The Metoclopramide for Avoiding Pneumonia after Stroke (MAPS-2) Trial: a single-blind, randomized controlled trial of metoclopramide for the prevention of pneumonia in patients with dysphagia after an acute stroke

Final Version 1.4

6th March 2023

Short title:	Metoclopramide for Avoiding Pneumonia after Stroke
Acronym:	MAPS-2
EudraCT number:	2021-003853-40
ISRCTN:	40512746
CTA reference:	03057/ 0075 / 001-0001
IRAS Project ID:	290474
Trial Sponsor:	University of Nottingham
Sponsor reference:	21051
Funding Source:	NIHR HTA

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2. SYNOPSIS

Title	The Metoclopramide for Avoiding Pneumonia after Stroke (MAPS-2) Trial: a single-blind, randomized controlled trial of metoclopramide for the prevention of pneumonia in patients with dysphagia after an acute stroke
Acronym	MAPS-2
Short title	Metoclopramide for Avoiding Pneumonia after Stroke
Chief Investigator	Christine Roffe
Objectives	1. To assess whether metoclopramide reduces mortality in patients with dysphagia after stroke 2. To assess whether metoclopramide reduces pneumonia and improves neurological recovery at 14 days 3. To assess whether metoclopramide improves long-term outcomes (6 months) 4. To assess cost-effectiveness and cost-utility
Trial Configuration	Two-arm parallel group single blind randomized controlled trial (Flow Chart) with an internal pilot
Setting	Emergency departments and stroke units of 90 or more NHS hospitals
Sample size estimate	The sample size has been calculated to detect a 20% relative reduction in mortality from 33% in the placebo control group to 26.4% in the metoclopramide group at 6 months (equivalent to hazard ratio = 0.7654) with a power of 90%, using a two-sided log-rank test (Schoenfeld method) with a significance level of 5%, and 1:1 allocation. Assuming patients are followed-up to a maximum of 6 months, 588 deaths need to be observed. This requires 1980 participants (990 per arm) to be recruited. With 5% loss to follow-up, we aim to recruit approximately 2100 participants.
Number of participants	2100
Eligibility criteria	Inclusion criteria 1. Adults ≥ 18 years old with a clinical diagnosis of acute stroke 2. Within 24 hours of symptom onset 3. One of the two below criteria: 3a. Moderate to severe neurological impairment (NIHSS Score ≥ 10), **or** 3b. Dysphagia and NIHSS ≥6, unable to take normal unmodified oral diet or fluids because: (a) Too drowsy to be assessed formally or (b) Failed bedside assessment of swallowing Exclusion criteria 1. Definite or probable pneumonia at screening 2. Contraindications to metoclopramide 3. Clinical indication for regular antiemetic treatment 4. Known cirrhosis of the liver 5. Known severe renal dysfunction (eGFR< 30 ml/min) 6. Pregnant or breast feeding 7. Moribund (expected to die within the next 48 hours) 8. Co-morbid conditions with life expectancy <3 months 9. Inability to gain consent (patient or legal representative) or consent declined
Description of interventions	Intervention: Metoclopramide solution for injection 10 mg/2 ml three times a day by slow IV injection or via nasogastric tube. For participants weighing less than 60 kg the dose will be reduced to 5 mg/1ml three times a day.

	Control: Normal saline solution for injection (placebo control) 2 ml three times a day by slow intravenous injection or via nasogastric tube. Intervention/control treatment will be continued for 14 days or until discharge into the community, whichever is earlier.
Duration of study	Study start date 01.10.2021 Duration for each participant: 6 months Study end date: 30.04.2025
Randomization and blinding	Participants will be individually randomized 1:1 via a web-based interface to metoclopramide or placebo control by minimization using NIHSS, age, mRS, time from stroke onset, and type of trial centre as factors. The trial will be single-blind (blinded assessment of primary outcome).
Outcome measures	Primary outcome All-cause mortality (time-to-event) by 6 months Secondary outcomes at 14 days 1. Pneumonia (clinician diagnosis) 2. Pneumonia (criteria-based) 3. No of days of antibiotic treatment 4. Ability to swallow (DSRS) 5. Neurological recovery (NIHSS Stroke Scale) 6. Quality of life (EQ-5D 5L™) Secondary outcomes at 6 months 1. Functional status (modified Rankin Scale) 2. Ability to swallow (DSRS) 3. Frailty (CFS) 4. Home time (no. of days spent at home rather than in hospital or care home) 5. Quality of life (EQ-5D 5L™) Health economic outcomes 1. Cost per death avoided over 6 months 2. Cost per QALY gained over 6 months 3. Cost per QALY gained over patient lifetime Safety outcomes to the end of treatment (14 days) Oculogyric crises Tardive dyskinesia Adverse events Discontinuations due to adverse events
Statistical methods	The primary analysis will compare time to death between the metoclopramide and placebo control, with analysis according to the allocated treatment regardless of treatment received (intention to treat). A Kaplan-Meier curve will compare the estimated survivor functions between arms. A Cox proportional hazards model will be used to calculate the hazard ratio and 95% confidence interval, censoring participants who have not died by 6 months or who are lost to follow-up. The model will be adjusted for the minimization factors. As a sensitivity analysis, we will repeat the primary analysis by: (i) additionally adjusting for any variables with marked imbalance at baseline and for post randomization factors that are expected to affect outcome and (ii) treating the outcome as binary to obtain between-arm adjusted risk difference and risk ratio along with corresponding 95% confidence intervals. Should there be substantial missing data we will perform sensitivity analysis using imputation representing best and worst-case scenarios, to assess the effect of possible informative censoring, and/or use appropriate multiple imputation procedures for time-to-event data. Non-adherence is likely to be minimal at primary

	follow-up point as efforts will be made to maximize adherence with allocated treatment, but a sensitivity analysis based on complier average causal effect (CACE) will be performed to investigate the effects of adherence. Between-group comparison of secondary outcomes will be based on an appropriate regression model for the outcome (linear for continuous, logistic for binary, and proportional hazards for time-to event), adjusted for the same variables as the primary analysis. The level of significance used for all statistical tests will be 5%, two-tailed ($p < 0.05$).

3. ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
CF	Informed Consent Form
CFS	Clinical Frailty Scale
CI	Chief Investigator overall
CRF	Case Report Form
CSI	Carer strain index
CT	Computed tomogram
DAP	Data Analysis Plan
DMC	Data Monitoring Committee
DSRS	Dysphagia Severity Rating Scale
eGFR	Electronic glomerular filtration rate (a measure of kidney function)
EOT	End of Trial
EQ-5D 5L™	EuroQol 5-Dimension 5-Level quality of life assessment tool
GCP	Good Clinical Practice
HE	Health economic
NIHR	National Institute for Health Research
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
mRS	modified Rankin Scale
NIHSS	National Institutes for Health Stroke Scale
ONS	Office of National Statistics
PI	Principal Investigator at a local centre
PIS	Participant Information Sheet
PPI	Patient and public involvement
REC	Research Ethics Committee
R&D	Research and Development department
SAE	Serious Adverse Event
SAP	Stroke-associated pneumonia
SAR	Serious Adverse Reaction
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee

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5. TRIAL / STUDY BACKGROUND INFORMATION AND RATIONALE

What is the problem?
MAPS-2 addresses prevention of stroke-associated pneumonia (SAP), which occurs in 12% of unselected stroke patients [3] and in 44-69% of stroke patients fed via a nasogastric tube [4][5]. SAP is associated with a 2 to a 6-fold increase in mortality [8] [9][10][11] [12], longer length of stay [7][11][12], and an increase in long-term disability [13][14][15][16]. It is the most common complication of stroke and responsible for over a third of deaths [17].

SAP is most likely in patients with severe strokes (relative risk 6.6 for NIHSS≥10) and dysphagia (relative risk 9.9 [18], odds ratio 8.6 [19]) and usually manifests within 72 hours of admission [20][21]. Early vomiting predicts poor response to antibacterial treatment [18]. Dysphagia screening with modification of oral intake and, if necessary, nasogastric tube feeding, reduces the incidence of pneumonia [22][23]. However, patients fed exclusively via the enteral rather than oral route still develop pneumonia. Indeed, stroke patients who require nasogastric feeding are at very high risk of pneumonia [4][5].

SAP is due to aspiration of regurgitated or vomited gastric and oropharyngeal secretions. This is common early after stroke, especially when the patient is moved, leading to hypoxia [2].

In this study we will assess the effect of early antiemetic treatment (metoclopramide) on pneumonia and mortality in stroke patients with dysphagia in a randomized controlled trial.

Why is this research important?
Stroke is the second most common cause of death worldwide [25], the fourth most common cause of death in England and Wales [26], and the foremost cause of complex disability in the UK [27].

Pneumonia causes more deaths after stroke than the neurological damage [15][17]. It increases length of stay in hospital and affects recovery, leading to greater long-term disability, and increases NHS costs by £5,800 for each patient with SAP [28].

Effective prevention of SAP has the potential to reduce mortality and to improve recovery whilst also reducing the need for antibiotic treatment, a major priority for the NHS [29].

Review of existing evidence for preventing pneumonia after stroke
The most effective intervention is dysphagia screening, which reduces the risk of SAP [19] by as much as 50% [23][30]. Dysphagia screening is now standard care after stroke [31] and is included as a quality marker in the National Stroke Audit. However, SAP remains a problem despite screening, dietary modification and enteral feeding, and new approaches are needed [32]. There are currently very limited alternative strategies to prevent SAP.

A meta-analysis of 5 studies of antihypertensive drugs acting via angiotensin converting enzyme inhibition with 8693 participants showed a significant reduction of pneumonia, probably due to stimulating a dry cough, which is a common side effect of these drugs [33]. However, only medically stable patients beyond the hyperacute phase of stroke were included. Angiotensin converting enzyme inhibitors given within the first two days of stroke may cause hypotension and neurological deterioration [34]. There is no evidence that they reduce pneumonia early after stroke.

Preventative antibiotics have been shown to reduce post-stroke infections overall (mainly urinary tract infections), but are not effective in preventing pneumonia and do not improve clinical outcomes [35]. A small randomized, placebo-controlled study of selective oral decontamination in 203 patients within 24 hours of acute stroke showed a lower incidence of pneumonia [2], but the findings have not been confirmed and the antibiotic paste is not available in the UK.

A recent meta-analysis of enhanced oral care [36] found only weak evidence for the effectiveness of this intervention in reducing aspiration pneumonia, and a randomized controlled feasibility trial comparing chlorhexidine or tooth paste and manual or powered brushing (CHOSEN) is due to start soon in 4 centres in the UK [personal communication C. Smith].

The MAPS pilot study, a single-centre randomized controlled trial of the antiemetic metoclopramide (10 mg three times a day for 21 days) compared to placebo in 60 patients with severe strokes fed via nasogastric tubes, reduced pneumonia significantly (rate ratio 5.2, $p<0.001$) with a signal for lower mortality (odds ratio 0.54, $p=0.29$) [1]. There were also fewer episodes of aspiration, a faster return to normal oral feeding, less hypoxia, fewer days on antibiotic treatment, and lower antibiotic use.

How can metoclopramide reduce the risk of pneumonia after stroke?
In addition to oropharyngeal dysfunction and dysphagia, stroke also affects gastric function, leading to gastroparesis, increased residual volume, reduced lower oesophageal sphincter closure pressures and gastro-oesophageal reflux. This is due partly to the neurological injury itself and partly to circulating stress hormones that affect gastric motility [37]. Lower oesophageal sphincter dysfunction is exacerbated by a nasogastric tube, further increasing the risk of reflux, regurgitation, and micro-aspiration [38].

While vomiting is obvious, and most likely to occur early after the stroke, regurgitation is more common but less apparent. Transient hypoxia may be the only manifestation of aspiration of regurgitated gastric contents [39], and this is most common during transfers between wards, and during the head scan [24], suggesting that motion sickness may be an exacerbating factor. Such micro-aspiration is likely to be more common than appreciated, and could be a major contributor to SAP.

Metoclopramide [40] is a dopamine antagonist with both central antiemetic and gastric prokinetic effects. Centrally, it prevents vomiting via its antagonist action on the chemoreceptor trigger zone in the medulla. In the upper gastrointestinal tract, it antagonizes D2-receptors increasing lower oesophageal sphincter pressure and forward peristalsis of the stomach and duodenum, whilst simultaneously decreasing pyloric sphincter pressure [41]. These mechanisms accelerate gastric emptying, reduce gastric stasis and residual volume, and thus decrease gastro-oesophageal reflux. Through these combined central and peripheral effects, metoclopramide prevents both vomiting and regurgitation. It has an established safety profile, with the main adverse events being reversible orofacial dyskinesia, and – very rarely (0.003%) and only with long-term (months) use – tardive dyskinesia. Use for up to 21 days was found to be safe in the MAPS pilot [1].

Why now?
Admission to a specialist stroke unit reduces mortality [42], mainly due to prevention of post-stroke complications, particularly pneumonia. Better management of dysphagia is likely to be a major determinant of this lower mortality. However, pneumonia remains the main cause of death following stroke, and new approaches are needed [10].

Antimicrobial resistance driven by antibiotic consumption is a growing global health threat [43], and a key issue at the top of the public health agenda worldwide [44]. Prevention of SAP would reduce the need for antibiotics.

The emergence of the Covid-19 pandemic has affected patients and healthcare systems worldwide with a high number of deaths. Stroke patients are at risk of Covid-19 [45] [46], with the infection either preceding or following the stroke. It is currently unclear how prevalent Covid-19 will be by the time this study starts, but some degree of persistence is expected. Co-existence of Covid-19 and SAP is likely to increase mortality significantly. Prevention of SAP is therefore even more important than before.

Metoclopramide has the potential to reduce both pneumonia and death. A large multicentre European study (PRECIOUS) [47] is currently testing metoclopramide, ceftriaxone and paracetamol in a 3x2 factorial design. However, the treatment duration is much shorter than in the MAPS pilot, and participants include mild strokes without dysphagia, who are unlikely to benefit. Furthermore, the other two treatments may affect pneumonia rate and diagnosis, making outcome interpretation difficult.

A large study following the design of the MAPS pilot and focusing on high-risk patients (severe strokes with dysphagia) is necessary to test whether metoclopramide can prevent pneumonia and reduce death after stroke.

6. DETAILS OF INVESTIGATIONAL MEDICINAL PRODUCT

The investigational medical Product (IMP) is metoclopramide, a widely used antiemetic with well-known effects and side effects. [40] [74] It has both central and peripheral antiemetic actions.

Metoclopramide stimulates activity of the upper gastro-intestinal tract and restores normal co-ordination of peristaltic action and sphincter tone through multiple mechanisms including inhibition of postsynaptic dopamine (D2) receptors, and presynaptic D2 and acetylcholine receptors, and stimulation of presynaptic excitatory serotonin (5 HT-4) receptors. Gastric emptying is accelerated and the resting tone of the gastroesophageal sphincter is increased. Metoclopramide also has central actions. It antagonizes both dopamine D2-receptors and serotonin (5 HT-3) receptors with a direct antiemetic effect on the medullary chemoreceptor trigger zone. [76]

Description

International Non-Proprietary Name (INN): Metoclopramide (metoclopramide hydrochloride)
CAS number: 54143-57-6
Formulation and Concentration: Solution for injection (5 mg/ml)
ATC code: A03F A01
Marketing Authorization Holder: The IMP is to be defined by its active substance only. Any brand of metoclopramide authorized in the UK may be used.

Manufacture

Not applicable, as any brand of metoclopramide authorized in the UK may be used.

Packaging and labelling

Standard pharmacy supplies of the IMP will be used. Trial–specific labelling is not required because the IMP does not need any particular manufacturing/packaging process; already has a marketing authorisation (MA) and the subjects in the trial have the same characteristics as those covered by the indication specified in the MA. Therefore it is exempt from trial specific labelling requirements in accordance with Regulation 46 (2) of SI2004/1031.

Storage, dispensing and return

The IMP will be stored below 30°C and protected from light as per medicines' management policies of the participating sites.

Placebo (placebo control)

Sodium chloride 0.9% solution for injection (2 ml) will be used as placebo treatment. The colour and volume of the solution match that of the IMP. Standard pharmacy supplies will be used. Storage will be as per medicines' management policies of the participating sites.

Known Side Effects

Side effects of the IMP (metoclopramide) are based on the SmPC of Hameln Pharma] and listed in Appendix 1.

The main adverse effects are acute dystonic reactions involving facial and skeletal muscle spasms and oculogyric crises. These are rare in adults and can be aborted by injections of antiparkinsonian agents, such as procyclidine, or subside spontaneously within 24 hours after discontinuation. Prolonged administration (months) of metoclopramide can be associated with tardive dyskinesia. This is more likely in the elderly population, and not always reversible after discontinuation of treatment. A review of metoclopramide by the European Medicines Agency [48] concluded that these risks outweighed the benefits of metoclopramide in conditions requiring long-term treatment, such as diabetic gastroparesis, and recommended that metoclopramide should only be prescribed for short-term use (up to five days) [49]. This recommendation was not based on new information on side effects, but rather on the lack of evidence for benefit with long-term treatment. In MAPS-2 metoclopramide will be used to prevent pneumonia, a potentially life-threatening complication of stroke. If the results of the MAPS pilot are confirmed the benefits would greatly outweigh the risks. In the MAPS pilot study [1] no adverse effects were seen, but the study was too small to detect infrequent complications. A recent review of the existing literature suggests that tardive dyskinesia occurs in about 1 in 1000 patient years. [76] For MAPS-2, where 1050 participants are exposed to metoclopramide 1 case would be expected if the treatment were taken for a year, with a proportionally reduced risk if treatment were only for 14 days. It is therefore unlikely to happen in this study. The development of tardive dyskinesia will be reported as a safety outcome and monitored by the DMSC, who will assess the risk and report to the TSC before the end of the pilot phase.

Compatibilities and incompatibilities with other drugs

There are no reported interactions between COVID-19 vaccines and metoclopramide (NICE-BNF) if given concomitantly.
Metoclopramide is predicted to increase the risk of methaemoglobinaemia when given with topical prilocaine, which is used as a topical anaesthetic in dental treatments and for anaesthesia (e.g. EMLA cream). Prilocaine should not be used in participants taking metoclopramide.

Metoclopramide can increase the effects of atracurium, cisatracurium, pancuronium, rocuronium, suxamethonium, and vecuronium. As this is an open study, anaesthetists will be aware of metoclopramide treatment and able to reduce the dose, if they consider this necessary. This is no different than for metoclopramide used for clinical indications.

Metoclopramide can reduce the effect of apomorphine, atovaquone, bromocriptine, cabergoline, levodopa, posaconazole, pramipexole, quinagolide, ropinirole, and rotigotine.

There are no reported incompatibilities or interactions with other antiemetic agents.

Reference Safety Information:

Although any brand of metoclopramide authorized in the UK may be used in this study, we refer to Hameln Pharma Ltd. summary of product characteristics section 4.8 as an exemplar for the RSI.

7. TRIAL OBJECTIVES AND PURPOSE

PURPOSE
To assess whether the antiemetic metoclopramide, given early after stroke onset and continued for 14 days, reduces mortality and prevents pneumonia.

PRIMARY OBJECTIVE
To assess whether metoclopramide reduces mortality in patients with dysphagia after stroke

SECONDARY OBJECTIVES
1. To assess whether metoclopramide prevents pneumonia and improves neurological recovery at 14 days
2. To assess whether metoclopramide improves long-term outcomes (6 months)
3. To assess cost-effectiveness and cost-utility

8. TRIAL/ STUDY DESIGN

Trial Configuration

This is a large multicentre phase III participant-blinded parallel two-arm randomized placebo-controlled trial with an internal pilot.

The internal pilot will run for 9 months and will assess key progression criteria using a red/amber/green traffic light system. The objectives of the internal pilot will be to assess feasibility of site set-up, achievement of projected recruitment rates and adherence. The same processes will be used in the internal pilot and the main phase, and all participants enrolled during the pilot will be included in the final analysis.

	Red	**Amber**	**Green**
Trial recruitment	<50%	50-99%	100%
Recruitment rate/ site /month	<0.5	0.5	0.9
No of sites opened	<34	34-67	≥68
Total no of participants recruited	<133	133-265	≥266
Study withdrawals	>10%	3-10%	2%
Action	Discuss trial viability with TSC and HTA	TSC meeting, protocol review, assess and resolve barriers, consider feasibility of increased recruitment at active sites, review site selection	Continue, but monitor performance regularly

Baseline clinical and demographic data

Data collected at baseline include patient name, unit number, and date of birth (identifiable data kept locally), hospital, inclusion and exclusion criteria, mode of consent, and baseline clinical and demographic details.

Follow-up

Where contemporaneous data can be completed, this will be done for as many individual days as possible up to and including 14 days or on transfer to another hospital/discharge (if this is earlier than day 14. As repatriation sites will also have been registered as data collection sites, patients will still be followed-up on day 14 in person and/or through consultation of medical records and hospital information systems by the local research team. All recruited participants will be followed up at 6 months by telephone or, if this is not possible, by letter/email, by the MAPS-2 central co-ordinating team.

Primary endpoint

All-cause mortality by 6 months (time-to-event)

All-cause mortality will be ascertained by contacting the general practitioner in the first instance. Missing data will be completed with the team who recruited the patient and via linkage with Hospital Episode Statistics and The Office of National Statistics.

Secondary endpoints

Secondary outcomes at 14 days

1. Clinical pneumonia (diagnosed by treating clinician and retrieved from notes and drug charts)
2. SAP (pneumonia diagnosis using standardized diagnostic criteria from the daily log, adjudicated by a blinded panel) [61]
3. Antibiotic use (total number days with antibiotic treatment and antibiotic days for pneumonia)
4. Ability to swallow (Dysphagia Severity Rating Scale Score: DSRS) [59]
5. Stroke severity (NIHSS) [51] change from baseline
6. Quality of life (EQ-5D 5L™) [60]

Secondary outcomes at 6 months

1. Functional status (mRS) [56]
2. Ability to swallow (DSRS) [59]
3. Frailty (CFS) change from baseline [73]
4. Quality of life (EQ-5D 5L™) [60]
5. Home time (no of days spent at home rather than in hospital or an institution) [62]

Health economic outcomes

1. Cost per death avoided over 6 months
2. Cost per QALY gained over 6 months
3. Cost per QALY gained over patient lifetime

Exploratory outcomes

Stroke diagnosis (infarct or haemorrhage) at 14 days
Reperfusion therapies (thrombolysis and/or mechanical thrombectomy) at 14 days
Viral pneumonia (influenza, Covid-19) at 14 days
Other infections at 14 days
Antiemetic use for clinical indications at 14 days
Urinary catheterization [63] at 14 days
Outcomes which have been highlighted as important by patients and carers (sleep, speech, ability to read, mood, memory, eyesight) [73] at 6 months

Caregiver strain (Caregiver Strain Index) [74] at 6 months
Length of hospital stay at 6 months
Whether participants remember which treatment group they were in at 6 months

Safety endpoints

These will be recorded at the end of treatment (14 days) and include:
Oculogyric crises
Tardive dyskinesia
Adverse events
Discontinuations due to adverse events

Stopping rules and discontinuation

There are no formal unblinded interim analyses of treatment effectiveness of patients' clinical outcomes planned, hence no pre-planned design changes or provisions to avoid an inflation of the Type I error rate. An internal pilot phase has been built-in to the trial and stop-go criteria will be assessed after the first 9 months of recruitment.

An independent Data Monitoring Committee (DMC) will be convened and meet regularly to review the data on recruitment and adherence from the internal pilot. The DMC will provide recommendations to the TSC and the Trial Funders in respect of study modification, continuation or termination. The DMC will inform the TSC if, in its view, there is proof beyond reasonable doubt that the data indicate that the trial should be modified or terminated prematurely.

9. RANDOMIZATION AND BLINDING

Enrolment

Patients will be enrolled as soon as possible after hospital admission, and no longer than 24 hours after stroke onset (see section Selection and Withdrawal for recruitment procedures, inclusion and exclusion criteria).

Randomization

Patients who consent (individually or by personal/professional legal representative) to participate in the trial will be randomized by a member of the local research team within 25 hours of stroke onset (this is to allow patients who consented within 24h to be included, mitigating against computer problems between consent and randomization). Treatment allocation will be 1:1 via a secure web-based system, maintained by the Nottingham Stroke Trials Unit, to metoclopramide or placebo control by minimization using risk factors for stroke-associated pneumonia [53] [54] and long-term outcome [55], i.e. National Institutes for Health Stroke Scale (NIHSS) score (6-9, 10-15, 16-20, 20-25,>25); age (<60, 60-80, >80 years); pre-stroke modified Rankin Scale (mRS) score (0-2, >2) [56]; time from stroke onset (0-3, 4-6, 6-9, >9 hours); and type of trial centre (repatriates ≥70%, repatriates 15%-69%, repatriates <15%). Minimization reduces differences in key baseline prognostic variables and improves statistical power [57]. We will incorporate a random element, which ensures concealment of allocation. The allocation sequence will remain concealed until interventions are all assigned and recruitment, data collection, and laboratory analyses are complete.

Age and stroke severity (NIHSS) are key elements of most pneumonia prediction tools in stroke patients, followed by dysphagia (inclusion criterion) and pre-stroke dependence [54]. Time from onset is important as vomiting and aspiration are most common early after the stroke. Mortality and the incidence of pneumonia differ between hospitals in the UK. While some of this is due to case mix [78], aspects of care and treatment may also vary. Type of stroke service affects outcome [58] and is therefore an important minimization variable. The key difference between stroke centres is whether they mostly take local patients and care for them locally to discharge, admit patients from a wide catchment area and repatriate to local hospitals within

72 hours or less, or mixed services where repatriation or transfer for rehabilitation is less common and occurs later. The repatriation hospitals will be identified together with the recruiting stroke centres so that both can be registered as data collection sites, however repatriation sites will not recruit participants. As the IMP is not trial-labelled but can be dispensed from the local site pharmacy, specific trial management and accountability is not applicable. The Day-14 data collection for repatriated participants will be carried out by the research nurse/local investigator in each hospital. Any data from treatment days up to Day 14 will be informative for secondary outcomes, the essential data collection being at day-14.

Blinding

Participants and their families and assessors for the 6-month outcome will be blind to the treatment. Research staff conducting the randomization and prescribing treatment, the pharmacist, the clinical team looking after the patient and research staff conducting the 14 days follow-up will be aware of treatment allocation because this is an open-label trial with no trial-specific labelling and all medical record entries will therefore clearly identify the treatment. The TMG and research staff at the coordinating centre will remain blind to treatment allocation until data collection is complete, statistical analysis plan finalized, and the database is locked. The DMC will have access to data split by treatment group, but will not be informed of group allocation, unless this is specifically requested. The TSC will remain blinded, unless a concern requiring unblinding is raised by the DMC. The TMG and the study statistician will only have access to data relating to the whole cohort. Reports split by intervention (as required by the DMC) will be prepared by an independent statistician in the Nottingham Clinical Trials Unit who will not have contact with participants.

As mortality is an objective outcome, and there are no strong beliefs relating to the effects of metoclopramide that might affect provision of treatment and care by the clinical team if they knew which treatment group the patient is in, open assessment of secondary outcomes with blinded endpoint assessment was chosen as a reliable, pragmatic and cost-effective option. The treatment will be prescribed as MAPS-2 trial drug (metoclopramide) and MAPS-2 trial drug (sodium chloride 0.9%) on the drug chart and referred to as MAPS-2 trial drug in communication with patients and their families. Both metoclopramide and saline are clear colourless liquids. The volume for intravenous injection and nasogastric use will be 2 ml for both metoclopramide and placebo.

Maintenance of randomization codes and procedures for breaking code

Both the IMP and placebo (placebo) are the same volume of a clear liquid. They are both dispensed in ampoules.

As this is an open trial, the clinical team are aware of the treatment allocation and code breaking will not be necessary.

10. TRIAL MANAGEMENT

The trial co-ordinating centre will be based in the Stroke Trials Unit at the University of Nottingham. The trial will be managed by the chief investigator and the trial management group.

Sponsor

This trial is sponsored by the University of Nottingham.

The Chief Investigator (CI)

The Chief Investigator has overall responsibility for the study and shall oversee all study management. The data custodian will be the Chief Investigator.

Trial Management Group (TMG)

The TMG is responsible for the day to day running of the study and will monitor all aspects of the design, conduct, analysis of the data, reporting and dissemination of results, ensuring that the protocol is adhered to and taking appropriate action to safeguard participants and the quality of data collected in the trial. It will report to the trial steering committee and the data monitoring committee. The trial management group includes the CI, co-investigators, the trial manager, a patient representative, the trial statistician, a representative of the sponsor and other project staff. It will meet monthly, or more frequently if required.

Data Monitoring Committee (DMC)

An independent data monitoring committee will be appointed to assess the progress of the clinical trial, safety data, and the critical efficacy endpoints and to recommend whether to continue, modify or stop the trial (as mentioned previously in the section on Stopping rules and discontinuation)They will be provided with safety reports prepared by an independent member of the Nottingham University Clinical Trials every 6 months, or more frequently, if requested. A DMC charter will be prepared with details of membership, terms and conditions, and trial stopping rules. The DMC will include a clinician with expertise in stroke, a statistician and a member with expertise in multicentre clinical trials.

Trial Steering Committee (TSC)

The TSC will comprise of at least 75% independent members: it will provide overall supervision of the trial on behalf of the sponsor and the funder and ensure that the trial is conducted to the standards set out in the Department of Health's Research Governance Framework for Health and Social Care and Good Clinical Practice (GCP). A TSC Charter will detail membership and outline the terms and conditions of operation.

Protocol Contributors

This protocol has been written by the CI and reviewed by the trial manager, the co-investigators, the sponsor, and chairs of the TSC and DMC. All final decisions regarding the trial design, conduct, data analysis and interpretation, manuscript writing and dissemination of results are to be made by the CI in consultation with the co-investigators.

11. DURATION OF THE TRIAL AND PARTICIPANT INVOLVEMENT

Participant Duration

The duration of each participant's involvement in the study will be 6 months.

Study Duration

Study duration will be 48 months.

End of the Trial

The end of the study will be completion of the last 6-month follow-up of the last participant.

12. SELECTION AND WITHDRAWAL OF PARTICIPANTS

Recruitment

Setting

The study will be set in emergency departments and stroke units of ≥90 UK hospitals admitting patients with acute stroke. Participants will be recruited from NIHR Clinical Research Network sites that have dedicated staff to facilitate recruitment and follow-up. Co-adoption on both the Stroke and Injuries & Emergencies portfolios will enable efficient recruitment from the emergency department. Patients will be admitted to the acute/hyperacute stroke unit. Depending on the type of service and degree of recovery, participants will stay on this unit for

the first 14 days, be repatriated to a local hospital within 24-72 hours, transferred to a rehabilitation hospital, once clinically stable, or discharged directly back to home.

Target population

Adult patients admitted to hospital with moderate to severe acute stroke and dysphagia within 24 hours of symptom onset will be recruited. There will be no upper age limit and no exclusion of patients on the grounds of frailty, dependency, sex, race, or religion. Aspiration pneumonia develops early, and often before the nasogastric tube is placed. Many patients have already vomited before they arrive in the stroke unit. It is therefore important to start preventive measures as soon as possible after admission, ideally before moving the patient out of the emergency department. The likelihood of persistent dysphagia can be predicted early from the severity of the neurological deficit, and is highest in those with an NIHSS of 10 or above, which has been chosen as the severity cut-off.

Recruitment

This will be as soon as possible after hospital arrival by a GCP-trained member of the stroke team, the research team, or the emergency department. Hyperacute stroke treatments such as thrombolysis or thrombectomy for ischemic strokes or blood pressure management patients with intracerebral haemorrhage will not be delayed for trial inclusion. For patients with wake-up stroke, the time of onset will be defined by the time they wake up with symptoms. As patients with both ischaemic and haemorrhagic strokes will be eligible for participation, the decision on enrolment will be made based on a clinical diagnosis and a computed tomography (CT) head scan is not required for inclusion. This will allow patients to receive the first dose of the trial treatment before being moved to the CT scan if the scan is not done immediately after arrival. If the condition of the patient changes to requiring palliative care, discontinuation of the trial medication will be at the discretion of the clinical care team.

The investigator or their nominee, e.g. from the research team or a member of the participant's usual care team, will inform the participant or his or her nominated representative (other individual or other body with appropriate jurisdiction) of all aspects pertaining to participation in the study.

If needed, the usual hospital interpreter and translator services will be available to assist with discussion of the trial, the participant information sheets, and consent forms, but the consent forms and information sheets will not be available printed in other languages.

It will be explained to potential participants that entry into the trial is entirely voluntary and that their treatment and care will not be affected by their decision. It will also be explained that they can withdraw at any time but attempts will be made to avoid this occurrence. In the event of their withdrawal, it will be explained that their data collected so far cannot be erased and we will seek consent to use the data in the final analyses where appropriate.

Eligibility criteria

Inclusion criteria

1. Adults (18 years and over) with a clinical diagnosis of acute stroke (WHO definition excluding duration) [50]
2. Within 24 hours of symptom onset (in wake-up stroke the onset is defined as the time the patient awoke or was found)
3. One of the two below criteria:
   3a. Moderate to severe neurological impairment (NIHSS Score ≥ 10) [9] [18] [51][52]**, or**
   3b. Dysphagia and NIHSS ≥ 6, unable to take normal unmodified oral diet or fluids because:
   (a) Too drowsy to be assessed formally or
   (b) Failed bedside assessment of swallowing

Exclusion criteria

1. Definite or probable pneumonia
    a. abnormal CXR suggestive of pneumonia or
    b. focal chest signs with fever ⩾38°C, or
    c. receiving antibiotic treatment at time of presentation
2. Contraindications to metoclopramide
    (a) hypersensitivity to metoclopramide
    (b) epilepsy
    (c) gastrointestinal obstruction, perforation, or haemorrhage
    (d) gastrointestinal surgery within the last week
    (e) Parkinson's disease
    (f) treatment with levodopa or dopaminergic agonists
    (g) phaeochromocytoma
    (h) neuroleptic malignant syndrome
    (i) history of neuroleptic or metoclopramide-induced tardive dyskinesia
    (j) known history of methaemoglobinaemia with metoclopramide or of NADH cytochrome –b5 deficiency
3. Clinical indication for regular antiemetic treatment
4. Known cirrhosis of the liver
5. Known severe renal dysfunction (eGFR< 30 ml/min)
6. Pregnant or breast feeding
7. Moribund (expected to die within the next 48 hours)
8. Co-morbid conditions with life expectancy <3 months
9. Inability to gain consent (patient or legal representative) or consent declined
10. Participants must not be taking part in or be co-enrolled into another CTIMP, device or interventional trial during the trial and follow-up period, other than the TICH-3 and RECAST-3 trials sponsored by the University of Nottingham.

Patients who are prescribed antiemetics as required rather than on a regular base are eligible for inclusion.

Where there is a possibility that a woman of childbearing age may be pregnant, if willing to participate, she will be consented for a pregnancy test to verify her eligibility for inclusion.

Expected duration of participant participation

Study participants will be participating in the study for 6 months.

Removal of participants from therapy or assessments

Withdrawal

Participation in the trial is voluntary. Participants are free to withdraw from the trial at any time without giving a reason. However, participants will be asked whether withdrawal relates to the treatment alone, or follow-up, or to any trial-related procedure. The participant will be asked if they wish to withdraw from any or all of: IMP treatment, follow-up with participant contact, or follow-up without participant contact. Unless the participant withdraws from follow-up, this will be continued as per protocol. If the participant declines continued personal participation, but allows data collection from other sources (such as the general practitioner and hospital databases), follow-up data will be collected via this route. If the participant is temporarily withdrawn from trial medication by a member of the clinical team he or she may return to the trial treatment within the original timescale.
If the condition of the participant deteriorates and care changes to palliation, discontinuation of the trial medication will be at the discretion of the clinical care team. Withdrawal, and the

reasons for withdrawal, if given, will be documented in the CRF. Participants will be made aware that withdrawal will not affect their medical care and non-trial follow-up.

Participants will be made aware (via the information sheet and consent form) that should they withdraw the data collected to date cannot be erased and may still be used in the final analysis.

Participant removal from the trial due to adverse events

In any participant who experiences an adverse event the trial medication may be withdrawn permanently or temporarily halted at the discretion of the Local Investigator. Should the participant not receive the complete intervention, they will remain in the trial and be followed up until the end of the trial, as completeness of follow-up is essential.

Loss to follow-up

Every effort will be made to trace participants lost to follow-up. Hospital databases, records from the general practitioner and details of third persons given by the participant will be checked to determine whether the participant is alive, what his or her health status is, and whether there are any new contact details. Participants will not be accepted as lost to follow-up unless phone calls, letters/emails have been fruitless.

Replacement

Enrolled participants who are not yet randomized can be replaced (though keeping their trial ID), but participants who withdraw after randomization will not be replaced.

Informed consent

Informed consent will be sought from patients after full and adequate oral and written information about the design and purpose of the trial, potential risks and benefits, and the right to refuse and to withdraw at any time has been provided. As we are recruiting patients with moderate-to-severe strokes to this study, it is anticipated that few will be able to give fully informed consent within the 24-hour recruitment window due to confusion, anxiety or potential cognitive impairment from the stroke. In cases where the patient does not have capacity to consent, every attempt will be made to seek consent from a personal representative first. In Scotland, a welfare attorney/guardian would be sought initially and then the nearest relative. In England/Wales/N Ireland, a person can act as a personal representative by virtue of their relationship with that adult i.e. a relative or person close to the participant (but not a professional carer) who would know what their feelings would be in this situation. A professional legal representative will only be approached for consent only after every attempt has been made to contact a personal legal representative. As the personal legal representative may equally be stressed by the situation a short, pictorial version of the information sheet and consent form will be used for patient and their representative to facilitate explanation and gain initial consent. However a longer, more detailed information sheet will also be offered at the same time for a fuller evaluation of the trial.

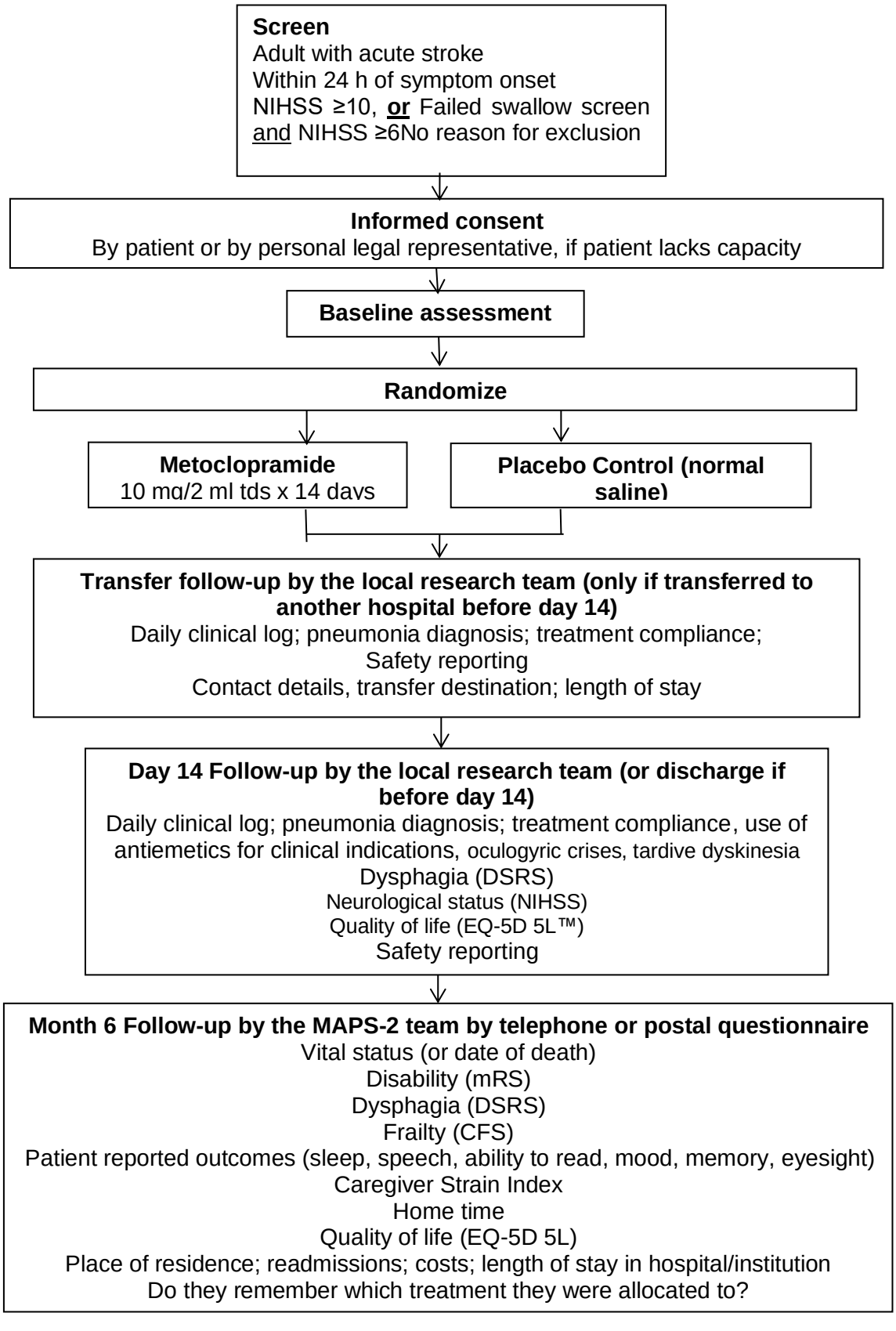
Similarly, as the time frame for enrolment is short, and it is not always possible for the personal or professional legal representative to attend in person for the consent procedure, witnessed verbal consent via the telephone will be accepted. This is particularly important if access to hospital is restricted due to Covid-19 or other emergencies. Nevertheless, written consent will still be obtained as soon as possible thereafter even if the participant is repatriated as this will be clearly noted in the transfer documentation. If the patient has capacity to consent but is unable to sign because of impairments, oral consent, witnessed and signed by an independent observer, will be documented. Where the patient has capacity to consent, but is only able to make a mark on the paper rather than sign as required, the same procedure will be followed. Informed consent will be obtained for all participants before they undergo any interventions related to the study. One copy of the consent will be kept by the participant, one will be kept by the Investigator, and a third will be retained in the patient's hospital records.

Confirmation of consent will be sought in patients who are recruited with consent from a personal or professional legal representative, but regain capacity to consent prior to the end of the trial. Transfer documentation will note that this needs to be done by the local research investigator at a repatriation site.

Should there be any subsequent amendment to the final protocol, which might affect a participant's participation in the trial, continuing consent will be obtained using an amended consent form, which will be signed by the participant.

13. TRIAL TREATMENT AND REGIMEN

This schematic diagram summarises the screening, procedures and stages, randomization, trial treatments, baseline and intermediate visits, final visit, and long-term follow-up.



Study Treatment

IMP: Metoclopramide hydrochloride (5 mg per 1 ml solution for injection) 2 ml (10 mg) to be given iv or via nasogastric tube three times a day for 14 days or until discharge into the community, if this is before 14 days. Reduce dose to 1 ml (5 mg) if body weight < 60 kg.

Control: Sodium chloride (0.9% solution for injection for injection) 2 ml to be given iv or via nasogastric tube three times a day for 14 days or until discharge into the community, if this is before 14 days. Reduce dose to 1 ml if body weight < 60 kg.

Both the IMP and the control will be administered in the same way. The first dose will be given by slow intravenous injection over 3 minutes. All other doses should be given via the nasogastric tube (if in place). If the nasogastric tube is not in place or not usable, metoclopramide will be given by slow intravenous injection over 3 minutes.

As the trial IMP will be non-branded and available at any hospital pharmacy, repatriated participants will continue to be given the trial medication as recorded in the transfer documentation. Where data can be completed contemporaneously for each of the 14 days of treatment, it will be done so. However data for all participants will be collected at day-14 and at 6 months. Confirmation that the patient is still alive will be sought from the GP or the Office for National Statistics. Then the 6 months' follow-up will be conducted by telephone or, if this is not possible, by letter/email, by the MAPS-2 central co-ordinating team.

All imaging performed for this study is part of standard clinical care. No additional scans or x-rays will be requested.

Concomitant and Rescue Medications and Treatments

Patients with stroke tend to be on multiple medications and treatments. These will be continued and adjusted according to clinical need at the discretion of the treating clinician.

New prescriptions of antibiotics will be recorded on the CRF at the 14 day follow-up.

Metoclopramide can induce acute dystonic reactions involving facial and skeletal muscle spasms and oculogyric crises. These usually subside within 24 hours of stopping it. Injection of an antiparkinsonian drug such as procyclidine 10 mg iv can be used to abort dystonic attacks.

Interactions with concomitant medications are listed under the earlier section 6 (details of the investigational medicinal product).

Compliance

The trial treatment is prescribed in the drug chart, and administration of each dose is recorded as per normal clinical practice. This will be continued even if the participant is repatriated.

Compliance will be considered acceptable if 80% or more of the trial drug (17-21 doses for those in hospital for the full 14 days, or 80% of the doses required until discharge for those discharged before 14 days).

Accountability for drugs & placebo treatment

Trial treatment will be recorded in the drug chart as per the standard care procedures of the participating site and documented in the CRF.

Management of study drug overdose

Extrapyramidal disorders, drowsiness, a decreased level of consciousness, confusion, hallucination and cardiorespiratory arrest may occur following overdose.

In case of overdose, cardiovascular and respiratory functions should be monitored continuously. Symptomatic treatment should be given, as clinically indicated.

If there are extrapyramidal symptoms, related or not to overdose, anticholinergic anti-parkinsonian medicinal products such as procyclidine 10 mg iv may be used to abort dystonic reactions.

Symptomatic treatment and continuous monitoring of the cardiovascular and respiratory functions should be carried out according to clinical status.

14. PROTOCOL DEVIATIONS AND VIOLATIONS

All protocol deviations and violations must be reported immediately to the Chief Investigator by email.

The CI will notify the Sponsor if a deviation or violation has an impact on participant safety or integrity of the trial data. The Sponsor will advise on appropriate measures to address the occurrence, which may include reporting of a serious GCP breach, internal audit of the trial and seeking counsel of the trial committees.

15. CRITERIA FOR TERMINATING THE TRIAL

Stopping of the trial at one centre may be prompted by unacceptable performance in recruitment, or poor compliance with the protocol.

The trial as a whole may be stopped at the request of the CI, the sponsor or the TSC. Stopping of the trial as a whole may be as a result of a formal or informal interim analysis and based on overwhelming evidence of efficacy/inefficacy, major safety concerns, new information, or issues with trial conduct (e.g. poor recruitment, loss of resources).

16. RADIATION EXPOSURE

Details of diagnostic or therapeutic ionizing radiation

All imaging performed for this study is part of standard care. No additional scans or X-rays will be requested.

Standard care usually includes:

1. CT(computed tomography) head scan: one soon after admission, another in some patients after recanalization therapy or to investigate clinical deterioration.
2. Chest X-ray: one on admission, one or more further X-rays as needed to check for pneumonia or correct position of the nasogastric tube.

X-rays of the chest and CT scans of the brain are part of routine care for people who have had a stroke. Participants taking part in this study will not undergo any additional chest X-rays or CT brain scan. These procedures use ionising radiation to form images of the body. Ionising radiation may cause cancer many years or decades after exposure. The chances of this happening to the participant are the same whether they take part in the study or not.

17. LABORATORY ANALYSES

No laboratory analyses will be conducted for this study. However, we will collect the results of tests conducted as part of routine clinical care. These will include full blood count, C-reactive protein, cultures of blood, urine, stool, and sputum, tests for Covid-19, influenza, and other respiratory pathogens.

18. STATISTICS AND DATA MANAGEMENT PLAN

DATA MANAGEMENT PLAN

A University of Nottingham Stroke Unit working practice document (WPD 001) has been developed to describe in detail the procedures for the management and maintenance of quality of all data collected within the trial. This incorporated the whole life-cycle of the trial, from CRF design through to publication of the data, long-term storage and data sharing and will be stored within the Trial Master File. In brief the document comprises**:**

General

Roles and responsibilities of all trial staff (central study team, study committees and participating site) with regard to data management, data access, data entry, data changes and indicating access controls and restrictions. The database will only be accessible to authorised personnel with their own log-in username and password. Accessibility will be restricted to relevant sections of the database according to user but will allow access by more than one user at a time. Access will be granted to the Sponsor, trial monitors, auditors and statutory inspectors on a read-only basis.

Data Capture and Data Queries

The Data Management Plan will detail the CRFs to be used, how these will be disseminated to sites, how sites should send completed forms to the trial coordinating centre or staff and within what timeframes. A record will be kept by the co-ordinating centre or central trial staff of all data queries sent out to participating sites and replies received. Participating sites should be given clear instructions on how to respond to data queries and how to change local records. All alterations to trial data will only be made by personnel authorised to do so and recorded as such on the Site Responsibility/Delegation Log,

Description of Data Entry Validation

All stages of data entry, reporting, exporting and checking will be subject to validation and testing, with printable evidence ensuring a clear and complete audit trail. Automatic data entry checks will be incorporated such that values that are out of expected range, implausible, incorrect or missing are flagged up to site staff and resolved at the time of data entry.

Data Cleaning and Database Lock

The process for defining the final dataset and that all the checks and cleaning have been done will be stipulated in the Data Management Plan. Responsibilities and time frames will also be defined.

Monitoring

The Principal Investigator will ensure the accuracy, completeness, legibility and timeliness of the data reported in the case report forms (CRFs) and/or eCRF. Any discrepancies will be clarified and resolved at this stage and any changes recorded, initialled and dated. The

original data entry will not be obscured as data derived from source documents should be consistent with the source documents or the discrepancy explained.
Site investigators, including the PI, will be given full details of the trial process during their site initiation training (SIV). They will then be responsible for the collection of data for their site, and in accordance with GCP training.
All trial data, whether paper CRF, eCRF or both will be subject to monitoring.

STATISTICAL CONSIDERATIONS

Sample size calculation and justification

The primary outcome is time to death. In the MAPS pilot, mortality at 30 days was 8/30 (27%) in the metoclopramide group and 12/30 (40%) in the control group, equating to a 32% reduction in deaths. As the sample size was small (n=60), this estimate may be unreliable and the reduction in mortality appears larger than plausible for a post-stroke intervention. Mortality in the MAPS pilot control group appears high at 40%, but included high-risk participants with severe neurological disability and nasogastric tube feeding.

For MAPS-2 we estimate a mortality of 33% at 6 months in the control group, based on the 6-month mortality of patients with the same stroke severity (NIHSS ≥10) in the Stroke Oxygen Study (SO2S, n=8003) [66],. This is much lower than 40% at 3 months in the MAPS pilot, and 38% at 30 days in a matched subgroup of the Sentinel Stroke National Audit Programme. As mortality in trials is lower than in clinical practice, we consider the SO2S mortality the most reliable source for baseline mortality.

MAPS-2 assumes a 20% relative reduction in mortality from 33% in the control group to 26.4% in the metoclopramide group at 6 months (equivalent to hazard ratio = 0.7654), which is half that of the MAPS pilot, but likely to be clinically important and consistent with more modest effect sizes of other interventions shown to reduce mortality after stroke (Cochrane review of stroke unit care odds ratio 0.75 [42] and CLOTS-3 intermittent pneumatic compression odds ratio 0.82 [67]).

To detect this decrease between group difference with a power of 90%, using the Schoenfeld method of log-rank test, 1:1 allocation and a two-tailed significance level of 0.05, assuming all patients are followed-up to a maximum of 6 months (administrative censoring at 6 months), 588 deaths need to be observed. This requires 1980 participants (990 per arm) to be recruited. With an anticipated maximum 5% loss to follow-up, we aim to recruit approximately 2100 participants.

Analysis of outcome measures

The analysis and reporting of the trial will be in accordance with CONSORT guidelines. A full Statistical Analysis Plan will be developed prior to completion of data collection, and agreed with the DMC and TSC before database lock.

Appropriate descriptive statistics (mean, standard deviation, median, lower and upper quartiles, minimum, maximum or frequencies and percentages) for the demographic and clinical outcome measures at baseline, will be used to assess balance between the randomized arms at baseline, but no formal statistical comparisons will be performed. Baseline characteristics will also be descriptively compared between those randomized and those analysed to see if the attrition has introduced any imbalances. Descriptive statistics appropriate for the outcome will also be presented for all outcomes at all collected time points by treatment arm.

The primary time-to-event analysis will compare time to death between the metoclopramide and placebo control, with analysis according to the allocated treatment regardless of treatment received (intention to treat). A Kaplan-Meier curve will compare the estimated survivor

functions between arms. A Cox proportional hazards model will be used to calculate the hazard ratio and 95% confidence interval, censoring participants who have not died by 6 months or who are lost to follow-up. The model will be adjusted for the minimization factors (stated under randomization). The proportional hazards assumption will be tested and if the assumption is in doubt, alternative approaches to Cox proportional hazards model will be explored. As a sensitivity analysis, we will repeat the primary analysis by: (i) additionally adjusting for any variables with marked imbalance at baseline and for post randomization factors that are expected to affect outcome, e.g. stroke type (infarct/haemorrhage/other), thrombolysis (yes/no), mechanical thrombectomy (yes/no, recovery of swallowing (DSRS score), urinary catheter (yes/no) and Covid-19 (yes/no), and (ii) treating the outcome as binary to obtain between-arm adjusted risk difference and risk ratio along with corresponding 95% confidence intervals.

We expect very little, if any, missing primary outcome data as every effort will be made to trace participants lost to follow-up by checking records including hospital databases and general practitioners to determine whether the participant is alive. However, should there be substantial missing data we will perform sensitivity analysis using imputation representing best and worst-case scenarios, to assess the effect of possible informative censoring and/or use appropriate multiple imputation procedures for time-to-event data. Non-adherence is likely to be minimal at primary follow-up point as efforts will be made to maximize adherence with allocated treatment, but a sensitivity analysis based on complier average causal effect (CACE) will be performed to investigate the effects of adherence.

Between-group comparison of secondary outcomes will be based on an appropriate regression model for the outcome (linear for continuous, logistic for binary, and proportional hazards for time-to-event), adjusted for the same variables as the primary analysis.

The level of significance used for all statistical tests will be 5% ($p < 0.05$).

Planned Sub-Group Analyses

Full details of subgroup analyses will be given in the statistical analysis plan. Appropriate interaction terms will be included in the primary time-to-event analysis in order to conduct subgroup analyses. These will include:

Age
Pre-stroke disability (mRS)
Stroke severity (NIHSS)
Stroke type (infarct/haemorrhage/other)
Time form Onset
Type of hospital (repatriation or not)
Sex
GCS
Frailty
Comorbidities
Antiemetic use before randomization
Thrombolysis (yes/no)
Mechanical thrombectomy (yes/no)
Recovery of swallowing (DSRS score)
Duration of nasogastric feeding
Urinary catheter (yes/no)
Covid-19 (yes/no)

Between-group treatment effects will be provided for each subgroup, but interpretation of any subgroup effects will be based on the treatment-subgroup interaction and 95% confidence interval. Subgroup analyses will be regarded as exploratory as the trial is not powered to detect any interactions.

Health economic analysis

The economic evaluation will compare metoclopramide with placebo control (normal saline) in patients with dysphagia after severe stroke, and will follow two approaches: a within-trial analysis over 6 months follow-up using individual-level costs and outcomes and a model-based analysis to extrapolate the potential cost-effectiveness of the intervention over patient lifetime. All analyses will be undertaken from an NHS and Personal Social Services (PSS) perspective.

Within-trial analysis

An economic evaluation will be undertaken alongside the trial to estimate cost-effectiveness and cost-utility over 6 months follow-up. A cost-consequence analysis will initially be reported, describing all the important results relating to resource use, costs and consequences, across the full range of clinical and economic outcomes. A cost-effectiveness analysis will be undertaken to determine the cost per death avoided and a cost-utility analysis to determine the cost per quality-adjusted life year (QALY) gained.

Resource use and costs: Health and social care resource use will be collected using study case report forms (using information from patient notes) and patient telephone interview in the first instance, or email/postal questionnaire, at 6 months. Resource use will include metoclopramide, use and delivery mode of antibiotics, number of days spent in hospital including length of stay in ICU and acute stroke units, readmissions to hospital, and discharge to non-home settings (e.g. residential care). Resource use will be multiplied by unit costs obtained from standard (national) sources and healthcare providers.

Outcomes: The outcome measure for the cost-effectiveness analysis is death avoided at 6 months. For the cost-utility analysis, the EQ 5D-5L questionnaire will be administered to patients (or their carers) at 14 days and 6 months in order that quality-adjusted life years (QALYs) can be calculated for each participant, using the area under the curve method. Any participants who die within the 6 months will be assigned a utility of zero from date of death. EQ-5D 5L data will not be collected at baseline, as it will not be possible for this patient population to complete the questionnaire on admission to hospital. Therefore, we will use a previously published method [68][69] and assume that the EQ-5D 5L score for all patients at baseline is zero, and the change in quality of life between baseline, 14 days and 6 months is linear. This approach will be explored in sensitivity analysis. The crosswalk value set will be applied to patient responses to obtain utility scores, in line with current NICE recommendations.

Where there are missing data on resource use or quality of life outcomes, multiple imputation techniques will be carried out to ensure that all trial participants are included in the final analysis. Adjustment for baseline covariates will focus on the same variables as outlined for the primary analysis. The robustness of the results will be explored using sensitivity analysis. This will explore uncertainties in the trial-based data itself, methods employed to analyze the data, for example, an available-case analysis as an alternative to using a multiple-imputed dataset. Uncertainty will be explored through the use of cost-effectiveness acceptability curves (CEACs); these plot the probability that the intervention is cost-effective against threshold values for cost-effectiveness.

Model-based analysis

Markov decision modelling will also be undertaken to extend the within-trial results beyond 6 months follow-up, taking into account level of disability measured at 6 months and discharge destination. The purpose of the model is to extrapolate costs, outcomes and QALYs to calculate the long-term cost-utility with discounting of costs and outcomes at 3.5%. A scoping review of the literature on existing economic models in acute stroke will be undertaken to inform the model structure, in consultation with the trial team. This will then allow a full description of the model structure and methods whilst the trial is ongoing. The Markov model health states

will take into account level of disability from stroke using Modified Rankin scale scores. A further review will be undertaken to source parameter values, including those for natural history of the disease (e.g. movement between levels of disability, mortality and recurrence of stroke), long-term health and social care resource use and costs, and utility values for different health states. The model will be subject to extensive deterministic sensitivity analysis by changing individual parameter values and changing model assumptions, and probabilistic sensitivity analysis to simultaneously incorporate all parameter uncertainty. Cost-effectiveness planes and cost-effectiveness acceptability curves will be presented to show the probability the intervention is cost-effective at different cost/QALY thresholds.

A health economics analysis plan (HEAO) will be produced to be considered alongside the statistical analysis plan. All reporting of the methods and results of the health economics analyses will be conducted in line with the recommendations in the CHEERS checklist [70].

Assessment of safety

Adverse events will be recorded on the daily log. Diagnosis of safety events will be made by the clinical team. No specific imaging or laboratory tests will be conducted. All adverse events will be recorded. This study is restricted to patients with moderate-to-severe strokes. In this patient group adverse events are part of the clinical course of the disease. Symptoms and complications of the stroke that are expected (see Appendix 1) will not be reported as adverse events. Safety endpoints (variables) are listed in Appendix 5.

Definition of samples analysed

The primary analysis will be by intention to treat, with the participants analysed according to allocated treatment group regardless of adherence to the allocated intervention. All randomized participants who take at least one dose of study medication will be included in the analysis. Participants not followed up will be censored.

Supplementary analysis for the primary outcome will include the participants who received their allocated intervention (active or placebo) with no major protocol violation. Acceptable adherence is defined as having received 80% or more of the trial drug (17-21 doses for those in hospital for the full 14 days, or 80% of the doses required until discharge for those discharged before 14 days).

For the secondary outcomes, participants will be analysed according to allocated treatment group regardless of adherence to the allocated intervention. The main analysis for each secondary outcome will be for participants with outcome data collected (i.e. without imputation for missing data).

The safety analysis will include all participants who received at least one dose of the investigational drug. For safety data, participants will be analysed according to:

- intervention received
- allocated treatment group regardless of adherence to the allocated intervention.

Procedures for missing, unused and spurious data

<u>Missing baseline data</u>

We anticipate missing baseline data to be minimal. For the primary analysis, only minimization variables will be adjusted for as covariates and we do not expect any to be missing as they are required for the participant to be allocated. For any other baseline scores that will be adjusted for as a covariate in the sensitivity analysis, any missing data will be imputed using the mean score at each centre.

<u>Missing outcome data</u>

We expect very little, if any, missing primary outcome data as every effort will be made to trace participants lost to follow-up by checking records including hospital databases and general practitioners to determine whether the participant is alive. The primary time-to-event analysis will include all participants, with those with missing outcome data censored assuming non-informative (random) censoring. However, should there be substantial missing data we will perform sensitivity analysis using imputation representing best- and worst-case scenarios, to assess the effect of possible informative censoring and/or use appropriate multiple imputation procedures for time-to-event data. Details of handling missing data will be included in the statistical analysis plan.

Any apparently spurious data will be queried and verified in line with our data management SOPs.

19. ADVERSE EVENTS

Definitions and actions to be taken

Adverse Event (AE)

An adverse event is any unfavourable and unintended sign, symptom, syndrome or illness that develops or worsens during the period of observation in the study. An AE does include a / an:

1. Exacerbation of a pre-existing illness.
2. Increase in frequency or intensity of a pre-existing episodic event or condition.
3. Condition detected or diagnosed after medicinal product administration even though it may have been present prior to the start of the study.
4. Continuous persistent disease or symptoms present at baseline that worsen following the start of the study.

Reference Safety Information of metoclopramide

Known side effects of metoclopramide are based on the SmPC of Hameln Pharma and are listed in Appendix 2. These will be classed as AEs and reported to the CI who will assess for expectedness against the reference safety information.

Events which are NOT considered AEs and do NOT require reporting

1. **Medical or surgical procedure** (e.g., surgery, endoscopy, tooth extraction, transfusion); but the condition that led to the procedure is an AE.
2. **Pre-existing disease** or conditions present or detected at the start of the study that did not worsen.
3. **Situations where an untoward medical occurrence has not occurred** (e.g., hospitalizations for cosmetic elective surgery, social and/or convenience admissions).
4. **Overdose of concurrent medication** without any signs or symptoms.
5. **Disease or disorder being studied (stroke**) or sign or symptom associated with the disease or disorder unless more severe than expected for the participant's condition. A list of symptoms, signs, and complications associated with stroke (Appendix 7).

Serious Adverse Events (SAEs)

A serious adverse event is any AE occurring following study mandated procedures, having received the IMP or placebo that results in any of the following outcomes:

1. Death

2. A life-threatening adverse event
3. Inpatient hospitalization or prolongation of existing hospitalization
4. A disability / incapacity
5. A congenital anomaly in the offspring of a participant

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

All adverse events will be assessed for seriousness, expectedness and causality:

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined using the criteria above. Hence, a severe AE need not necessarily be serious.

Causality

Not related or improbable: a clinical event including laboratory test abnormality, with temporal relationship to trial treatment administration that makes a causal relationship incompatible or for which other drugs, chemicals or disease provide a plausible explanation**.** This will be counted as "unrelated" for notification purposes.

Possible: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration that makes a causal relationship a reasonable possibility, but which could also be explained by other drugs, chemicals or concurrent disease. This will be counted as "related" for notification purposes.

Probable: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration that makes a causal relationship a reasonable possibility, and is unlikely to be due to other drugs, chemicals or concurrent disease. This will be counted as "related" for notification purposes.

Definite: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration that makes a causal relationship a reasonable possibility, and that can definitely not be attributed to other causes. This will be counted as "related" for notification purposes.

An AE whose causal relationship to the study IMP is assessed by the Chief Investigator as "possible", "probable", or "definite" is an Adverse Drug Reaction.

With regard to the criteria above, medical and scientific judgment shall be used in deciding whether prompt reporting is appropriate in that situation.

Reporting of adverse events

Participants or the person/staff looking after them will be asked to contact the study site immediately in the event of any serious adverse event. All adverse events will be recorded and closely monitored until resolution, stabilization, or until it has been shown that the study medication or treatment is not the cause. The Chief Investigator (delegated responsibility by the Sponsor) shall be informed immediately (within 24 hours) of any serious adverse events and shall determine seriousness and causality in conjunction with any treating medical practitioners.

All serious adverse events will be recorded and reported to the MHRA and REC as part of the annual Development Safety Update Reports. SUSARs will be reported within the statutory

timeframes to the MHRA and REC as stated below. The Sponsor shall ultimately be responsible for adverse event reporting.

Urgent Safety Measures

Urgent safety measures will be taken as necessary to protect a research participant when that participant is identified as being at risk of harm in relation to his or her involvement in the study.

An Urgent Safety Measure is a procedure taken to protect a research participant when that participant is identified as being at risk of harm in relation to his or her involvement in a research project and urgent action that deviates from the approved protocol, is required to manage the event and protect the participant. Any urgent safety measure will be communicated to the MHRA immediately. The sponsor will phone the MHRA Clinical Trial Unit and discuss the event with a safety scientist. The sponsor must then follow-up with notification in writing within three days of the action being taken. The notification should be in the form of a substantial amendment and should describe the event, the measures taken and justification for the measures taken.

SUSARs

A serious adverse event that is either sudden in its onset (anaphylaxis), unexpected in its severity and seriousness or not a known side effect of the IMP *and* related or suspected to be related to the IMP is classed as Suspected Unexpected Serious Adverse Reaction and requires expedited reporting as per the clinical trials regulations.

All serious adverse events that fall or are suspected to fall within these criteria shall be treated as a SUSAR until deemed otherwise.

The event shall be reported immediately (within 24 hours) of knowledge of its occurrence to the Chief Investigator.

The Chief Investigator will:

- Assess the event for seriousness, expectedness and relatedness to the study IMP
- Take appropriate medical action, which may include halting the trial and inform the Sponsor of such action
- If the event is deemed a SUSAR, shall, within seven days, enter the required data on the MHRA's eSUSAR web site
- Shall inform the REC using the reporting form found on the HRA web page within 7 days of knowledge of the event
- Shall, within a further eight days send any follow-up information and reports to the MHRA and REC
- Make any amendments as required to the study protocol and inform the ethics and regulatory authorities as required

Trial Treatment Related SAEs

A serious adverse event that is unexpected in its severity and seriousness *and* deemed directly related to or suspected to be related to the trial treatment but not the IMP shall be reported to the ethics committee that gave a favourable opinion as stated below.

The event shall be reported immediately on knowledge of its occurrence to the Chief Investigator.

The Chief Investigator will:

- Assess the event for seriousness, expectedness and relatedness to the trial treatment.
- Take appropriate medical action, which may include halting the trial and inform the Sponsor of such action.
- If the event is deemed related to the trial treatment shall inform the REC using the reporting form found on the HRA web page within 7 days of knowledge of the event.
- Shall, within a further eight days send any follow-up information and reports to the REC.
- Make any amendments as required to the study protocol and inform the REC as required

Participant removal from the study due to adverse events

Any participant who experiences an adverse event may be withdrawn temporarily or permanently from the study at the discretion of the Investigator. Wherever possible and acceptable, withdrawal will relate to the IMP only, with follow-up continued as per protocol.

20. ETHICAL AND REGULATORY ASPECTS

ETHICS COMMITTEE AND REGULATORY APPROVALS

Details of the consent procedures are given in the Trial/Study Design section (subsection Selection and Withdrawal of Participants/Consent.

The trial will not be initiated before the protocol, informed consent forms and participant and GP information sheets have received approval/favourable opinion from the Medicines and Healthcare products Regulatory Agency (MHRA), Research Ethics Committee (REC), the respective National Health Service (NHS) or other healthcare provider's Research & Development (R&D) department, and the Health Research Authority (HRA) if required. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant and GP information sheets (if appropriate) have been reviewed and received approval / favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the MHRA, R&D and REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, in accordance with the Medicines for Human Use Regulations, Statutory Instrument 2004, 1031 and its subsequent amendments and the UK Department of Health Policy Framework for Health and Social Care, 2017.

INFORMED CONSENT AND PARTICIPANT INFORMATION

The process for obtaining participant informed consent or assent and legal representative informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The investigator or their nominee and the participant or other legally authorized representative shall sign and date the Consent Form or provide witnessed consent via the telephone, where in-person consent is not possible, before the person can participate in the study.

The participant/legal representative will receive a copy of the signed and dated forms and the original will be retained in the Trial Master File. A second copy will be filed in the participant's

medical notes and a signed and dated note made in the notes that informed consent was obtained for the trial.

The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasize that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No trial-specific interventions will be done before informed consent has been obtained.

The investigator will inform participants of any relevant information that becomes available during the course of the study, and will discuss with them, whether they wish to continue with the study. If applicable, they will be asked to sign revised consent forms.

If the Informed Consent Form is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Informed Consent Form by the REC and use of the amended form (including for ongoing participants).

21. RECORDS

Drug accountability

The IMP will be taken from ward stock and administration will be documented on the drug chart by the member of staff administering the drug, as per standard hospital practice. No additional documentation will be required.

Drug supplies will be kept in a secure, limited access storage area under the storage conditions specified by Pharmacy.

Case Report Forms

Each participant will be assigned a trial identity code number, allocated at randomization for use on CRFs other trial documents and the electronic database. This will be composed of the centre number/patient initials only/trial enrolment number.

CRFs will be treated as confidential documents and held securely in accordance with regulations. The investigator will make a separate confidential record of the participant's name, date of birth, local hospital number or NHS number, and Participant Trial Number (the Trial Recruitment Log), to permit identification of all participants enrolled in the trial in accordance with regulatory requirements and for follow-up as required.
CRFs shall be restricted to those personnel approved by the Chief or local Principal Investigator and recorded on the 'Trial Delegation Log.'

All paper forms shall be filled in using black ballpoint pen. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initialled and dated.
The Chief or local Principal Investigator shall sign a declaration ensuring accuracy of data recorded in the CRF.

Source documents

Source documents shall be filed at the investigator's site and may include but are not limited to, consent forms, current medical records, laboratory results and pharmacy records. A CRF may also completely serve as its own source data. Only trial staff as listed on the Delegation Log shall have access to trial documentation other than the regulatory requirements listed below.

Direct access to source data / documents

The CRF and all source documents, including progress notes and copies of laboratory and medical test results shall made be available at all times for review by the Chief Investigator, Sponsor's designee and inspection by relevant regulatory authorities (MHRA).

22. DATA PROTECTION

All trial staff and investigators will endeavour to protect the rights of the trial's participants to privacy and informed consent, and will adhere to the Data Protection Act, 2018 [79]. The CRF will only collect the minimum required information for the purposes of the trial. CRFs will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the trial staff and investigators and relevant regulatory authorities (see above). Computer-held data including the trial database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one-way encryption method).Information about the trial in the participant's medical records/hospital notes will be treated confidentially in the same way as all other confidential medical information.

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

23. QUALITY ASSURANCE & AUDIT

INSURANCE AND INDEMNITY

Insurance and indemnity for trial participants and trial staff are covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures.

The University of Nottingham as research Sponsor indemnifies its staff, with both public liability insurance and clinical trials insurance in respect of claims made by research subjects.

TRIAL CONDUCT

Trial conduct will be subject to systems audit of the Trial Master File for inclusion of essential documents; permissions to conduct the trial; Trial Delegation Log; CVs of trial staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion/exclusion criteria, correct randomization, timeliness of visits); adverse event recording and reporting; drug accountability, pharmacy records and equipment calibration logs.

The Trial Coordinator, or where required, a nominated designee of the Sponsor, shall carry out a site systems audit at least yearly and an audit report shall be made to the Trial Steering Committee.

TRIAL DATA

Monitoring of trial data shall include: confirmation of informed consent, source data verification, data storage and data transfer procedures, local quality control checks and procedures, back-up and disaster recovery of any local databases, and validation of data manipulation. The Trial Coordinator, or where required, a nominated designee of the Sponsor, shall carry out monitoring of trial data as an ongoing activity.

Entries on CRFs will be verified by inspection against the source data. A sample of CRFs (10% or as per the trial risk assessment) will be checked on a regular basis for verification of all entries made. In addition, the subsequent capture of the data on the trial database will be checked. Where corrections are required, these will carry a full audit trail and justification.

Trial data and evidence of monitoring and systems audits will be made available for inspection by the regulatory authority as required.

RECORD RETENTION AND ARCHIVING

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Code of Research Conduct and Research Ethics, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The Trial Master File and trial documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the University of Nottingham. This archive shall include all trial databases and associated meta-data encryption codes.

DISCONTINUATION OF THE TRIAL BY THE SPONSOR

The Sponsor reserves the right to discontinue this trial at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice from the Trial Steering Committee and Data Monitoring Committee as appropriate in making this decision.

STATEMENT OF CONFIDENTIALITY

Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted above. Participant confidentiality will be further ensured by utilizing identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare. If information is disclosed during the study that could pose a risk of harm to the participant or others, the researcher will discuss this with the PI and where appropriate report accordingly.

Data generated as a result of this trial will be available for inspection on request by the participating physicians, the University of Nottingham representatives, the REC, local R&D Departments and the regulatory authorities.

24. PUBLICATION AND DISSEMINATION POLICY

We will use our extensive relationships with professional organizations, the NIHR clinical research network, the wider international research community, guideline producers and patient groups to share findings widely. A dissemination plan will be put together prior to the start of the trial and regularly reviewed and updated for further dissemination opportunities. The main areas of planned dissemination are:

High-impact peer reviewed publications

The study protocol and statistical analysis plan will be submitted for publication before analysis of data begins. The primary study outcome will be submitted to an internationally recognized peer-reviewed publication e.g. *The Lancet* or *NEJM*. The secondary outcomes will be disseminated via publications such as *Stroke, the European Stroke Journal,* and the

International Journal of Stroke. The PPI group will also be encouraged to submit an article for publication in a peer-reviewed journal describing the PPI pledge and how it was implemented throughout the course of the research. The full research report will also be submitted to the *NIHR HTA Journal*.

Conferences
The research findings will be disseminated via oral presentation at national and international meetings, e.g. UK Stroke Forum conference, the European Stroke Conference, the International Stroke conference and at PPI events e.g. UK Stroke Assembly. A member of the PPI group will be asked to present the findings of the research jointly with the Chief Investigator at those conferences where patients attend.

National and International Guidelines
Published results of MAPS-2 will inform the National Clinical Guideline for Stroke in the UK, and feed into the European Stroke Guidelines, the American Stroke Association Guidelines, and other international guidelines.

Patient/user group meetings
The PPI group will identify local and, if appropriate, national, patient group meetings where a member of the PPI group and research team will attend and present the study and findings. A PPI-friendly leaflet detailing the trial and outcomes will be prepared by the PPI group and will be made available to the Stroke Association and other patient groups.

NIHR clinical research network
An article describing the study and final outcomes will be prepared and distributed to all local clinical research networks who helped with the study to disseminate via their own publications.

Principal investigators and participating research sites
An online webinar will be used to present the findings of the study to participating centres prior to the first major presentation of the results. The coordinating centre will produce regular newsletters throughout the time of the study; the final newsletter will cover the findings of the research.

Participants
Participants will be asked when they complete their 6-month follow-up, if they wish to be informed of the study results; if so the research findings summary from the PPI group will be sent either via letter or e-mail.

Participants will not be identified in any of the publications.

25. USER AND PUBLIC INVOLVEMENT

The MAPS-2 PPI group includes stroke survivors and carers of people who have had a stroke. It is chaired by one of our patient representative co-investigators (Brin Helliwell). Pre-grant PPI meetings were funded by a bursary from the West Midlands Research Design Service. The group developed a PPI pledge detailing how patients, carers and members of the public will be involved in the trial. The PPI group has been involved in the development of the protocol. They commented on the relevance of the intervention and on the importance of preventing pneumonia. One group member described how unwell he felt with pneumonia, which delayed his recovery significantly. PPI representatives stated survival was a very important outcome, even if this means survival with disabilities. Finding out if metoclopramide can prevent pneumonia and reduce mortality was considered important.

The issue whether the primary outcome was more meaningful as a dichotomous dead/alive outcome or is better represented by a time-to-event outcome was discussed in detail in a Zoom meeting with the PPI group. The information gained by seeing the survival curves on the

Kaplan-Meier Plot was considered important and meaningful, supporting the use of a time-to-event outcome. The PPI chair will represent the PPI group on the trial management group (TMG) and the trial steering committee (TSC). The chair and trial manager will regularly review and report to the TMG and TSC as regards PPI involvement in relation to the PPI Pledge to ensure the pledge's goals are achieved. The PPI chair will mentor other members of the PPI group who attend the TMG and TSC. The PPI group will comment on manuscripts for publication.

The protocol and patient information sheets were reviewed by members of the PPI group.

26. STUDY FINANCES

Funding source

This study is funded by the NIHR Health Technology Assessment Programme.

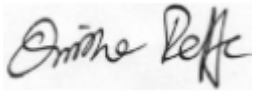
Participant stipends and payments

Participants will not be paid to participate in the trial. Travel expenses will be offered for any hospital visits in excess of usual care.

27. SIGNATURE PAGES

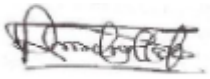
Signatories to Protocol:

Chief Investigator: Christine Roffe

Signature: 

Date: 06th March 2023

Trial Statistician: Reuben Ogollah

Signature: 

Date: 06th March 2023

Trial Pharmacist: Maria Scott

Signature: 

Date: 06th March 2023

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29. APPENDICES

APPENDIX 1: Side-effects of metoclopramide (based on the Hameln Pharma Ltd SmPC)

General side-effects, Common (1 in 100 to 1 in 10) or very common (> than 1 in 10)
Asthenia
Depression
Diarrhoea
Drowsiness
Hypotension
Menstrual cycle irregularities
Movement disorders
Parkinsonism

Uncommon (1 in 1,000 to 1 in 100)
Arrhythmias
Hallucination
Hyperprolactinaemia
Level of consciousness decreased

Rare 1 in 10,000 to 1 in 1,000) or very rare (less than 1 in 10,000)
Confusion
Galactorrhoea
Seizure
Frequency not known
Atrioventricular block
Blood disorders
Cardiac arrest
Gynaecomastia
Hypertension
Neuroleptic malignant syndrome
QT interval prolongation
Shock
Syncope
Tremor

Specific side-effects, frequency not known with parenteral use
Anxiety
Dizziness
Dyspnoea
Oedema
Skin reactions
Visual impairment

Side-effects, further information
Metoclopramide can induce acute dystonic reactions involving facial and skeletal muscle spasms and oculogyric crises. These dystonic effects are more common in the young (especially girls and young women) and the very old; they usually occur shortly after starting treatment with metoclopramide and subside within 24 hours of stopping it. Injection of an antiparkinsonian drug such as procyclidine will abort dystonic attacks.

APPENDIX 2: Centre for Disease Control CDC definition of pneumonia

1. Generalized signs
    a. Fever >38°C **or**
    b. Leukopenia (WBC<4,000mm^3) **or**
    c. Leucocytosis (WBC >12,000mm^3) **or**
    d. For adults ≥ 70 years **or** new **or** worse confusion with no other cause

2. Respiratory Symptoms or signs: at least **TWO** of the following:
    a. New onset of purulent sputum **or** change in character of sputum over 24 h **or** increased respiratory secretions **or i**ncreased suctioning requirements
    b. New onset cough **or** worsening cough **or** dyspnoea **or** tachypnoea (respiratory rate >25/min)
    c. Rales, crackles, or bronchial breath Sounds
    d. Worsening gas exchange (oxygen desaturation, increased oxygen requirements)

3. Abnormal chest radiograph
    a. New or progressive and persistent infiltrate **or**
    b. consolidation **or**
    c. Cavitation

A diagnosis of pneumonia is made if points 1-3 are true (1).

Pneumonia in Stroke Consensus Group diagnosis of pneumonia

This is the same as CDC (above), but allows an additional diagnosis of probable pneumonia made when 1 and 2 are true, but there is no confirmation by chest radiograph (2).

For the primary endpoint we will use the probable pneumonia definition of the PISCES recommendation.

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MAPS-2 definition of pneumonia

Presence of three of the following variables:

1. Fever (>38°C) ***or*** *two successive readings of >37.5 °C or WBC> 12,000/ml or <4,000/ml* ***or*** *C-reactive protein > 40 mg/L*
2. New onset cough **or** worsening cough or new or increased respiratory secretions
3. Abnormal respiratory examination

   -tachypnoea with a respiratory rate >*25*/min or
   -inspiratory crackles or
   -bronchial breathing
4. Arterial hypoxemia (*oxygen saturation <90%)*
5. Abnormal chest radiograph *(new pulmonary infiltrates)*
6. Isolation of a relevant pathogen (positive gram stain and culture).

Adapted from Mann et al 1999 (1) using cut offs derived from the MAPS-pilot (2,3). Items in italics have been added by the investigators to the original Mann criteria. As paracetamol and cooling is commonly given to suppress pyrexia, pyrexia >38°C are rare in modern stroke care. More recent studies have therefore included two *readings of >37.5 °C as diagnostic criteria* (4). An abnormal WBC and high CRP levels are increasingly used as adjuncts to the diagnosis and have been added as an alternative to point 1 (4, 5). Purulent upper airway secretions have been added to the cough item, as the cough reflex is reduced in patients with severe stroke and at high risk of pneumonia. The cut-off for tachypnoea in Mann et al was 22, we increased this to 25. Hypoxia was defined as a partial pressure of oxygen of 9.3 kPa or less, this was replaced by an oxygen saturation of 90% or less. A definite diagnosis of pneumonia is made if 3 or more points are true. We removed the heart rate from criterion 3, as it is likely to have frequent false positives in patients with AF.

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APPENDIX 3: Expected Stroke Symptoms and Complications
to be recorded in patient notes but not subject to expedited reporting

These events are aspects of the original qualifying disease and do not constitute adverse events.

- Stroke symptoms (reduced level of consciousness, confusion, hemianopia, double vision, facial paresis, other cranial nerve palsies, hemiparesis, hemi sensory loss, ataxia, incoordination, speech problems, dysarthria, hemi inattention, dysphagia)
- Extension of the initial stroke
- Haemorrhagic transformation of the stroke
- Malignant cerebral oedema
- Venous thromboembolism
- Atrial fibrillation
- Carotid artery stenosis
- Decubitus ulcer
- Shoulder pain
- Other musculoskeletal pains
- Urinary incontinence
- Urinary retention
- Dehydration
- Renal impairment
- Hypertension (unless it is very severe and has only started after randomization)
- Dyslipidaemia
- Headaches
- Confusion
- Delirium
- Falls
- Fractures
- Elective and diagnostic procedures (carotid endarterectomy, PEG insertion, endoscopy)

APPENDIX 4: Protocol amendment table

Protocol version:	Date:	Change made by:	Summary of changes

1.1	28/06/2022	Prof. Christine Roffe (CI)	**Page 5:** Inclusion criteria has been adapted so patients are no longer required to have both NIHSS ≥ 10 **and** a failed bedside swallowing assessment to be included. Patients can now be enrolled if they instead (a) have an NIHSS ≥ 10, or (b) have an NIHSS ≥ 6 **and** a failed swallowing assessment. **Page 19:** In relation to minimisation, an NIHSS range of 6-9 has been added (for any patients who enrol with an NIHSS <10). **Page 22:** Inclusion criteria has been adapted so patients are no longer required to have both NIHSS ≥ 10 **and** a failed bedside swallowing assessment to be included. Patients can now be enrolled if they instead (a) have an NIHSS ≥ 10, or (b) have an NIHSS ≥ 6 **and** a failed swallowing assessment. The part of the sentence (in relation to the recruitment window) *"unless this is more than 12 h from last known well"* has been removed. **Page 26:** The screening box has been amended to incorporate the new inclusion criteria. **Page 54:** Protocol amendment table has been added.
1.2	13/07/2022	Prof. Christine Roffe (CI)	**Page 5:** Typo: "eGFR< 30 ml/hour" has been amended to "eGFR< 30 ml/min". **Page 23:** "eGFR< 30 ml/hour" has been amended to "eGFR< 30 ml/min". **Page 29:** Typo amended ("pr more" amended to "or more"). **Page 54:** Protocol amendment table has been updated to include protocol v1.2 changes.
1.3	08/11/2022	Prof Christine Roffe (CI)	**Page 53:** Typo: WBC> 12,000/ml or <3,000/ml has been amended to "or < 4,000/ml" **Page 53:** Typo amended from "C-reactive protein > 65 mg/L" changed to ">40mg/L"
1.4	06/03/2023	Prof Christine Roffe (CI)	**Page 1:** CTA reference number corrected. **Page 3:** New Trial Pharmacist details added. **Page 5:** *"Within 9 hours"* amended to *"within 24 hours".* **Page 18:** *"No longer than 9 hours"* amended to *"No longer than 24 hours".* **Page 19:** *"…*randomized by a member of the local research team within 10 hours of stroke onset (*this is to allow patients*

			who consented within 9h to be included, mitigating against computer problems between consent and randomization)" amended to *"…*randomized by a member of the local research team within 25 hours of stroke onset (*this is to allow patients who consented within 24h to be included, mitigating against computer problems between consent and randomization)."* *"0-3, 4-6, >6 hours"* amended to *"0-3, 4-6, >6-9, >9 hours".* **Page 21:** *"Adult patients admitted to hospital with moderate to severe acute stroke and dysphagia within 9 hours"* amended to *"Adult patients admitted to hospital with moderate to severe acute stroke and dysphagia within 24 hours".* **Page 22:** *"Within 9 hours of symptom onset"* amended to *"Within 24 hours of symptom onset".* **Page 24:** *"…it is anticipated that few will be able to give fully informed consent within the 9-hour recruitment window"* amended to *"…it is anticipated that few will be able to give fully informed consent within the 24-hour recruitment window".* **Page 25:** *"Within 9 h of symptom onset"* amended to *"Within 24 h of symptom onset".* **Page 43:** Trial Pharmacist details updated.