trial (TSC and IDMC).

9.15.2 Principal Investigator (PI)

- Checking for AEs and ARs when participants attend for treatment/follow-up
- Ensuring that AEs are recorded in line with the requirements of the protocol
- Using medical judgement in assigning seriousness, causality, and severity of events with reference to the trial protocol and Reference Safety Information

9.15.3 Chief Investigator (CI) and Co-CI

- Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk/benefit.
- Using medical judgement to determine expectedness of SAEs.
- Preparing the clinical sections and final sign-off for the Development Safety Update Report (DSUR).

9.15.4 Sponsor

- Verification of data collection, AEs, SAEs, SARs and SUSARs according to the trial protocol
- Reporting safety information to the CI or delegate for the ongoing assessment of the risk/benefit
- Ensuring that SAE forms are completed fully and the data contained therein has been fully sense checked
- Reviewing the expectedness of SARs with reference to the RSI and reviewing all events related to the IMP or trial specific procedures
- Expedited reporting of SUSARs to the Competent Authority (MHRA in UK) and REC within required timelines
- Notifying Investigators of SUSARs that occur within the trial
- Checking for (annually) and notifying PIs of updates to the Reference Safety Information for the trial
- Preparing standard tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the MHRA and REC.

9.15.5 Trial Steering Committee

In accordance with the TSC Charter, periodically reviewing recruitment and the overall progress of the trial and liaising with the IDMC and sponsor regarding safety issues.

9.15.6 Independent Data Monitoring Committee

In accordance with the IDMC Charter, periodically reviewing safety data in individual cases and to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis, reporting concerns to the TSC and sponsor.

10 STATISTICS AND DATA ANALYSIS

10.1 Sample size calculation

In our preliminary study of antibiotic classes [36] based on observational data we reported a common Odds Ratio (OR) of approximately 0.5 for those receiving macrolides. This observation was not a pre-specified hypothesis. We have applied the 'rule of thumb' to target an effect size that is half that observed in such circumstances. Working on the log OR scale, half the effect size can be back-transformed to our target OR of 0.7.

A sample size of 524 participants per group would give 90% power at a two-sided 5% significance level to detect a common OR of 0.7. This is based on analysis by ordinal logistic regression of the mRS at 90 days, assuming the distribution of 90 day mRS in the control arm to be 2:8:8:5:20:20:37 across mRS 0-6. We propose an adaptive (group sequential) design, with an interim analysis after 50% have provided primary outcome data. If the interim analysis z-statistic for the treatment effect is less than -3.09 (i.e. is in favour of clarithromycin at a one-sided $p<0.001$), then we shall stop the trial for efficacy. If the interim analysis statistic is greater than -0.5, we shall stop for futility. Otherwise, we shall complete the trial as planned, without adjustment of the final analysis p-value.

Simulations of this approach under alternative assumptions regarding the true common OR (N=10,000 simulated trials at ORs from 0.5 to 1.0) suggest that there is minimal loss of power, and no inflation of the Type I error rate (see Table 3 below). Under the null hypothesis of no treatment effect, the one-sided probability of a false positive result is 0.025, slightly lower than running the full trial (0.026), and there is a 69% probability that the trial will stop early for futility, leading to an expected total sample size of 685. If the true OR is equal to 0.7 (the target value

for the sample size calculation), the power of the adaptive design is 88.3%, close to that achieved by running the full trial (89.8%), but with 25.5% chance of trial stopping early (21.7% for efficacy, 3.8% for futility), the expected sample size is 914. Should the true common OR be 0.5 (as observed in observational studies), the adaptive approach gave a positive result in all simulated trials, with 91.7% stopping early, leading to an expected sample size of 568 (Table 3).

Odds ratio	Standard Approach		Adaptive Approach			
	Sample Size	% Positive Trials	Mean Sample Size	% Positive Trials	% Stopped (Futile)	% Stopped (Effective)
0.5	1048	100%	568	100%	0.0%	91.7%
0.6	1048	99.7%	750	99.5%	0.2%	56.7%
0.7	1048	89.8%	914	88.3%	3.8%	21.7%
0.8	1048	51.6%	929	50.1%	17.9%	4.7%
0.9	1048	15.5%	819	14.8%	43.1%	0.7%
1.0 (Null Hypothesis)	1048	2.6%	685	2.5%	69.3%	0.1%

Table 3: Results from 10,000 simulated trials at assumed common odds ratios of 0.5, 0.6, …, 1.0.

We feel that if the interim analysis is strongly in favour of clarithromycin, then there is no ethical reason to continue the trial, for example, to gain better information about treatment safety, since the trial treatment has a well-known safety profile. We believe that a trial of 524 patients with a strong treatment effect benefit will be sufficient to convince the majority of the medical community of the benefit of this treatment. Similarly, should the interim results appear futile, then there is no value in continuing to recruit additional patients.

We will recruit a total of up to 1166 participants to allow for up to 10% attrition.

10.2 Planned recruitment rate

In the 18-month internal pilot phase we aim to recruit 36 sites (80% of total sites) and 246 participants (21% of the total sample) at a rate of 0.55 participants/site/month during the first 6 months and 0.76 participants/site/month for the remaining 12 months.

Following the internal pilot phase if criteria are met for progression, the main recruitment phase (27 months) will recruit the remaining additional 9 sites (during the first 6 months) and 920 participants. The trial will aim for a recruitment rate of 0.7 participants/site/month for the additional 9 sites during set-up and 0.8 participants/site/month otherwise.

10.3 Statistical analysis plan

The interim analysis will be carried out according to a detailed Statistical Analysis Plan (SAP). This will be approved by both the TSC and IDMC. The SAP will be written by the trial statistician who will not have access to randomised treatment codes. The interim analysis program will be written and validated by statistical staff without access to randomised treatment codes. The program will be run (using live treatment codes) by a dedicated IDMC statistician who is not otherwise involved with the analysis for the study.

The final analyses will be carried out according to a detailed Statistical Analysis Plan, to be written and approved prior to database lock and unblinding of treatment allocations, according to GCTU SOPs.

10.3.1 Summary of baseline data and flow of participants

Baseline data to be collected is described in section 7.5. Numbers of participants completing each study assessment point will be reported. Numbers of participants completing or not completing the study will be reported, with reasons for non-completion.

10.3.2 Primary outcome analysis

The primary efficacy analysis will estimate the average treatment effect in those randomised to receive clarithromycin, according to the intention to treat principle.

Ordinal logistic regression will be used to analyse the primary outcome (mRS at 90 days). ORs, corresponding 95% confidence intervals and p-values will be reported.

10.3.3 Secondary outcome analysis

Secondary outcome measures will be analysed using the following methods:

- Mortality at 90 days will be analysed using Cox proportional hazards models.
- Any urgent or unplanned re-admission to 90 days and recurrent stroke or vascular events will be analysed using logistic regression.
- Home time, stroke-related health status, health and social care resource use and caregiver burden will be analysed using general linear models.
- EQ-5D-5L at 90 days will be compared between treatment groups using a general linear model adjusted for the baseline EQ-5D-5L.
- Length of stay will be analysed using a negative binomial model.

10.4 Subgroup analyses

Subgroup analyses are planned in relation to:

- Age (<80 v ≥80 years)
- Sex (male v female)
- Baseline NIHSS (<12 v ≥12)
- Pre-morbid mRS (0-1 v 2-3 v 4-5)
- Ethnicity (white v non-white)
- Stroke type (ischaemic stroke v ICH)
- Interval since admission (<72 v 73-168 v 169-336 hours)
- Received thrombolysis (yes v no)
- Received thrombectomy (yes v no)
- Highest recorded CRP concentration prior to starting antibiotics (<75 v ≥75 mg/l)
- Highest recorded NEWS-2 score prior to starting antibiotics (dichotomised at median)

Differences in treatment effects between subgroups will be assessed by extending the primary analysis regression model to include treatment-by-subgroup interactions. Within-subgroup treatment effects estimates will be reported with 95% CIs, interaction p-values will be reported, and results will be presented with a forest plot.

10.5 Adjusted analysis

All analyses will be adjusted for the minimisation variables, baseline age (<80 v ≥80years), stroke severity (NIHSS score <12 v ≥12) and trial centre. Given the large number of centres involved, mixed effects regression models will be used, with trial centre included as a random effect.

10.6 Interim analysis and criteria for the premature termination of the trial

A group sequential approach will be taken. An interim analysis of the primary outcome will be presented to the IDMC after 524 participants (50%) have provided 90-day mRS (primary outcome).

In the event of the following conditions, a recommendation will be made to cease recruitment:

1. A treatment effect estimate with $z<(-3.09)$ (one-sided $p<0.001$ in favour of clarithromycin) on the grounds of efficacy
2. A treatment effect estimate with $z>(-0.5)$ on the grounds of futility

If neither condition is met, recruitment will continue to the original target.

The final primary analysis will be judged at a one-sided p value of $p<0.025$.

10.7 Participant population

Primary efficacy analyses will be undertaken according to the intention to treat principle. Complier average causal effects analysis will be used to estimate the average treatment effect in those treated.

10.8 Potential risk of missing or spurious data

The main analyses will use complete case data. Factors associated with availability of follow-up data will be assessed using logistic regression. Sensitivity analyses will include multiple imputation of missing outcome data.

Data will be gathered from the medical record by investigators. Missing data will be identified and queried by data management on a regular basis.

Participants and consented caregivers will provide their contact details at enrolment for the Day 90 follow-up. Outcome assessors will attempt to contact participants and caregivers to arrange a suitable time to complete the questionnaires. Where possible, data not obtained via telephone follow-up will be gathered from the participants' medical records.

10.9 Other statistical considerations

Interim and final analyses will be carried out according to separate SAPs, written by the trial statistician who will not have access to randomised group allocations. These will be approved prior to unblinded data being seen.

Any deviations to these SAPs (e.g. changes to planned analysis method due to non-compliance with modelling assumptions) will be documented as part of the statistical outputs produced.

10.10 Economic evaluation

Economic evaluation will be performed by the Manchester Centre for Health Economics, University of Manchester. It will compare the cost and outcomes of standard care with standard care plus clarithromycin in PSP from the NHS/Personal Social Services perspective, using established quality criteria [38,39]. The impact of caregiver health and cost burden will also be explored [40].

Within-trial Cost-effectiveness Analysis – Will compare the difference in total health and social care cost and health outcomes for standard care with standard care plus clarithromycin over the study follow-up period (90 days).

Healthcare resource use per participant will be measured at baseline and at day 90 using routine data collection and a purposely designed healthcare services utilisation form (developed with the PPIE Group). Individual-level costs will be created by combining measured resource use with published unit costs. Costs will comprise:

- Secondary care (days spent on stroke unit, rehabilitation wards, general medical wards, intensive care unit, readmissions, Accident & Emergency, outpatient visits)
- Primary care (GP practice visits and phone contacts with the GP practice personnel)
- Time in care homes.

We will collect downstream health and social care costs and informal caregiver costs using an adapted Client Service Resource Inventory (CSRI) [41], combined with an adapted version of the Costs of Family Caregiving in Palliative Care(COFAC tool [42]). The COFAC tool has been shown to be valid, acceptable to caregivers and feasible to administer. The COFAC questionnaire seeks to capture data from a broad societal perspective which includes family caregiver costs. Health outcomes will be expressed as quality-adjusted life-years (QALYs). The EQ 5D-5L questionnaire will be administered to patients (or a proxy score from their caregivers) at baseline and at Day 90, so that QALYs can be calculated for each participant, using the area under the curve method. Following the NICE Reference Case, EQ-5D-5L responses will be converted to EQ-5D-3L utility values [43]. We will collect EQ-5D for caregivers and generate QALYs in the same way.

Generalised linear model regression will estimate the total cost and total QALYs per arm controlling for baseline cost, baseline health utility, and other relevant participant characteristics. Bootstrapping will be used to handle stochastic uncertainty. The incremental cost-effectiveness ratio (ICER) will be calculated if either strategy is not dominated. Missing data will be handled using multiple imputation. Sensitivity analyses will investigate the robustness of the estimated ICER to different analysis assumptions.

Model-based Cost-effectiveness Analysis – Will compare the difference in cost and health outcomes for standard care with standard care plus clarithromycin over a lifetime time horizon (discount rate: 3.5%). A de novo cohort-level Markov model with an embedded decision tree will be developed to simulate the natural history of PSP and the impact of the intervention, with input from patients and clinicians.

Systematic reviews of existing cost effectiveness models in PSP, HAP, CAP and stroke will inform model structure. The Markov model health states will take into account level of disability from stroke using mRS scores [44]. Patient characteristics, transition probabilities, resource use and utilities associated with the two regimens will be taken from the trial population. Transition probabilities, resource use and utilities associated with stroke disease progression will be obtained from published evidence.

A probabilistic base case analysis will account for all input parameter uncertainty simultaneously. We will report total and incremental cost and QALYs, and ICER (if relevant). A cost-effectiveness threshold of £20-30,000 per QALY gained will be used to determine cost-effectiveness. A cost-effectiveness acceptability curve will report the probability of cost effectiveness and incremental net monetary benefit will be derived. Deterministic one-way sensitivity analyses will identify key drivers of cost-effectiveness. Potential scenario analyses include:

1. Alternative mapping methods to estimate EQ-5D-3L utility values from mRS
2. Inclusion of carer utility
3. Inclusion of carer costs.

Subgroup analysis will include stroke type, interval since admission, and whether the patient had received thrombolysis or thrombectomy.

11 DATA MANAGEMENT

11.1 Source data

ICH GCP defines source data as 'All information in original records and certified copies of original records of clinical findings, observations or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.' In this study, the location of the source data will be detailed in Source Data Plans completed by each site. The source data transcribed into the eCRF from the medical records must be accurate and verifiable.

Outcome data for mRS, SIS, EQ-5D-5L and Zarit Caregiver Burden (ZBI-12) will be entered directly into the eCRF by assessors at the central unit carrying out follow-up. The eCRF entry will act as source data for follow-up information.

Where postal questionnaires are required to gather outcome data, paper copies of these questionnaires will be the source data.

11.2 Data collection

An eCRF, developed by the Robertson Centre for Biostatistics, will capture all data required to meet this protocol's requirements. Data will be stored in a MS SQL Server database. Access to the eCRF will be restricted via a study-specific web portal.

Authorised site staff will be able to make entries to their patients' data via the web portal. The Investigator (or their designee) will be responsible for all entries into the eCRF and will confirm that the data are accurate, complete and verifiable excluding the Day 90 visit.

Trained staff assessing Day 90 visit clinical outcomes (centralised and blinded assessments) will be authorised access to the web portal to make entries to the Day 90 visit pages.

Direct access to the web portal will be granted on request to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

11.3 Data validation

Where it is practical, data will be validated at the point of entry into the eCRF. Any additional data discrepancies will be flagged to the investigator and any data changes will be recorded to maintain a complete audit trail (reason for change, date change made, who made change).

11.4 Data security

Robertson Centre for Biostatistics systems are fully validated in accordance with industry and regulatory standards, and incorporate controlled access security. High volume servers are firewall protected and preventative system maintenance policies are in place to ensure no loss of service or data. Web servers are secured by digital certificates. Data integrity is assured by strictly controlled procedures, including secure data transfer procedures. Data are backed up on-site nightly and off-site to a commercial data vault weekly. The RCB has an ISO 9001 quality management system and ISO 27001 for Information Security, and is regularly inspected against the standards by the British Standards Institution.

11.5 Archiving

Study documentation will be archived by the Co-Sponsors at the end of the trial for a minimum period of 25 years.

Medical notes will be archived in accordance with the principles outlined in NHS standard care guidance. As the medical notes are related to research there will be a requirement to retain them for a

period of 25 years. Involvement in the trial should be documented in the participant's medical notes by the local PI or delegated individual and clearly marked with 'do not destroy' and a retention date provided.

Archiving of Site Files will also be for a minimum of 25 years from completion of the trial, and this action will be delegated to the sites in the Clinical Trial Site Agreement that will be put in place between the Co-Sponsors and sites. Sites will be notified by the Co-Sponsors when site files can be archived. Destruction of site files can only take place with the approval of the Co-Sponsors.

12 MONITORING, AUDIT & INSPECTION

Monitoring will be conducted by NHS Greater Glasgow & Clyde (GG&C) monitor(s) in accordance with local SOPs. The level, frequency and priorities of monitoring will be based on the outcome of the completed sponsor and monitoring risk assessment, and will be clearly documented in the monitoring plan which will be approved by the NHS GG&C Research Governance Manager or Lead Clinical Trial Monitor. As standard, monitoring visit(s) will cover site file review, review of informed consent forms (ICFs), Source Data Verification (SDV) and Serious Adverse Event (SAE) review as per monitoring plan objectives.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Research Ethics Committee (REC) review & reports

Before the start of the trial, the CI will seek favourable opinion from a Research Ethics Committee (REC) which has specific competence for adults with incapacity. The REC will review the trial protocol, Informed Consent Forms and other relevant documents.

Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the amendment. It is noted that amendments may also need to be reviewed and accepted by the MHRA and/or NHS R&D departments before they can be implemented in practice at sites.

All correspondence with the REC will be retained and copies kept in the Trial Master File and Investigator Site Files.

An annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended (this is the Chief Investigator's responsibility).

At the conclusion or early termination of the trial, it is the CI's responsibility to notify the REC and document any reasons for a premature termination, in accordance with HRA guidance. A final report will be prepared and submitted to the REC within one year of the conclusion of the trial and will include any publication of results.

13.2 Peer review

The application for funding the study was approved by the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) Programme.

13.3 Patient and Public Involvement and Engagement

The PPIE lead for the CLASP study is a stroke survivor with several years of experience of both public engagement and PPIE in stroke. She has had key leadership roles in previous NIHR-funded studies (STOPtoolkit and CHOSEN) with appropriate support and mentoring. She has shared her lived experience of stroke to undergraduates at the University of Manchester, led on stroke public

engagement activities (e.g. Brain Health Day, Manchester 2023 https://stroke-impact.org/brain-healthday/) and works closely with regional stroke support groups.

During the trial design and funding application, partnership with The Stroke Association's Stroke Voices in Research (SViR) Group ensured that the trial design includes the priorities and views of stroke survivors. Prior to the Stage 1 Application, a PPIE workshop (Workshop 1) was co-developed to establish how stroke survivors and their caregivers would contribute to the proposal. In advance of the workshop, PPIE priorities for the trial design were identified. Workshop 1 comprised 4 stroke survivors and 1 family caregiver and took place online. The PPIE group confirmed the need for a clinical trial, in terms of importance of the unmet need and poor prognosis of patients with stroke-associated pneumonia (PSP). The intervention, where some participants would get extra antibiotics but all participants would still get usual antibiotic and other stroke unit care was felt to be justified. The panel were reassured that randomisation into the trial would not result in delays to patients care. In the workshop, the group considered participant eligibility and how to obtain consent. It was acknowledged that the majority of participants would have relatively severe stroke and many would lack capacity so personal or professional consultee consent would be appropriate in view of the poor prognosis of PSP. Finally, trial outcome measures were discussed. The group felt that the modified Rankin Scale (mRS) was the most appropriate outcome measure, because improving functional outcome rather than reducing mortality alone was considered important. Other outcomes, for example relating to caregiver burden and time spent at home were proposed.

A second workshop was convened in partnership with the Stroke Association SViR group (Workshop 2) which included 5 stroke survivors and 1 family caregiver. In Workshop 2, the panel comments from Stage 1 were reviewed and it was agreed that a more stroke-related patient-reported outcome measure should be included. The Stroke Impact Scale is now included as a secondary outcome measure. The focus of Workshop 2 was how PPIE would contribute to the set-up, delivery and dissemination of the trial. This included in what form the PPIE panel would take, how many PPIE members would be required, ensuring diversity and inclusion, mentoring and training, the main tasks/roles and frequency and method of meeting.

A bespoke PPIE panel for the trial comprising 4 members in total (led by the PPIE lead stroke survivor co-applicant) will be convened. The importance of equality and diversity and balanced representation of age, sex, ethnicity and geography will be taken into account in the recruitment of membership. The PPIE panel will be supported by the trial management team and the Stroke Association SViR team, and will be offered appropriate training tailored to their requirements and needs. The panel will meet regularly (independent of the Trial Management Group (TMG)) to pool expertise, discuss progress pertinent to the PPIE agenda and review their activities and involvement, feeding back to the Chief Investigator and TMG. Specific roles of the PPIE panel will be to:

1. Undertake pro-active engagement with the TMG, which will include feeding back from (and into) the PPIE panel meetings and Trial Steering Committee. An important role will be to review trial recruitment progress to ensure diversity of the recruited participants and included sites and to liaise with regional PPIE groups to publicise the trial as needed.
2. Co-design participant information resources (e.g. Participant Information Sheets) in appropriate formats, including guidance for aphasia-friendly formats.
3. Participate in preparation of regulatory approvals, including attendance at ethics committee meetings to ensure the views and experiences of stroke survivors are incorporated.
4. Dissemination of the study at all stages including strategies to disseminate study results to participants and their families, the stroke community and wider public.

The SviR group felt strongly about consideration of alternative formats for dissemination, including use of social media, podcasts, websites, networks of regional stroke groups and relevant conferences and these will be explored.

13.4 Regulatory compliance

This study will not commence recruitment until the MHRA provides a Clinical Trial Authorisation and it has received a favourable opinion from the REC.

This Protocol and conduct of the trial will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and all relevant amendments.

Prior to site commencing enrolment, the CI and the Principal Investigator or designee will apply for NHS permission from the site's Research and Development (R&D) department.

For any amendment that will potentially affect a site's NHS permission, the Chief/Principal Investigator or designee will confirm with that site's R&D department that NHS permission is ongoing (note that both substantial amendments, and amendments considered to be non-substantial for the purposes of REC and/or MHRA may still need to be notified to NHS R&D).

13.5 Protocol compliance

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used, e.g. it is not acceptable to enrol a participant if they do not meet the eligibility criteria or restrictions specified in the trial protocol.

While every effort must be made to comply with the approved protocol to demonstrate regulatory compliance, it is acknowledged that protocol deviations occur commonly with varying frequency in clinical trials. Protocol deviations are assessed based on their impact to patient safety, data integrity or trial integrity and must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.

Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

13.6 Notification of Serious Breaches to GCP and/or the protocol

Serious breach to GCP and/or the protocol will be defined as a breach which is likely to effect to a significant degree:

1. The safety or physical or mental integrity of the participants of the trial; or
2. The scientific value of the trial.

If a breach occurs during trial conduct that fulfils either of these criteria, the sponsor must be notified immediately. The sponsor will notify the appropriate authorities in writing of any serious breach in accordance with their SOPs.

13.7 Data protection and participant confidentiality

All investigators and trial site staff must comply with the requirements of the Data Protection Act 2018 and the General Data Protection Regulation with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

Personal information collected via the eCRF to enable Day 90 assessments to be carried out will be encrypted and held in a study database separate from the database containing other trial data. Signed informed consent forms will be scanned and securely uploaded into the eCRF and stored with restricted access for study monitoring purposes. Access will be limited to the trial monitoring team wherever possible but it may become necessary for other members of the trial team from NHS Greater Glasgow and Clyde and the University of Glasgow to access this data under certain exceptional circumstances. All members of the trial team are appropriately trained in the use of data collected from participants and will not access this data without reason.

All electronic data will be held securely in accordance with ISO 27001 at the Robertson Centre for Biostatistics, part of the Glasgow Clinical Trials Unit. All Centre staff are required to sign confidentiality agreements and to follow Standard Operating Procedures in accordance with Good Clinical Practice and ISO certification.

The trial data managers, statisticians, or any other staff who will perform data related tasks will only be able to access depersonalised data where the participant's identifying information is replaced by a unique study identifier.

Only those that have been trained and approved will be able to enter or view any data via the web portal. Each site can only see their own patients' data. Consent forms will be stored at the study site in a secure location accessible only to study teams.

13.8 Financial and other competing interests for the Chief Investigator, PIs at each site and committee members for the overall trial management

A log of financial or other competing interests for the CI, PIs and committee members will be held centrally by trial management throughout the trial. The Trial Coordinator will request this information at the site initiation visit and at regular intervals during study conduct, and it will be made available to the Sponsor.

13.9 Indemnity

The Co-Sponsors will ensure that provision has been made for insurance or indemnity to cover the liability of the investigator and sponsor which may arise in relation to the clinical trial in accordance with Part 2 (14) of Schedule 1 to SI 2004/1031.

The substantive employer of the Chief Investigator is the University of Manchester. Provision has been made to cover liability and indemnity for claims made by participants regarding design of the trial protocol, interactions with ethics committees and/or clinical trials authorisation process. Agreements between Co-Sponsors and the University of Manchester will be detailed in a collaboration agreement.

13.10 Amendments

Any change in the study protocol or REC-approved trial documents will require an amendment. Any proposed amendments will be initiated by the CI following discussion with the Sponsor and any required amendment forms will be submitted to the regulatory authority, REC and sponsor.

The sponsor will determine whether an amendment is non-substantial or substantial. All amended versions of the protocol will be signed by the CI and sponsor representative.

Following a substantial amendment, favourable opinion/approval must be sought from the original reviewing REC, MHRA (where appropriate) and Research and Development (R&D) office prior to implementation. The Chief Investigator will be responsible for informing the Trial Management Group of all protocol amendments.

13.11 Post trial care

Study treatment will occur for 5 days alongside participants standard care pathway. Upon completion of study treatment, participants will continue with standard clinical care and no provision for additional care is required.

13.12 Access to the final trial dataset

During the trial and in the period prior to publication of the main study results as described in the protocol, only GCTU will have access to the full dataset. After that period, the Trial Steering Committee will conduct further data analyses for a period of three years. After that time, the Trial

Steering Committee will consider requests from external parties for further analyses of the study data. Proposals that are scientifically well founded and have an academic basis and where relevant data extractions and analyses are appropriately funded will not be refused. These will be considered as collaborative exercises where the contributions related to study design, conduct, database creation and maintenance and data analysis will be recognised in authorship of any scientific publication. The approach we will take will be to minimise any possibility of breach of participant confidentiality. Normally this will be achieved by minimising data travel. However, for the purposes of individual patient meta-analysis and other reasons, data may be transferred to other sites. Such transfer will require assurances on information security systems at the sites that data are to be transferred to and will involve a legal data transfer agreement. A log of all data requests and subsequent data transfers will be held at GCTU.

14 DISSEMINIATION POLICY

14.1 Dissemination policy

The study database will be owned by the University of Glasgow and maintained on behalf of the study investigators, represented by the Trial Steering Committee as it is constituted during and after the trial.

The study protocol and a description of the recruitment experience and participant baseline characteristics will be published before study completion. On completion of the trial, the database will be locked and analysed by staff of the Robertson Centre for Biostatistics, University of Glasgow. A final study report will be prepared and the results will be published in a major medical journal.

For the participating patients, the stroke community and wider public, the progress and complete trial results will be reported to a range of user platforms such as PPIE groups, conferences and on social media. Findings will also be published to a range of websites such as the Stroke Association and Stroke Voices in Research.

14.2 Authorship eligibility guidelines and any intended use of professional writers

The main results of the study will be compiled, written up and published by the study grant holders and others taking responsibility for the study results (e.g. the statistician conducting the final analysis) on behalf of the CLASP investigators. The CLASP investigators will include all site PIs, all committee members and key members of relevant study coordinating groups (including the Sponsor and GCTU). A separate publications policy will be developed.

No professional writers will be used. All grant holders will be included as authors on the main trial publication, provided they meet the International Committee of Medical Journal Editors authorship criteria for manuscripts submitted for publication. Additional authors can be added if they meet these criteria.

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16. APPENDICES

Appendix 1: Definition of women of childbearing potential and contraception requirements

Women of childbearing potential

Women of childbearing potential are defined as those who have experienced menarche; AND not undergone successful surgical sterilisation (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy); AND are not post-menopausal i.e. amenorrhea for ≥12 consecutive months (without another medical cause).

Contraception requirements

Highly effective contraception: Defined as those that can achieve a failure rate of less than 1% per year when used consistently and correctly OR

Such methods include:

- combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
    - oral[1]
    - intravaginal
    - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation[1]
    - oral
    - injectable
    - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion

Other contraception methods with a failure rate of more than 1% per year

- progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action[1]
- male or female condom with or without spermicide
- cap, diaphragm or sponge with spermicide

A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable

1. Patients taking oral contraceptives should be warned that if diarrhoea, vomiting or breakthrough bleeding occur there is the possibility of contraceptive failure.

Appendix 2: Prohibited concomitant medicines

This list is not exhaustive but is based on drugs listed as contraindicated in the SmPC, as 'manufacture advises avoid' in the BNF, and additional drugs identified by the Sponsor to maximise safety. Please refer to the relevant Summary of Product Characteristics or contact the Sponsors for further advice.

Prohibited Medicines
Abemacicib
Alprazolam
Amiodarone
Anti-arrhythmic drugs (e.g. Quinidine)
Astemizole,
Atypical antipsychotics (e.g. quetiapine)
Avanafil
Avapritinib
Axitinib
Bedaquiline
Cabergoline
Carbamazepine
Cariprazine
Ciclosporin
Chloroquine
Cisapride
Colchicine
Crizotinib
Daridorexant
Darifenacin
Disopyramide
Domperidone
Dronedarone
Eletriptan
Ergometrine
Ergot alkaloids – ergotamine and dihydroergotamine

Prohibited Medicines *(cont)*
Everolimus
Fidaxomicin
Fineronone
Grazoprevir
HIV infection drugs. e.g. efavirenz, nevirapine, saquinavir, ritonavir, atazanavir, zidovudine
Hydroxychloroquine
Ibrutinib
Irinotecan
Itraconozole
Ivabradine
Lapatinib
Lercanidipine
Lomitapide
Lurasidone
Methadone
Midazolam
Mizolastine
Mobocertinib
Naloxegol
Nilotinib
Phenytoin
Pimozide
Pimozide
Quetiapine
Ranolazine

Prohibited Medicines *(cont)*
Reboxetine
Rifabutin
Rifampicin
Rifapentine
Rimegepant
Rupatadine
Salmeterol
Phosphodiesterase 5 inhibitors e.g. sildenafil, tadalafil, vardenafil. This applies to concurrent use only.
Sirolimus
Statins / HMG CoA enzyme reductase inhibitors. For purposes of this study, all statins are contraindicated
Tacrolimus
Temsirolimus
Tepotinib
Terfenadine
Theophylline
Ticagrelor
Tolterodine
Valproate
Vardenafil
Verapamil
Vinblastine
Voclosporin

Appendix 3: Medicines with known interactions with clarithromycin but may be used with caution at investigator's discretion

Medicines where there may be drug interactions and caution is advised	Comments
Direct acting oral anticoagulants e.g. dabigatran, rivaroxaban, apixaban and edoxaban	Use concurrently with caution and consider individual risk of bleeding.
Warfarin	Risk of serious haemorrhage and significant elevations in International Normalised Ratio (INR) and prothrombin time when clarithromycin is co-administered with warfarin. INR and prothrombin times should be frequently monitored while patients are receiving clarithromycin and oral anticoagulants concurrently.
Calcium channel blockers eg. amlodipine, diltiazem (note verapamil which is prohibited)	Risk of hypotension. Monitor blood pressure during concurrent use.
Digoxin	May increase digoxin concentrations. Measure digoxin levels during concurrent use.
Insulin	Risk of hypoglycamia. Monitor glucose levels carefully during concurrent use.
Oral hypoglycaemic agents eg, sulphonylurea, nateglinide repaglinide	Risk of significant hypoglycamia. Monitor glucose levels carefully during concurrent use.
Corticosteroids	Potential for increased systemic exposure to corticosteroid. Monitor closely for corticosteroid undesirable effects.
Omeprazole	May increase omeprazole concentrations. Suggest review if concurrent use is needed and use alternative agent.
Cilostazol	May alter cilostazole concentrations. Should be withheld during duration of clarithromycin use.
Oral contraceptives	If diarrhoea, vomiting or breakthrough bleeding occur there is a possibility of contraceptive failure. Women of childbearing potential should use other forms of contraception during clarithromycin use.

Appendix 4: modified Rankin Scale (mRS)

The Modified Rankin Scale (mRS)

(Use web calculator at www.modifiedrankin.com)

0 No symptoms

1 No significant disability; able to carry out all usual activities, despite some symptoms

2 Slight disability; able to look after own affairs without assistance, but unable to carry out all previous activities

3 Moderate disability; requires some help, but able to walk unassisted

4 Moderately severe disability; unable to attend to own bodily needs without assistance, and unable to walk unassisted

5 Severe disability; requires constant nursing care and attention, bedridden, incontinent

6 Dead

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Appendix 5: EQ-5D-5L

Health Questionnaire

English version for the UK

Version 1.0 – 12 December 2024

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

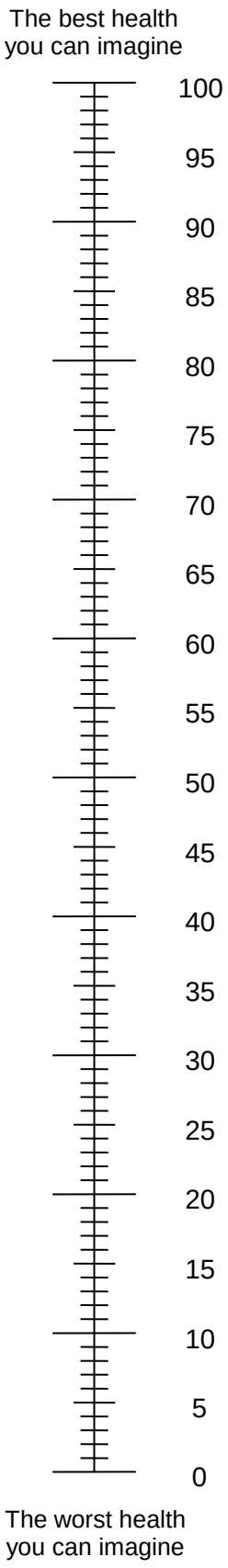
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.
- Please mark an X on the scale to indicate how your health is TODAY.
- Now, write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 6: National Institutes of Health Stroke Scale (NIHSS)

1a Level of Consciousness

Instructions – Level of Consciousness (LOC): The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.

Scale Definition	
0	**Alert;** keenly responsive.
1	**Not Alert;** but arousable by minor stimulation to obey, answer, or respond.
2	**Not Alert;** requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped).
3	Responds only with reflex motor or autonomic effects, or totally unresponsive, flaccid, and areflexic.
	Score

1b Level of Consciousness

Instructions – LOC Questions: The patient is asked the month and his/her age. The answer must be correct — there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.

Scale Definition	
0	**Answers** both questions correctly.
1	**Answers** one question correctly.
2	**Answers** neither question correctly.
	Score

1c Level of Consciousness

Instructions – LOC Commands: The patient is asked to open and close the eyes and then to grip and release the nonparetic hand. Substitute another one-step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (i.e., follows none, one, or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.

Scale Definition	
0	**Performs** both tasks correctly.
1	**Performs** one task correctly.
2	**Performs** neither task correctly.
	Score

2 Best Gaze

Instructions: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV, or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.

Scale Definition	
0	**Normal.**
1	**Partial gaze palsy;** gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present.
2	**Forced deviation**, or total gaze paresis is not overcome by the oculocephalic maneuver.
	Score

3 Visual

Instructions: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to respond to item 11.

Scale Definition	
0	**No visual loss.**
1	**Partial hemianopia.**
2	**Complete hemianopia.**
3	**Bilateral hemianopia** (blind including cortical blindness).
	Score

4 Facial Palsy

Instructions: Ask — or use pantomime to encourage — the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/ bandages, orotracheal tube, tape, or other physical barriers obscure the face, these should be removed to the extent possible.

Scale	Definition
0	**Normal** symmetrical movements.
1	**Minor paralysis** (flattened nasolabial fold, asymmetry on smiling).
2	**Partial paralysis** (total or near-total paralysis of lower face).
3	**Complete paralysis** of one or both sides (absence of facial movement in the upper and lower face).

Score	

5 Motor Arm

Instructions: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN) and clearly write the explanation for this choice.

Scale	Definition
0	**No drift;** limb holds 90 (or 45) degrees for full 10 seconds.
1	**Drift;** limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support.
2	**Some effort against gravity;** limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity.
3	**No effort against gravity;** limb falls.
4	**No movement.**
UN	**Amputation** or joint fusion, explain: _____

Score	5a: Left Arm		5b: Right Arm	

6 Motor Leg

Instructions: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN) and clearly write the explanation for this choice.

Scale Definition	
0	**No drift;** leg holds 30-degree position for full 5 seconds.
1	**Drift;** leg falls by the end of the 5-second period but does not hit the bed.
2	**Some effort against gravity;** leg falls to bed by 5 seconds but has some effort against gravity.
3	**No effort against gravity;** leg falls to bed immediately.
4	**No movement.**
UN	**Amputation** or joint fusion, explain: _____

Score	6a: Left Leg		6b: Right Leg	

7 Limb Ataxia

Instructions: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN) and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.

Scale Definition	
0	**Absent.**
1	**Present in one limb.**
2	**Present in two limbs.**
UN	**Amputation** or joint fusion, explain: _____

Score	

8 Sensory

Instructions: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.

Scale Definition	
0	**Normal;** no sensory loss.
1	**Mild-to-moderate sensory loss;** patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched.
2	**Severe or total sensory loss;** patient is not aware of being touched in the face, arm, and leg.
	Score

9 Best Language

Instructions: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture (p. 11), to name items on the naming sheet (p. 12), and to read from the list of sentences (p. 13). Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.

Scale Definition	
0	**No aphasia;** normal.
1	**Mild-to-moderate aphasia;** some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response.
2	**Severe aphasia;** all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response.
3	**Mute, global aphasia;** no usable speech or auditory comprehension.
	Score

10 Dysarthria

Instructions: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list (p. 12). If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN) and clearly write the explanation for this choice. Do not tell the patient why he or she is being tested.

Scale	Definition
0	**Normal.**
1	**Mild-to-moderate dysarthria;** patient slurs at least some words and, at worst, can be understood with some difficulty.
2	**Severe dysarthria;** patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric.
UN	**Intubated** or other physical barrier, explain: _____
	Score

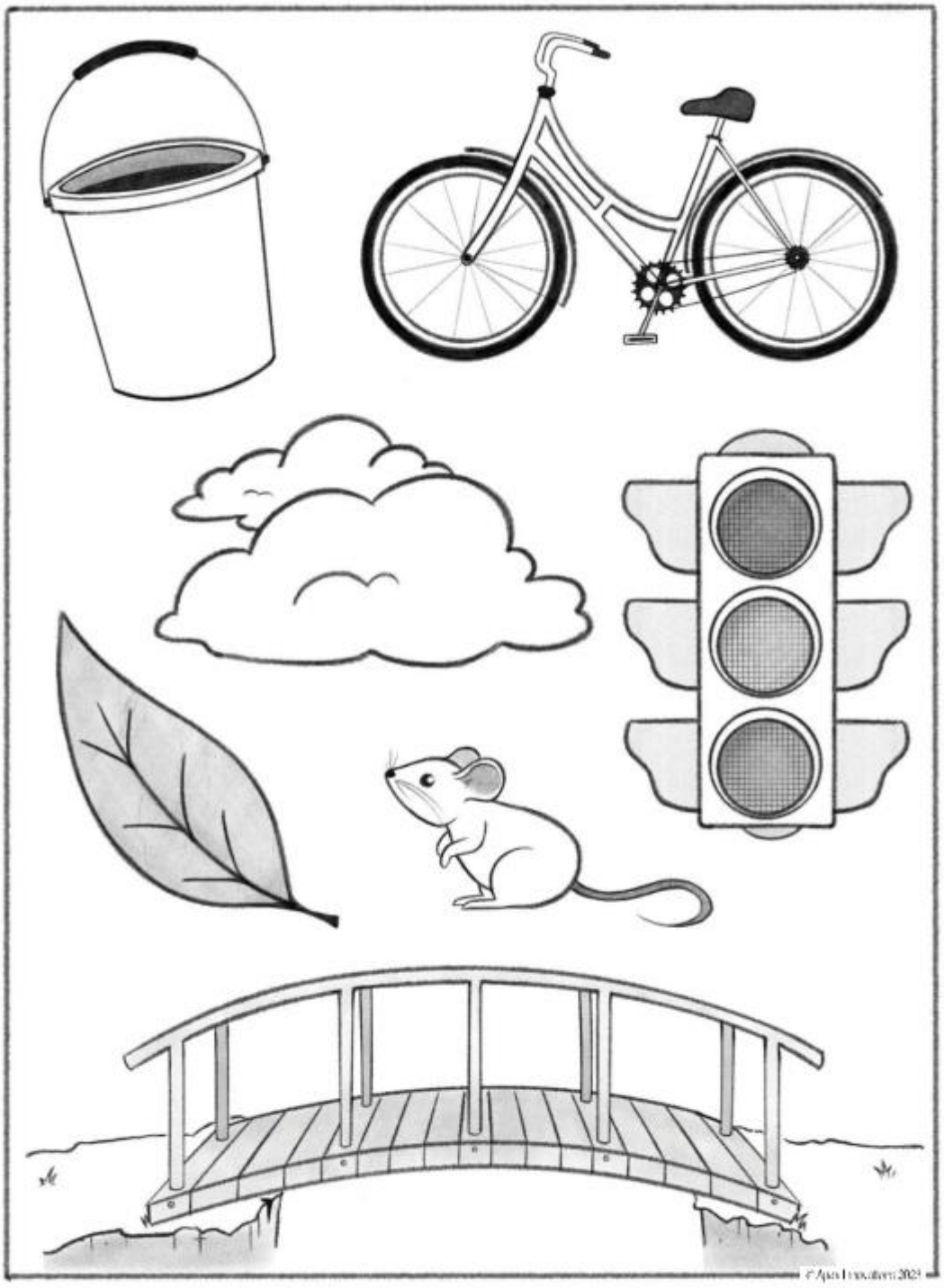
11 Extinction and Inattention

Instructions – Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.

Scale	Definition
0	**No abnormality.**
1	**Visual, tactile, auditory, spatial, or personal inattention,** or extinction to bilateral simultaneous stimulation in one of the sensory modalities.
2	**Profound hemi-inattention or extinction to more than one modality;** does not recognize own hand or orients to only one side of space.
	Score

Total Score of Patient

ITEM	SCORE
1a	
1b	
1c	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
TOTAL SCORE	



MAMA

TIP-TOP

FIFTY-FIFTY

THANKS

HUCKLEBERRY

BASEBALL PLAYER

CATERPILLAR

You know how.

Down to earth.

I got home from work.

Near the table in the dining room.

They heard him speak on the radio last night.

Appendix 7: Short form Stroke Impact Scale (SIS)

In the past week, how would you rate the strength of your leg that was most affected by your stroke? In the past week, how difficult was it for you to think quickly? In the past week, how often did you feel that you have nothing to look forward to? In the past week, how difficult was it to understand what was being said to you in a conversation? In the past 2 weeks, how difficult was it to do light household tasks/chores (eg, dust, make a bed, take out the rubbish, do the dishes)? In the past 2 weeks, how difficult was it to walk without losing balance? In the past 2 weeks, how difficult was it to use your hand that was most affected by your stroke, to pick up a coin? During the past 4 weeks, how much of the time have you been limited in your social activities?
Score each statement from 1 to 5: 1 = Could not do at all; 2 = very difficult; 3 = somewhat difficult; 4 = a little difficult; 5 = not difficult at all.

Appendix 8: Zarit Caregiver Burden (ZBI-12) interview

Zarit Caregiver Burden Assessment **(Short, 12-items)**

Name: _____ Date:_____

The following is a list of statements that reflect how people sometimes feel when taking care of another person. After reading each statement, indicate how often you experience the feelings listed by circling the number that best corresponds to the frequency of these feelings.

	Never	Rarely	Sometimes	Frequently	Nearly Always
1) Do you feel you don't have enough time for yourself?	0	1	2	3	4
2) Do you feel stressed between caring and meeting other responsibilities?	0	1	2	3	4
3) Do you feel angry when you are around your relative?	0	1	2	3	4
4) Do you feel your relative affects your relationship with others in a negative way?	0	1	2	3	4
5) Do you feel strained when are around your relative?	0	1	2	3	4
6) Do you feel your health has suffered because of your involvement with your relative?	0	1	2	3	4
7) Do you feel you don't have as much privacy as you would like, because of your relative?	0	1	2	3	4
8) Do you feel your social life has suffered because you are caring for your relative?	0	1	2	3	4
9) Do you feel you have lost control of your life since your relative's illness?	0	1	2	3	4
10) Do you feel uncertain about what to do about relative?	0	1	2	3	4
11) Do you feel you should be doing more for your relative?	0	1	2	3	4
12) Do you feel you could do a better job in caring for your relative?	0	1	2	3	4

Scoring Instructions: Add Items 1-12 **Total 1-12 (maximum score = 48)** _____

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Appendix 9 – Schedule of Procedures

Procedure	Baseline	Day 7 (+3)	Day 90 (+/-7 for local follow-up)	Day 90 (+/-14 for central follow-up)
Screening	✓			
Review eligibility	✓			
Informed consent	✓			
Data collection*	✓	✓	✓	✓
mRS	✓			✓
Vital signs assessment* (admission to randomisation)	✓			
Vital signs assessment* (randomisation to Day 5)	✓	✓		
Randomisation	✓			
Start of antibiotic treatment	✓			
Safety (SAEs)		✓	✓	
Treatment compliance assessment		✓		
Follow-up*			✓	✓

*See protocol sections 7.5 and 7.6 for full details

Appendix 10: Authorisation of participating sites

Required documentation

Site documentation will be collected in accordance with sponsor SOPs. Required documentation will include but is not limited to:

- CVs for the research team
- Evidence of GCP, protocol and study initiation training
- Contact details
- Delegation log

Procedure for opening a new site

In consultation with participating R&D departments and study teams, a Site Initiation Visit (SIV) will be completed by the trial management team and will involve the CI, trial managers and, where required, members of the sponsor team including monitors, pharmacy and pharmacovigilance. The SIV will be performed as close as possible before local R&D permission is granted. Confirmation of attendance at the SIV will be documented.

Principal Investigator responsibilities

The PI's legal responsibilities will be listed in the Participating Site Agreement. Responsibilities include but are not limited to:

- Attendance at SIV
- Training new members of the trial team in the protocol and its procedures
- Ensuring that the ISF is accurately maintained
- Dissemination of important safety or trial related information to all stakeholders within their site
- Safety reporting within specified timelines

Appendix 11: Amendment history

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made