RESEARCH PROTOCOL

Trial title: The **M**etoclopramide and selective oral decontamination for **A**voiding **P**neumonia after **S**troke (MAPS-2) Trial: a 2x2 double-blind, randomised controlled trial of metoclopramide and selective oral decontamination for the prevention of pneumonia in patients with dysphagia after an acute stroke

Short title: Metoclopramide and selective oral decontamination for Avoiding Pneumonia after Stroke (MAPS-2) Trial

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Sponsor: University Hospitals of North Midlands NHS Trust

Funder: National Institute for Health Research – Health Technology Assessment

This protocol has regard for the HRA guidance

Protocol Amendment History

Version	Date	Status	Reason for Revision
1.0	25 Oct 2016	Draft	
2.0	19 Dec 2016	Final	Sponsor quality review completed
2.1	10 Mar 2017	Final	Ethical review required clarification on early stopping and the legal Status of IMP before approval issued.
2.2	17 Jul 2017	Final	Updating of contact details for pharmacy and trial office. Addition of IRT into abbreviations and clarification of use. Addition of 21 day Follow up section. Guidance for locating detailed trail procedures added. Manual randomisation process edited for clarification. Clarification of detail for Emergency Unblinding process. Clarification that SAEs collected in CRF are research not pharmacovigilance data. Addition of information that IMP compliance data is collected on the Daily Clinical Logs. Addition to clarify 'catch-up' process of missed doses and dosing regime Acknowledgement of the repatriation process as part of the standard care pathway. Guidance about trial-specific processes. In relation to trial treatment and assessments once transferred or repatriated. Treatment times altered from 1 to 2 hours for treatment to start following admission. Addition to title section 16.5.7 to include repatriation. Addition to title section 7.10 to include transfer/repatriation Amended reference to 'independent observer record' to 'consent form', to reflect trial-specific consent procedures. Addition of IMP storage and temperature monitoring guidance and updated IMP-D version and date. Removal of reference to and description of Teleform and replaced with reference to MACRO database. To record whether first dose of IMP is administered within 2 hours of Randomisation, as per protocol. To record the occurrence of vomitting between Randomisation and first dose of IMP. To record the number of doses of metoclopramide/placebo/SOD administered and route of administration for each dose. Addition of fields to record the number of lost or damaged doses of IMP from Days 1-14. Change of CRF section title from 'Adverse Events' to 'Safety Outcome Data' to clarify that this is research data and any reference to this also changed. Addition of 21-day Follow-Up CRF, for the purpose of recording compliance and loss/damage of IMP. Addition of fields to record the number of lost or damaged doses of IMP from Days 15-21. Addition of CRF titles ('Notification of Death' and 'Withdrawal' to reflect full complement of CRFs. Table of contents updated to reflect any additions along with section numbers where applicable. following addition of 'Day 21' CRF.
2.3	09 Nov 2017	Final	Removal of named individual on sponsor contact details. Clarification that a pregnancy needs to be reported on a study specific pregnancy form not as an SAE.
2.4	08 Dec 2017	Final	Daily Compliance Summary to be completed to day 21. Schedule of events updated to show log completed to day 21. Kit number to replace batch number in baseline data collection.

SIGNATURE PAGE

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

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

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

For and on behalf of the trial Sponsor:

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SYNOPSIS

Trial Title	The Metoclopramide and selective oral decontamination for Avoiding Pneumonia after Stroke (MAPS-2) Trial: a 2x2 double-blind, randomised controlled trial of metoclopramide and selective oral decontamination for the prevention of pneumonia in patients with dysphagia after an acute stroke	
Internal ref. no. (or short title)	Metoclopramide and selective oral decontamination for Avoiding Pneumonia after Stroke (MAPS-2) Trial	
Clinical Phase	Phase III	
Trial Design	2x2 factorial double-blind randomised controlled trial	
Trial Participants	Patients with severe acute stroke (NIHSS≥10) and dysphagia, within 9 h of symptom onset	
Planned Sample Size	1160	
Treatment duration	21 days or until patient nasogastric tube no longer needed.	
Follow up duration	To the end of the trial for the primary outcome, and to 90 days for secondary outcomes.	
Planned Trial Period	01.04.2017 until 30.06.2019	
	Objectives	**Outcome Measures**
Primary	To assess whether metoclopramide and/or selective oral decontamination reduce mortality in patients with dysphagia after stroke	Mortality up to the end of the trial
Secondary	To assess the effect of metoclopramide and selective oral decontamination on secondary outcomes: clinical outcomes, pneumonia incidence, disability, safety, and costs	1. Pneumonia within 14 d 2. No of days of antibiotic treatment for pneumonia within the first 30 days 3. Neurological recovery (NIHSS) at 30 d 4. Disability at 90 d (mRS) 5.Quality of life at 90 d (EQ-5D™)
Health Economic Analyses	To assess cost-effectiveness and cost-utility	Cost per death avoided over 90 days QALYs gained over 90 days
Explanatory outcomes	To assess wider effects of the interventions	- Vomiting, hypoxia within 14 d - White blood cell count, C-reactive protein, results of sputum cultures, antibiotic resistance, *C. difficile*, and antibiotic treatment to 30 d - Return to oral feeding to 90 d
Investigational Medicinal Product(s)	1. Metoclopramide 2. Oral decontaminant paste containing 2% w/w colistin, 2% tobramycin and 2% amphotericin B	

Formulation, Dose, Route of Administration	Metoclopramide solution for injection 10 mg 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 three times a day. Selective oral decontamination paste applied four times a day to the oral mucosa via an applicator.
Statistical Analysis	Mortality will be compared between groups across the trial period using competing risks survival analysis.

FUNDING AND SUPPORT IN KIND

The MAPS-2 trial is funded by the National Institute for Health Research (NIHR) Health Technology Assessment Programme

FUNDER(S)

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Evaluation, Trials and Studies
Coordinating Centre
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ROLE OF TRIAL SPONSOR AND FUNDER

The Sponsor (University Hospitals of North Midlands NHS Trust) assumes overall responsibility for the initiation and management of the trial and for adherence to Good Clinical Practice.

The Chief Investigator is responsible for the trial design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results in consultation with the MAPS-2 Co-investigators. The Chief Investigator controls the final decision regarding these aspects of the trial.

The funder (The National Institute for Health Research) has no input in the original design of the trial, data analysis and interpretation, or manuscript writing, and dissemination of results. However, they can refuse to support changes in the protocol that deviate from the originally funded project. They will review any outputs before dissemination.

ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

The trial will be managed by the chief investigator and the trial management group (TMG). The trial coordinating centre will be based in the Guy-Hilton Research Centre, Thornburrow Drive, Hartshill, Stoke-on-Trent, Staffordshire, ST4 7QB. The trial will be sponsored by the University Hospitals of North Midlands NHS Trust.

The Chief Investigator (CI)

The named Chief Investigator (CI) is the data custodian and takes primary responsibility for the conduct of the trial.

Trial Management Group (TMG)

The TMG is responsible for the day to day running of the trial, the overall design and conduct of the trial, analysis of the data, reporting and dissemination of results. 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. They will be provided with unblinded safety reports prepared by a member of the Anglia-Ruskin Clinical Trials Unit independent of the TMG every 6 months, or more frequently, if

requested. A formal unblinded interim analysis of the data will not be conducted, unless requested. A DMC charter will be prepared with details of membership, terms and conditions, and trial stopping rules. The DMC will report to the independent chair of the trial steering committee, who will report to the sponsor and the funder. The DMC will include a clinician with expertise in stroke, a statistician and a member with expertise in multicentre clinical trials. The DMC will meet twice a year or more frequently if required.

Trial Steering Committee (TSC)

The independent TSC will provide overall supervision of the trial on behalf of the sponsor and the funder and to 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 GCP. Its tasks are to approve the protocol and substantial changes, receive 6 monthly reports from the DMC, provide advice and resolve problems brought to it by the TMG, and ensure publication of the results. It will report to the sponsor and the funder of the trial. It will include an independent chair, an independent statistician, an independent clinician, a patient and carer representative, and other members as determined by the chair. At least 75% of the members will be independent. It will meet before the start of the trial, and then at least annually until the end of the trial and publication of the key results. Minutes will be sent to TSC members, the CI, the sponsor, the funder, and filed in the trial master file.

Protocol Contributors

This protocol has been written by the CI, trial manager and the co-investigators. A Quality by Design process, provided through the clinical trials transformation initiative[1] has been followed. 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.

KEYWORDS

Acute stroke; pneumonia; nasogastric feeding; enteral feeding; dysphagia; metoclopramide; selective oral decontamination.

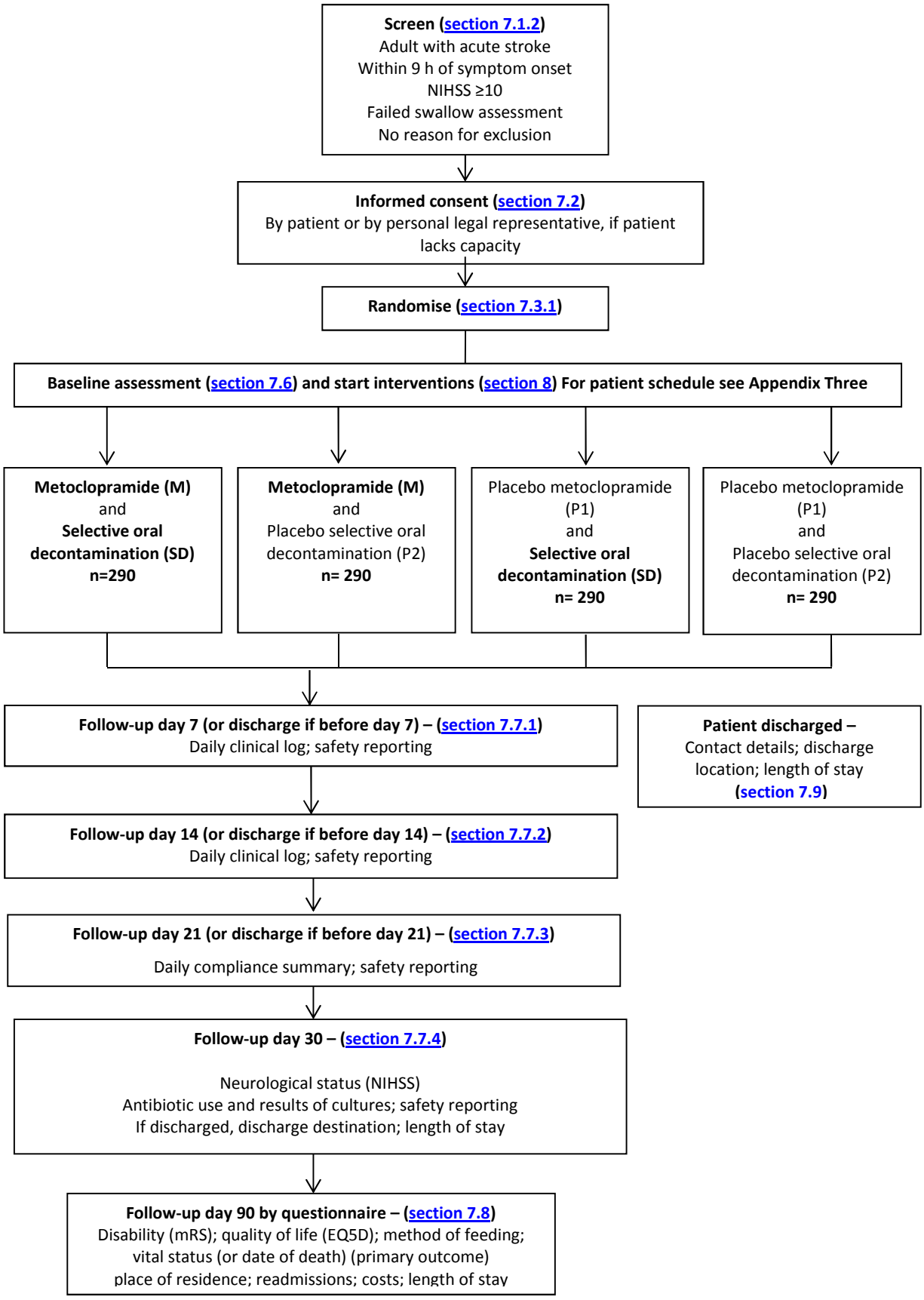
ABBREVIATIONS

A&E	Accident & Emergency
AE	Adverse Event
APR	Annual Progress Report
AR	Adverse Reaction
CA	Competent Authority
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRP	C-reactive protein
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trial Unit
CXR	Chest radiograph
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EC	European Commission
ECG	Electrocardiogram
EEG	Electroencephalogram
eGFR	Estimated Glomerular Filtration Rate
EMEA	European Medicines Agency
EQ5D	EuroQol 5 Dimensions
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
FBC	Full Blood Count
G6PD	Gluose-6-phosphate-dehydrogenase
GCP	Good Clinical Practice

GCS	Glasgow Coma Scale
GMP	Good Manufacturing Practice
GP	General Practitioner
H	Hour(s)
HRA	Health Research Authority
HTA	Health Technology Assessment
IB	Investigators Brochure
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use
IRT	Interactive Response Technology
IMP	Investigational Medicinal Product
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
LACS	Lacunar Syndrome
MAPS	Metoclopramide for Avoiding Pneumonia after Stroke
mcg/kg	Micrograms per kilogram
mRS	Modified Rankin Scale
MHRA	Medicines and Healthcare products Regulatory Agency
NGT	Nasogastric Tube
NRES	National Research Ethics Service
NHS R&D	National Health Service Research and Development
NIHR	National Institute for Health Research
NIHSS	National Institutes for Health Stroke Scale
PACS	Partial Anterior Circulation Syndrome
PEG	Percutaneous endoscopic gastrostomy
PI	Principal Investigator
PIC	Participant Identification Centre
PID	Patient Identification Number
POCS	Posterior Circulation Syndrome
QA	Quality Assurance

QALY	Quality-Adjusted Life Year
QC	Quality Control
QP	Qualified Person
R&D	Research & Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RR	Relative risk
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDD	Selective Decontamination of the Digestive Tract
SDV	Source Data Verification
SPC	Summary of Product Characteristics
SSNAP	Sentinel Stroke National Audit Programme
SOD	Selective Oral Decontamination
SOP	Standard Operating Procedure
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
TACS	Total anterior circulation syndrome
tds/TDS	Three times a day
TMF	Trial Master File
TMG	Trial Management Group
tPID	Temporary Participant Identification number
TSC	Trial Steering Committee
UHNM	University Hospitals of North Midlands NHS Trust
WBC	White Blood Cell count

TRIAL FLOWCHART



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1. BACKGROUND

Stroke is the second most common cause of death worldwide[2]. With approximately 110,000 strokes per annum in England, it accounts for 11% of deaths[3]. Stroke Mortality is cited as 20-30% within one month in the 2007 National Stroke Audit report[3]. More recent data suggest lower rates between 14% and 17% in the UK[4] and 14.5% in the US[5]. Improvements in processes of care have contributed significantly to this reduction[6]. Half of all stroke survivors are left dependent on others for everyday activities[3], making stroke the largest cause of complex disability[7].

1.1 - Stroke associated pneumonia, incidence and risks

Pneumonia is a common complication of stroke and associated with a 2-6 fold increase in mortality in individual studies[8 9 10 11 12 13], longer length of stay[10 13], and an increase in long-term disability[10 11 13]. In the UK the incidence of stroke-associated pneumonia was 8.3% in the first week after stroke in the Stroke National Sentinel Audit Programme, which included 18,839 patients from 160 hospitals[14]. The reported incidence of pneumonia varies widely and depends on the population of stroke patients studied, and on how pneumonia is assessed and defined. A meta-analysis of 64 studies including 639, 953 stroke patients identified the overall occurrence of pneumonia as 14%, with higher rates (19-23%) in studies that applied standard diagnostic criteria[15]. An earlier meta-analysis including over 10,000 stroke patients has shown an incidence of 10% for stroke-associated pneumonia with a more than three-fold increase of the risk of death[11]. Thirty-one per cent of stroke-related deaths are caused by pneumonia, while only 10% are directly due to neurological deficits[16]. While thrombolysis improves neurological impairment and significantly reduces post-stroke disability, it has no impact on survival. The only interventions that have been shown to affect both mortality and morbidity after stroke (stroke unit care and use of intermittent pneumatic compression to prevent thromboembolism)[17 18] address complications rather than the neurological injury itself. Pneumonia weakens patients, and affects their ability to engage with therapy. A stroke survivor in our PPI group described vividly how pneumonia delayed his ability to participate in physiotherapy and delayed his recovery. Prevention of pneumonia as the most common severe complication of stroke has the potential to make a large impact on stroke mortality and recovery.

1.2 - Who is most at risk of pneumonia after stroke?

Stroke-associated pneumonia is most likely to occur in patients who have problems swallowing. A meta-analysis of 24 studies has shown an overall prevalence of dysphagia after stroke of 50-55% by

clinical testing and 64-78% by instrumental assessment (video fluoroscopy). In this review, dysphagia increases the risk of pneumonia three-fold (relative risk (RR) 3.17, 95% CI 2.07-4-87). Up to 68% of dysphagic stroke patients, but no more than 8% with normal swallowing, develop pneumonia within the first 14 days after stroke[19]. Four independent risk factors were found to predict stroke-associated pneumonia with 76% sensitivity and 88% specificity. The most important of these was dysphagia (RR of 9.9), followed by stroke severity (National Institutes of Health Stroke Scale (NIHSS) ≥ 10, RR 6.57), non-lacunar basal-ganglia infarction (RR 3.10), and any other infection present on admission (RR 3.78). Initial vomiting, especially if associated with impaired vigilance, predicted poor response to antibacterial treatment[20]. Mild dysphagia can be managed by modification of diet and fluids, whereas severe dysphagia requires cessation of oral intake and nutrition via the enteral route using feeding tubes. However, patients fed exclusively via the enteral rather than oral route still develop pneumonia[21]. Indeed, stroke patients who require nasogastric feeding are at very high risk of pneumonia (39-68%)[22 23 24 25]. Data from the UK National Sentinel Stroke audit show a 44% incidence of pneumonia in tube-fed patients, but only 13% in the patients not requiring enteral feeding[26]. In patients fed via nasogastric tubes gastro-oesophageal reflux is common (56%), and doubles the risk of pneumonia (89% with vs. 43% without gastro-oesophageal reflux)[27]. Additional measures are therefore needed to prevent pneumonia in this patient group.

1.3 - Prevention of pneumonia after stroke: what is already known?

Several approaches to prevention of pneumonia after stroke have been described. These include processes of care and pharmacological agents. Most are supported by observational data or secondary analysis of large randomised controlled studies.

Dysphagia screening reduces the incidence of stroke-associated pneumonia by over 50%[21 28]. This is now standard care after stroke[29] and included as a quality marker in the Sentinel Stroke National Audit programme[30]. A large (n=11,757) observational study of 9 processes of care identified early mobilization as the most effective intervention in preventing pneumonia (OR 0.43)[31]. This was not confirmed in the AVERT study[32].

Systemic antibiotic prophylaxis is associated with a significant reduction in infections, but no favourable effects on mortality and disability in a meta-analysis of five randomised controlled trials including 506 participants[33]. A subsequent randomised trial of intravenous prophylactic ceftriaxone in 2250 unselected acute stroke patients reduced the overall rate of infections (mainly urinary tract), but has no effect on pneumonia, even in a subgroup with severe strokes, and did not improve functional outcome[34]. One further large study of systemic antibiotic prophylaxis in 1200 stroke patients with dysphagia has recently completed[35]. Systemic antibiotic prophylaxis exposes patients

to antibiotics they may not need and carries the risk of increasing the prevalence of antibiotic resistance, a key concern in the modern NHS[36].

Selective decontamination of the digestive tract (SDD), using both systemic and topical antibiotics has been shown to be effective in reducing both pneumonia and mortality in a meta-analysis including 4595 patients on intensive care units[37]. However, the potential of increasing antibiotic resistance requires further research[38]. In stroke patients one small (n=203) randomised controlled trial of selective oral decontamination (SOD) using antibiotic paste (2% w/w colistin, 2% w/w tobramycin, and 2% w/w amphotericin B) applied to the oral mucosa but no systemic antibiotics was associated with a significant reduction in the incidence of pneumonia[39]. While promising, this has been not translated into routine practice, as the trial was small, and the antibiotic paste has to be made up by pharmacy, as it is not routinely available in the NHS. Current UK guidelines recommend that all stroke patients, especially those who have difficulty swallowing, and are tube fed, should have oral and dental hygiene through brushing of teeth, dentures and gums with a suitable cleaning agent (toothpaste or chlorhexidine gluconate dental gel)[40 41]. Chlorhexidine dental gel is commonly used as part of a digestive decontamination regime in intensive care units, and could be a potential alternative for SOD. A small phase II randomised trial in stroke patients showed that chlorhexidine-based oral hygiene interventions had no impact on the prevalence of oral Gram-negative organisms, *S. aureus* or yeasts; and was not powered for clinical outcomes[42]. In a recent meta-analysis of randomised trials in the critical care setting, selective oral decontamination had a favourable effect on mortality, whilst oral chlorhexidine based interventions were associated with increased mortality[43].

Prevention of vomiting and regurgitation using the antiemetic metoclopramide was associated with a significant reduction of pneumonia in a small (n=60) randomised controlled trial[44]. This is promising, but needs to be confirmed in a larger trial. The safety and efficacy of other antiemetics in the prevention of pneumonia after stroke have not been tested in randomised controlled trials.

Cough is a well-known side effect of angiotensin converting enzyme inhibitors (ACEIs). Such cough induction could potentially reduce the risk of pneumonia after stroke. There is some evidence from a secondary analysis of the PROGRESS trial, from a large Chinese case cross-over study, and a meta-analysis of 8,693 patients enrolled in blood pressure trials that ACEIs reduce pneumonia after stroke, but these were studies of less severe strokes well beyond the hyperacute phase[45 46 47]. The effect of early introduction of ACEIs on the development of pneumonia has not been tested, and as a large study of candesartan given within 30 h of stroke onset suggested a higher risk of early neurological deterioration[48] and poor functional outcome, such studies are unlikely[49]. Retrospective analyses of

studies of cilostazol, an antiplatelet agent with vasodilator effects, for secondary prevention during the chronic stage of stroke have shown a significant reduction in pneumonia in the actively treated group[50]. The mechanism of action is unknown, but is hypothesized that cough induction might be via bradykinin and substance P as in ACEIs. However, as the primary effect of cilostazol is prevention of stroke recurrence, this in itself may explain the lower incidence of pneumonia.

Current recommendations for prevention of pneumonia after stroke relate to processes of care and are based on evidence from observational studies. Results of two small randomised controlled studies show that pharmacological interventions (metoclopramide, selective oral decontamination) are safe, and effectively reduce the incidence of pneumonia in dysphagic patients. This needs to be confirmed in a larger trial with longer-term functional outcomes.

2. RATIONALE

Pneumonia is the most common cause of death in stroke patients. It is also associated with poor recovery, higher levels of long-term disability, and longer length of stay. Patients with severe strokes and dysphagia who require nasogastric feeding are at highest risk of pneumonia. There are two interventions that are associated with significant reductions in pneumonia in pilot studies, metoclopramide, and oral decontamination. This is promising, but more evidence is needed before either of these two treatments can be introduced as standard care in stroke patients.

2.1 - Metoclopramide

2.1.1 - Evidence for the use of metoclopramide for the prevention of pneumonia

In the Metoclopramide for the prevention of Aspiration Pneumonia after Stroke (MAPS) trial it was shown that metoclopramide 10 mg tds started within 48 h after inserting the nasogastric tube reduced the incidence of pneumonia within the first 21 days by 69% ($p<0.001$), with fewer episodes of aspiration, a faster return to normal oral feeding, less hypoxia, and fewer days on antibiotic treatment[44]. There was also a trend towards lower mortality with metoclopramide (odds ratio 1.85, $p=0.29$). This trial was conducted in a single centre and included 60 participants. The aim of the MAPS-2 trial is to confirm the reduction in pneumonia in a multi-centre trial, and to determine whether there is a significant effect on mortality in a patient population representative of UK stroke units and large enough to achieve appropriate power to answer the question.

2.1.2 - How metoclopramide could reduce the risk of pneumonia after stroke

In addition to oropharyngeal dysfunction and dysphagia, stroke also causes dysfunction of the lower oesophageal sphincter and the stomach, 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 such as adrenaline and dopamine, which affect gastric motility[51]. Lower oesophageal sphincter dysfunction is further exacerbated by the presence of an NGT, which predisposes to reflux of stomach contents and micro-aspiration[52].

Metoclopramide 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 pre- and postsynaptic dopamine D2-receptors. Dopamine has a direct relaxant effect on the lower oesophageal sphincter, the gastric fundus and the antrum; it also inhibits the release of prokinetic acetylcholine. By antagonizing the action of dopamine, metoclopramide increases the lower oesophageal sphincter pressure, gastric tone, forward peristalsis of the stomach and the duodenum, whilst simultaneously decreasing pyloric sphincter pressure[53]. These mechanisms accelerate gastric emptying, reduce gastric stasis and residual volume, and thus decrease gastro-oesophageal reflux. In patients fed via NGT the combined reduction in vomiting and reflux should restrict gastric contents from reaching the dysfunctional pharynx, thereby lowering the risk of aspiration and pneumonia.

There are several potential mechanisms to explain how metoclopramide can reduce pneumonia after stroke. As a potent antiemetic, metoclopramide is expected to reduce vomiting. This was confirmed in the MAPS trial, where fewer episodes of vomiting and witnessed aspiration were observed in patients treated with metoclopramide[54]. However, while vomiting is a frequent complication of cerebral haemorrhage and posterior circulation strokes, it is not a common complication in the much more prevalent anterior circulation strokes. It is therefore unlikely that the antiemetic effect alone accounted for the large reduction in pneumonia seen in the MAPS trial. Metoclopramide also increases the tone of the lower gastro-oesophageal sphincter and accelerates gastric emptying, thus reducing the risk of regurgitation. As the latter is quiet, and might only present as drooling, its incidence and relevance is likely to be underestimated. Transient hypoxia may be the only manifestation of aspiration of regurgitated gastric contents[55]. It is likely that prevention of reflux and the resultant silent aspiration contributed to the reduction in the incidence of pneumonia in patients who received metoclopramide. Early after stroke hypoxia is most frequent during transfers between wards, and within the head scanner[56]. Vomiting and regurgitation due to motion sickness could potentially explain this finding, and would suggest that vomiting and regurgitation might be more common in this patient group than hitherto appreciated.

2.1.3 - Benefit-risk assessment

There is a risk assessment summary in Appendix 1. Metoclopramide is a commonly prescribed antiemetic, which has been in regular clinical use for over 30 years with well-established effects and side effects (Appendix 4.1)[57].

The main adverse effects are acute dystonic reactions involving facial and skeletal muscle spasms and oculogyric crises. These are seen mainly in children, young women and the very old, especially within first few doses after initiation of therapy. They are aborted by injections of antiparkinsonian agents, such as procyclidine, or subside spontaneously within 24 h after discontinuation. Tardive dyskinesia has been associated with prolonged (several months) administration, and may not be reversible after discontinuation of treatment. It is a very rare complication and is unlikely within the 21 days of treatment in this trial. Other side effects listed in the summary of product characteristics are:

Very common (≥1/10): somnolence

Common (≥1/100, <1/10): diarrhoea, asthenia, extrapyramidal disorders, Parkinsonism, akathisia, depression, and hypotension (particularly with intravenous formulation).

Uncommon (≥1/1000, <1/100): bradycardia (particularly with intravenous formulation), amenorrhoea, hyperprolactinaemia, hypersensitivity, dystonia, dyskinesia, depressed level of consciousness, and hallucination.

Rare (≥1/10000, <1/1000): galactorrhoea, convulsion (especially in epileptic patients), and confusional state.

Not known (cannot be estimated from the available data): methaemoglobinaemia (largely in patients with g6pd deficiency), sulfhaemoglobinaemia, cardiac arrest (occurring shortly after injectable use), and which can be subsequent to bradycardia, atrioventricular block, sinus arrest particularly with intravenous formulation, electrocardiogram qt prolonged, torsade de pointes, gynaecomastia, anaphylactic reaction (including anaphylactic shock) particularly with intravenous formulation, shock, syncope after injectable use, acute hypertension in patients with phaeochromocytoma, transient increase in blood pressure, skin reactions such as rash, pruritus, angioedema and urticarial.

In MAPS-2 metoclopramide will be used to prevent pneumonia, a potentially life threatening complication of stroke. If the results of MAPS are confirmed the benefits will greatly outweigh the risks.

2.2 - Selective oral decontamination

2.2.1 - Evidence for the use of selective oral decontamination for the prevention of pneumonia

A randomised placebo controlled trial of 203 participants with acute stroke and dysphagia conducted by M. Gosney showed that selective oral decontamination (SOD) using a paste containing colistin, tobramycin, and amphotericin B reduces colonization of the mouth by pathogenic anaerobic Gram negative bacilli[39]. SOD paste or placebo was applied 4 times daily to the mucous membranes of the mouth for 21 days for participants with unsafe swallow and for 14 days in participants with safe swallow. SOD was associated with a significant reduction of pneumonia (1/103 vs 7/100, p=0.029) in the treated group. Selective oral decontamination could reduce pneumonia after stroke without the need for systemic antibiotic treatment.

2.2.2 - How selective oral decontamination could prevent pneumonia after stroke

In patients who are fed orally aspiration of saliva carrying pathogenic organisms is a major cause of pneumonia. The oral cavity harbours thousands of species of micro-organisms (oral biofilm) and may therefore be an important reservoir for aspiration of bacteria contributing to development of pneumonia in dysphagic patients. The healthy oropharynx contains predominantly facultative Gram-positive bacteria, such as alpha haemolytic streptococci. Gram-negative organisms (e.g. *Pseudomonas aeruginosa, Escherichia coli, Porphyromonas gingivalis, Serratia marcescens, Enterobacter spp*), *Staphylococcus aureus* and yeasts (e.g. *Candida albicans)* are present transiently, but increase in patients with acute stroke[39 42 58 59 60]. Several of these have also been identified as causative organisms in aspiration pneumonia and/or stroke-associated pneumonia, providing a plausible link between oral flora, aspiration and pneumonia in stroke patients.

2.2.3 - Benefit risk assessment

Use of antibiotics, even if only as an oral paste, could potentially induce antibiotic resistance. This has not been shown in trials of patients in critical care or in the original trial of SOD in stroke patients by Gosney et al.

A controlled cross-over study of SOD versus SDD in Dutch critical care units included 1904 patients given SOD (topical tobramycin, colistin, and amphotericin B). No increase in Clostridium difficile infection or in the detection of resistant bacteria in surveillance cultures of rectal and respiratory tract samples was seen during follow-up compared to with standard therapy or SDD. SDD included systemic cefotaxime in addition to topical application of the antibiotics to the stomach and oropharynx. There was no increase in Clostridium difficile infection in the SOD group when

compared to standard therapy[61]. A recently published follow-up study by the same group[62] included outcomes for 5881 patients randomised to SOD, and 6116 randomised to SDD. The prevalence of rectal carriage of aminoglycoside-resistant Gram-negative bacteria significantly increased during SDD (7% per month, 95% CI, 1%-13%) but for patients receiving SOD a smaller increase in prevalence was seen (4% per month, 95% CI, 0%-8%). A meta-analysis of 35 ICU studies containing data on antimicrobial resistance detected no relationship between the use of SDD or SOD and the development of antimicrobial-resistance in pathogens (whether Gram negative or Gram positive) in patients in critical care[63]. While longer term studies are needed to confirm this, there is no clear evidence of a major risk. Furthermore, there are no data relating to patients on stroke units.

Treatment of post-stroke pneumonia often requires prolonged and recurrent courses of antibiotics. This increases the risk of antibiotic-associated diarrhoea and of *Clostridium difficile* infection which can have a significant mortality in these patients. Effective prevention of pneumonia will reduce the need for systemic antibiotic treatment, reducing these risks and also reducing the drug pressure which promotes the development of antibiotic resistance, an increasing problem globally.

2.3 - Reason for using a 2x2 factorial trial design

Both metoclopramide and selective oral decontamination are supported by evidence from one small trial each. While promising, it cannot be excluded that the reduction of pneumonia was due to differences in case mix, or linked to details of local service provision such as mouth care regimes, positioning of patients in bed, and therapy practices. Before implementing these treatments in routine care, more evidence from a wider range of patients and services is needed. As neither treatment is currently accepted as standard care for stroke patients, use of a placebo-controlled trial design is appropriate.

Both of the interventions reduce pneumonia via different mechanisms, i.e., prevention of vomiting and regurgitation for metoclopramide, and prevention of pathological bacterial overgrowth for SOD. Both of these are independent of each other. There is no reason to assume that presence of one treatment would affect the effectiveness of the other. It is therefore possible to test both concurrently in a factorial design in the same patient population. This will provide answers to two important research questions in one trial, reducing both costs and the time taken to establish whether they might benefit stroke patients.

2.4 - Timing of the interventions

2.4.1 - When to start treatment

Colonization with pathological anaerobic Gram-negative bacteria occurs within hours of stroke onset[39]. In 67% of stroke patients, pneumonia manifests within 48 h of admission[64]. It is almost invariably associated with swallowing problems. The most important reason for exclusion in the MAPS trial[54] was that potential participants already had pneumonia (202 out of 296 screened). In MAPS-2 therefore the intervention will be started much earlier (within 9 h rather than within 72 h of onset). While this will ensure better recruitment, and cause the treatment to be given when it is most likely to be needed, there is a risk that some participants will recover and not require nasogastric feeding. To reduce the likelihood of this happening, only patients with severe strokes will be included as they have a high risk of persistent dysphagia[65].

2.4.2 - Duration of treatment

In the MAPS trial the duration of treatment was 21 days or until nasogastric tube feeding was no longer needed, if this was before 3 weeks. The majority of the cases of pneumonia occurred within the first week, few in the second week and only one in week 3. Metoclopramide has also been demonstrated to be effective medium-term in the treatment of gastroparesis for up to several weeks[66]. There is no evidence for long-term efficacy beyond one month[67]. Metoclopramide should not be given for longer than 3 months, because of a lack of evidence for effectiveness of long-term treatment and the risk of tardive dyskinesia, which increases with duration of treatment (see Benefit risk assessment). In the MAPS trial, no adverse events were reported. As the risk of tardive dyskinesia is considerably lower than the risk of potentially fatal pneumonia in the target population for the MAPS-2 trial, it was decided to give metoclopramide for a maximum of 21 days, or until enteral feeding is no longer needed (if this occurs before 21 days) as all but one of the pneumonias in MAPS occurred within the first 2 weeks. Using a shorter duration of administration in this trial could potentially reduce the effectiveness in prevention of pneumonia. Duration of SOD will also be for a maximum 21 days, or until enteral feeding is no longer needed (if this occurs before 21 days), covering the time period when the patient is at greatest risk of pneumonia.

3. TRIAL OBJECTIVES

3.1 - Aim

To evaluate whether early interventions aimed at the prevention of pneumonia reduce mortality and improve recovery after stroke.

3.2 - Primary objective

To conduct a phase III multi-centre prospective double-blind, randomised, 2x2 factorial placebo-controlled trial to determine if early treatment with metoclopramide or selective oropharyngeal decontamination reduce mortality after stroke.

Four intervention groups will be created:

1. Metoclopramide and oral decontaminant paste
2. Metoclopramide and placebo paste
3. Metoclopramide placebo and oral decontaminant paste
4. Metoclopramide placebo and placebo paste

Hypothesis 1: metoclopramide reduces mortality in patients with dysphagia after stroke.

Hypothesis 2: selective oral decontamination reduces mortality in patients with dysphagia after stroke.

3.3 - Secondary objectives

To assess the effect of metoclopramide and selective oral decontamination on secondary outcomes: clinical outcomes, pneumonia incidence, dependency, safety, and costs.

3.4 - Primary outcome measure

The primary outcome is mortality up to the end of the trial.

3.5 - Secondary outcome measures

1. Diagnosis of pneumonia up to day 14 using daily log and standard definition of pneumonia: pneumonia will be defined as fulfilment of 3/6 diagnostic criteria (fever, productive cough, abnormal chest examination, abnormal chest radiograph, arterial hypoxaemia, positive microbiology), based on the Mann criteria for the diagnosis of stroke associated pneumonia[68] with modifications based on the MAPS Pilot study[69] (see Appendix Two for detail)
2. Any new diagnosis of pneumonia up to day 15 using clinician diagnosis and antibiotic prescription data
3. Antibiotic use: number of days of antibiotic treatment for pneumonia within the first 30 days
4. Neurological recovery: Change in NIHSS[70] between admission and day 30
5. Functional recovery: modified Rankin Scale (mRS)[71] score at 90 days with an additional category [6] added to include participants who died

6. Quality of life (EQ-5D™)[72 73]

3.6 - Other outcome measures

1. Time to first episode of pneumonia (if any) within the first 14 days
2. Vomiting: number of days with recorded vomiting in the first 14 days
3. Infection and inflammation: Highest temperature, white blood cell count (WBC), and C–reactive protein (CRP) within the first 14 days
4. Time to return to oral feeding (days)
5. Hypoxia: number of days on oxygen treatment and lowest oxygen saturation during the first 7 days

3.7 - Safety endpoints

Safety endpoints will be recorded up to 30 days (Appendix Three) and include acute dystonic reactions, tardive dyskinesia, evidence for antibiotic associated infections (*C. difficile*, ESBL, MRSA), and serious cardiac arrhythmias. Death is the primary outcome and will be recorded as such up to the end of the trial.

3.8 - Health economics endpoints

Antibiotics, duration of enteral feeding, length of stay on the acute stroke unit, the number of days treated on the intensive care unit, the acute stroke unit, the stroke rehabilitation unit, and in other hospital wards the number and type of interventional and surgical procedures performed, length of stay in hospital, readmissions, 'home time'[74 75] and institutionalisation will be recorded.

4. TRIAL DESIGN

This is a phase III multi-centre prospective double-blind, randomised, 2x2 factorial placebo-controlled trial.

4.1 - Measures to minimise/avoid bias

Using a minimised randomisation process (see section 7.3), participants will be randomised 1:1:1:1 to one of four groups:

1. Metoclopramide and oral decontaminant paste
2. Metoclopramide and placebo paste
3. Metoclopramide placebo and oral decontaminant paste
4. Metoclopramide placebo and placebo paste

Participants and outcome assessors will be blind to treatment allocation. The allocation code will not be broken until the last participant has completed follow-up and the database is locked, unless a code break for an individual patient is requested by the DMC, is required for regulatory reporting, or is necessary for clinical reasons.

5. TRIAL SETTING

This will be a multi-centre trial with at least 50 sites within England, Northern Ireland, Wales and Scotland. The site-specific requirements for a centre to be eligible for MAPS-2 trial are:

- Admit patients with acute stroke
- Dysphagia screening within 4 h of patient admission to hospital
- Rapid transfer of patient from A&E to acute stroke unit (<4 h) or able to recruit in A&E
- Daily consultant ward rounds
- 4-hourly monitoring of physiological parameters during the hyperacute phase
- 6-hourly monitoring of physiological variables during the acute phase
- Ability to continue trial intervention for 3 weeks (on site or in downstream hospital)

A list of the participating sites will be available on the trial website (www.keele.ac.uk/maps2).

6. TRIAL POPULATION

6.1 - Trial participants

The target population is dysphagic patients with acute stroke, within 9 hours of stroke onset, where feeding via nasogastric tubes is planned or already in place. Many patients have already vomited by the time they arrive in the stroke unit. It is therefore important to start preventative measures as soon as possible after admission, and before transfer to the acute stroke unit. The need for nasogastric feeding can be predicted early from the severity of the neurological deficit and the swallow screen. Patients will therefore be recruited if the clinical presentation suggests that there is a high likelihood that they are going to require nasogastric feeding.

6.2 - Inclusion Criteria

1. Adult (18 years and over) patients with a clinical diagnosis of acute stroke (as defined by the World Health Organization, excluding the requirement of a duration of 24 h or more)[76]
2. Within 9 h of stroke onset (in wake-up stroke the onset is defined as the time the patient awoke or was found unless this is more than 12 h from last known well)
3. Moderate to severe neurological impairment with a NIHSS Score $\geq$10[77 78]
4. Unable to take a normal oral diet or fluids because
    a. too drowsy to be assessed formally or
    b. failed bedside swallowing screen

6.3 - Exclusion Criteria

1. Evidence of vomiting since stroke onset
2. Pre-existing swallowing problems
3. Known oesophageal pathology that might interfere with placement of a nasogastric tube (e.g. malignancy, achalasia, pharyngeal pouch or web)
4. Probable or definite pneumonia (abnormal chest exam or pyrexia >37.7 °C, or receiving antibiotic treatment at time of presentation)
5. Contraindications to metoclopramide (hypersensitivity to metoclopramide or any of the excipients (sodium chloride, citric acid monohydrate, sodium citrate, dilute hydrochloric acid, dilute sodium hydroxide, nitrogen, or water for injection), epilepsy, gastrointestinal obstruction, perforation, or haemorrhage, gastrointestinal surgery within the last week, Parkinson's disease, treatment with levodopa or dopaminergic agonists, phaeochromocytoma or neuroleptic malignant syndrome or tardive dyskinesia or methaemoglobinaemia or NADH cytochrome –b5 deficiency),

6. Patients with severe liver disease (cirrhosis) or severe kidney disease (eGFR<30 L/min)[57]
7. Known allergy to colistin (polymyxin E), tobramycin, aminoglycosides in general, or amphotericin B
8. Pregnant or breast feeding[57]
9. Other co-morbid conditions with a life expectancy of less than 3 months at the discretion of the clinical treating team
10. Inability to gain consent from the patient or a personal legal representative or refusal of consent

7. TRIAL PROCEDURES

Strict adherence to all specifications laid down in this protocol is required for all aspects of the trial conduct. A patient schedule can be found in Appendix three. Detailed procedures are laid out in the trial manual.

7.1 - Recruitment

Patients will be recruited from A&E departments and acute stroke units in England, Wales, Northern Ireland, and Scotland.

7.1.1 - Patient identification

Patients will be identified by research nurses and doctors who are part of the normal clinical team at the research sites. No trial advertising will be required and there will be no participant identification centres (PIC) for this trial.

7.1.2 - Screening and Eligibility Assessment

Participants will be screened, assessed for eligibility, and recruited in the emergency admissions department or on the stroke unit by a member of the local research team. Patient eligibility will be confirmed by a medical practitioner. No imaging is required at screening, but renal function (eGFR), which is part of routine clinical assessment, needs to be available.

The proportion of stroke patients screened, eligible, recruited, and refusing participation will be monitored. Anonymised information on patients who are not eligible to participate in MAPS-2 will be collated for Consolidated Standards of Reporting Trials (CONSORT), including their age and gender.

If, after randomisation, a patient is found to be ineligible the following guidance must be followed:

Ineligibility due to safety reason – all trial-related treatments are to stop immediately. Explain to patient/personal legal representative why treatments have been stopped and complete a breach of protocol form (scan and email to trial coordinating centre). Continue with patient follow-ups, if patient willing to do so, and safety reporting until day 30.

Ineligible but NGT still in place – continue trial-related treatments if patient (or personal legal representative) is happy to do so. Explain to patient/personal legal representative and complete a breach of protocol form (scan and email to trial coordinating centre). Continue with patient follow-ups, if patient willing to do so, and safety reporting until day 30.

Ineligible and NGT removed – stop trial-related treatments. Continue with patient follow-ups and safety reporting as per this protocol.

7.2 - Informed Consent

The Principal Investigator (PI) retains overall responsibility for the informed consent of participants at his/her site and must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to this protocol and principles of Good Clinical Practice (GCP). The PI also takes responsibility for ensuring that all potential participants are protected and participate voluntarily in an environment free from coercion or undue influence.

Informed consent will be sought from patients after full and adequate oral and written information (see participant information sheet and consent form) 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. In cases where the patient does not have capacity to consent, consent will be sought from the patient's personal legal representative. In cases where the patient is informed as much as he/she is able to understand but does not have the capacity to give fully informed consent then this will be sought from a personal legal representative (see legal representative information sheet and consent form). The oral and written information will be provided to the personal legal representative including the same information as would be given to the patient. If the patient has capacity to consent but is unable to sign because of impairments, verbal consent, witnessed and signed by an independent observer, will be documented (see consent form). 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. Confirmation of consent will be sought in patients who are recruited with consent from a personal legal representative, but regain capacity to consent prior to the end of the trial (see confirmation of consent form).

Due to the design of the trial, patients or their personal legal representatives will have to decide within a few hours of admission to hospital. They will be given the opportunity to discuss the trial with a relative or friend. Participants or their personal legal representatives will be free to withdraw from the trial at any time without giving reasons and without affecting further treatment.

The original signed consent form will be filed in the investigator site file. One copy will be given to the patient or personal legal representative and another copy will be filed in the patient's notes.

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

If a participant is able to consent for the trial but later becomes incapacitated, the original consent will endure for the loss of capacity.

7.3 - Randomisation, Participant Identification, Blinding and Unblinding

7.3.1 - Randomisation

Participants will be randomised by minimisation using known risk factors for stroke-associated pneumonia[78 79 80 81] and long-term outcome, i.e. NIHSS, the eye and motor components of the Glasgow Coma Scale (GCS), Six Simple Variables risk index for 30-day survival (derived from age, pre-stroke independence, living alone, normal verbal component of the GCS, ability to lift both arms, ability to walk[82 83]) [<=0.81 or > 0.81], whether the patient was thrombolysed or not, and time from stroke onset. The minimisation will incorporate a 10% random element. This ensures concealment of allocation, reduces differences in key baseline prognostic variables, and slightly improves statistical power[84]. The actual minimisation protocol will be kept in a separate document with restricted access. Allocation will not be stratified by trial centre, because this may result in unacceptably high rates of allocation prediction and selection bias[85]. However, key aspects of centre characteristics and performance (numbers recruited, median age, median NIHSS, n (%) with pneumonia, n (%) with urinary catheters, n (%) of deaths by 30 days) will be recorded and monitored by the trial management group. Data for outliers will be checked, and, if necessary, additional site visits will be planned. A retrospective analysis by centre will be performed with and without the outlying centres to adjust for any heterogeneity of treatment effect by centre.

If the online allocation IRT system is unavailable a paper system will be used. All required details will be recorded in a paper form and a temporary patient identification number (tPID) assigned to the patient. Once the system is recovered, the details will be entered and a permanent patient

identification number (PID) assigned, the assigned treatment will be overridden to match that which was allocated. See Appendix Seven.

7.3.2 - Participant Identification

Upon randomisation, each patient will be assigned a unique PID number which will be used to identify the patient throughout the trial.

7.4 - Blinding

All clinicians, nurses, patients and other research staff including the Chief Investigator, trial management personnel and Sponsor staff will be blinded to the treatment. During randomisation a pack number that will correspond to a treatment pack containing the blinded treatment for administration will be assigned to each participant. The metoclopramide placebo and oral decontaminant placebo will be matched in appearance, smell and taste where appropriate. The final unblinding of all trial participants will take place after the analysis data set is locked.

7.5 - Unblinding

In general, there should be no need to unblind the allocated treatment. If some contraindication to metoclopramide or the selective oral decontaminant develops after randomisation, the trial treatment should simply be stopped. Unblinding should be done only in those rare cases when the treating physician believes that clinical management depends importantly upon knowledge of whether the participant received an intervention or a placebo. In those few cases when urgent unblinding is considered necessary, the PI (or delegate) will be able to unblind the treatment for a participant by using the same IRT system used for randomisation (Tenalea). Log-in details for the Tenalea system, providing access to unblinded information for individual participants, will be contained in the Site Investigator File. The PI will then be required to notify the sponsor of an unblinding event within 24 hours, without revealing the treatment information. In the unlikely event that the Tenalea system is unavailable, the sponsor will provide unblinded treatment information which will be manually accessed from a paper copy of the treatment allocation x kit number list . An emergency unblinding telephone number has been set up to provide additional support and advice during normal working hours and a recorded message for outside of normal working hours confirming the instructions for emergency unblinding. This message will include Sponsor contact information in case of the Tenalea system being unavailable. The rate of unblinding will be monitored and audited by the trial coordinating team and the data monitoring committee for review in accordance with the DMC Charter.

In the event of breaking the treatment code, this occurrence will normally be recorded as part of

managing a medical emergency, without disclosing unblinded information to the trial team. In the event of a SUSAR, expedited reporting including unblinded information will be made to the REC and the MHRA by a delegated member of the Sponsor Research & Development team. The DMC will produce unblinded analysis reports as required for the annual Development Safety Update Report to the MHRA and annual safety report to the REC. The parts of these reports containing unblinded data will be confidential and not disclosed to any member of the trial coordinating team, trial statistician or sponsor.

Instances of unblinding will also be documented at the end of the trial in the final trial report.

7.6 - Baseline data

At baseline, following informed consent, key demographic, clinical and prognostic details will be recorded (see Appendix five for detail). The daily log of symptoms, signs, laboratory and antibiotic treatment (see Daily log Appendix five) will also be commenced.

7.7 - Trial Assessments

7.7.1 - Day 7 Follow-up

At day 7 post randomisation, or on the day of discharge if earlier, the clinical notes and drug charts will be checked to determine whether and when a diagnosis of pneumonia has been made. A record of a diagnosis of pneumonia in the clinical notes or commencement of antibiotics with a documented indication of pneumonia or lower respiratory tract infection will be accepted. The daily log (see appendix five for detail) of temperature, oxygen saturation, chest symptoms, vomiting, aspiration, antibiotic use, x-rays and lab tests, presence of urinary catheter, presence of nasogastric tube or date enteral feeding no longer required, IMP compliance will be collected, and emailed to the trial centre. The information reported in the daily logs will be used by the trial centre to make an assessment of pneumonia based on the modified Mann criteria listed in Appendix Two. Pneumonia diagnosis according to the Centre of Disease Control criteria and the Pneumonia in Stroke Consensus Group criteria will also be recorded.

7.7.2 - Day 14 Follow-up

At day 14 post randomisation, or on the day of discharge if earlier, the same assessments as on day 7 will be repeated, if the participant is still in hospital or readmitted, and entered into the CRF (see Table 3). It is unlikely that patients are discharged home at day 14, but if this is the case the discharge status will be taken as the day 14 result.

7.7.3 - Day 21 Follow-up

At Day 21, or on the day of discharge if earlier, the compliance information from Day 15 to Day 21 for each of the IMPs will be recorded on the CRF and emailed to the trial coordinating centre.

7.7.4 - Day 30 Follow-up

At day 30 post randomisation, or on the day of discharge if earlier, the NIHSS and mRS will be documented. Drug charts will be reviewed to determine which antibiotics were given, for how long, and for which indication. Lab reports up to 30 days will be reviewed to determine *C. difficile* status, results of sputum cultures, and antibiotic resistance. The trial medication will be collected, and the number of remaining ampoules/sachets recorded (see appendix 5 day 30).

7.7.5 - Adverse Events

Adverse events will be collected prospectively and systematically on day 30. See Section 9 for full details of pharmacovigilance requirements.

At 7, 14 and 30 days the CRF records any of the following SAEs as Research Outcome Data:

- A further stroke (yes/no) If yes, give date and type (infarct/ haemorrhage/no imaging diagnosis). If yes, give date and complete SAE form.
- A collapse or cardiac/ respiratory arrest requiring resuscitation (yes/no) /- bradycardia/ torsade de pointes/ ventricular tachycardia/ asystole/ electromechanical dissociation/ hypotension/ haemorrhage/ respiratory arrest/ other. If yes, give date and complete SAE form
- Severe bradycardia requiring atropine or pacemaker insertion (yes/no). If yes, give date and complete SAE form
- Definite epileptic seizure (focal or generalized) If yes, give date and complete SAE form
- Orofacial dyskinesia (yes/no). If yes, give date and complete SAE form
- Tardive dyskinesia (yes/no) If yes, give date and complete SAE form
- A NEW diagnosis of Parkinson's disease (yes/no) If yes, give date and complete SAE form
- Any serious adverse event that is NOT a known complication of stroke

7.8 - Day 90 Follow-up

The participant's vital status will be ascertained, and the date of death in the case of those who have died, from hospital or general practice records will be recorded on the CRF. For participants still alive and discharged from the acute stroke ward, a telephone interview will be carried out with participants 3 months after randomisation to record place of residence, if, and for how long, they have been readmitted to hospital, mRS score, quality of life (EQ5D), and current method of feeding (see appendix 5 day 90). The telephone interview will be conducted by a trained member of the

team at the trial coordinating centre. Prior to making the call, a member of the trial coordinating team will contact the patient's GP to confirm that the patient is alive and able to carry out the interview. If the patient is no longer registered with the GP, the recruiting hospital will be contacted to see if there are new contact details for the patient. If the coordinating centre are not able to contact the patient or their designated alternative contact (if appropriate) the GP will be contacted for information on the participant's health status. If the patient is still in hospital a research nurse will complete the 90-day assessment.

7.9 - Vital status at the end of the trial

This will be assessed towards the end of the trial. This will be done by phone call to the general practitioner, and where necessary, the participant or the contacts they provided (see appendix 5 vital status check). Missing data will be ascertained with the team who recruited the patient, and via linkage with Hospital Episode Statistics, Office of National Statistics, and Sentinel Stroke National Audit datasets.

7.10 - Day of discharge/ transfer/ repatriation

On the day of discharge, contact details, information on ward stays, the length of stay and discharge destination will be recorded in the CRF (see appendix 5 transfer to another hospital and appendix 5 discharge into the community). If discharge to the community (home or institution) is before 30 days, the day 30 patient assessment will be completed at discharge rather than at day 30.

In the case of discharge to another hospital (transfer or repatriation) within 21 days while the participant is taking an IMP then they will continue in the trial according to the protocol at another trial site. Detailed processes are outlined in the trial manual.

7.11 - Withdrawal criteria

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-ups, 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, follow-up without participant contact, and use of data. Unless the participant withdraws from any follow-ups, these 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. Withdrawal will be documented in the CRF. Participants will be made aware that withdrawal will not affect their medical care and non-trial follow-up.

If the participant is temporarily withdrawn from trial medication by a member of the clinical team they may return to the trial treatment within the original timescale.

7.11.1 - Participant removal from the trial due to adverse events

Any participant who experiences an adverse event may be withdrawn from the trial at the discretion of the Principal Investigator. Should the participant not receive the complete intervention due to, for example, an adverse event, they will remain in the trial until the end of the trial (see 7.12), as completeness of follow-up is essential. However, should they wish to do so, any participant is free to withdraw from the trial at any time and without giving a reason.

7.11.2 - 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/her health status is, and whether there are any new contact details.

7.11.3 - Replacement

There will be no replacement of withdrawn participants.

7.12 - End of Trial

The trial will end when the final participant has completed the 90-day follow-up. The Sponsor will notify the MHRA and the REC within 90 days of the end of the trial.

7.12.1 - Early stopping of trial

Data on recruitment rate, baseline clinical and demographic data, outcomes and adverse events will be provided in strict confidence to the Data Monitoring Committee (DMC) on a 6-monthly basis, or more frequently, if requested. Reports will be generated by a statistician independent of the trial team.

The remit of the DMC will be to safeguard the interests of trial participants, assess the safety and efficacy of the interventions during the trial, and monitor the overall conduct of the clinical trial by reviewing interim analyses, adverse events and issues relating to trial conduct. If either of the two interventions really provides substantial benefit or harm, then this may become apparent before the target recruitment has been reached. Alternatively, new evidence might emerge from other sources that metoclopramide or selective oral decontamination is definitely effective, ineffective, or adverse. To protect against this, during the period of recruitment to the study, the DMC will review the interim analyses along with updates on results of other related studies, and any other analyses that

the DMC may request. The DMC will advise the chair of the Trial Steering Committee (TSC) if, in their view, the randomised comparisons in the trial have provided both (a) “proof beyond reasonable doubt” that for all, or for some, types of patient one particular treatment is definitely indicated or definitely contraindicated in terms of a net difference in the major endpoints, and (b) evidence that might reasonably be expected to influence the patient management of many clinicians who are already aware of the other main trial results. Determining appropriate criteria of proof beyond reasonable doubt will be the prerogative of the DMC, but it is anticipated that one of the commonly used methods of interim analysis will be used as a stopping rule (e.g. the Haybittle-Peto approach or the O’Brien-Fleming approach). The frequency with which the chosen interim analysis is carried out will be determined by the DMC (with regard to the stopping rule – the Haybittle-Peto approach does not require a specified number of times that the interim analysis should be performed, but other approaches do), but for a survival outcome their timing should relate to the number of events that have accrued rather than the number of participants that have been recruited.

On the basis of the information outlined above, the TSC can decide whether to close or modify any part of the trial. Unless this happens, however, the Trial Management Group, TSC, the investigators and all of the central administrative staff (except the statisticians who supply the confidential analyses) will remain unaware of the interim results. The reporting template and stopping rules will be reviewed and agreed by the DMC before the trial starts.

7.13 - Storage of samples

No samples will be collected or stored in relation to this trial.

8. TRIAL INTERVENTIONS

Participants will be randomised 2x2 to the following investigational medicinal products (IMPs):

Metoclopramide hydrochloride solution 10 mg (M) or matching placebo (P1) three times a day

AND to

Selective oral decontamination paste (SD) containing 2% (w/w) colistin, 2% (w/w) tobramycin, and 2% (w/w) amphotericin B or matching placebo (P2) applied topically to the mucous membranes of the mouth four times a day giving the combinations:

1. Metoclopramide and oral decontaminant paste
2. Metoclopramide and placebo paste
3. Metoclopramide placebo and oral decontaminant paste

4. Metoclopramide placebo and placebo paste

The interventions will be given until nasogastric feeding is no longer required or for a maximum of 21 days.

8.1 - Description of the IMP

8.1.1 - Metoclopramide description

The first investigational medicinal product is metoclopramide solution for injection (5 mg/ml). Metoclopramide is a widely used antiemetic with well-known effects and side effects. Its pharmacological properties are outlined below and described in the summary of product characteristics (appendix 4).

The action of metoclopramide is closely associated with parasympathetic nervous control of the upper gastro-intestinal tract, where it encourages normal peristaltic action. Metoclopramide stimulates activity of the upper gastro-intestinal tract and restores normal co-ordination and tone. Gastric emptying is accelerated and the resting tone of the gastrooesophageal sphincter is increased. Metoclopramide also has central actions. It is a dopamine-receptor antagonist with a direct anti-emetic effect on the medullary chemoreceptor trigger zone.

8.1.2 - Selective oral decontaminant description

The second investigational medicinal product is selective oral decontamination (SOD) paste. The SOD paste contains a combination of three antibiotics, 2% w/w amphotericin B, colistin, and tobramycin in a Vaseline and paraffin base. SOD paste and matching placebo are unlicensed products and the product formulation, stability studies, manufacturing processes and labelling are outlined in the Investigational Medicinal Product Dossier.

8.2 - Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s)

8.2.1 - Metoclopramide route of administration, dosage, regimen and treatment period

Metoclopramide solution for injection or placebo will be given at a dose of 10 mg three times a day at evenly spaced intervals. Metoclopramide will be given via the nasogastric tube, whenever possible. The first dose, and any dose thereafter when the nasogastric tube is not in place or not usable will be given via slow intravenous injection. Treatment will start within 11 hours of onset (e.g.

no longer than 2 hours after randomisation) and continue until nasogastric feeding is no longer required or for a maximum of 21 days (whichever is earlier).

The dose and duration of treatment are based on the results of the MAPS trial, which used 10 mg three times a day for 21 days[44]. The most common reason for exclusion in the MAPS trial was that potential participants already had pneumonia (202 out of 296 screened). In MAPS-2 therefore the intervention will be started much earlier (within 9 h rather than within 72 h of onset). In MAPS metoclopramide was given as a liquid via the nasogastric tube. As only very few patients have nasogastric tubes in place within the first few hours of admission, and it is important to start treatment as early as possible, the metoclopramide will be given metoclopramide intravenously until the nasogastric tube is in place and usable. The timing of placement of nasogastric tubes varies between patients and hospitals and, but usually occurs within the first 72 hours of admission. Nasogastric tubes are frequently displaced, requiring position checks and replacement, if no longer in the stomach. Placement of nasogastric tubes induces a strong gag reflex, putting patients at risk of vomiting and aspiration. To cover times when the tube is not in place it is therefore allowed for metoclopramide to be given intravenously.

We would therefore need both metoclopramide for intravenous injection and metoclopramide solution for nasogastric use and their respective placebos. This could potentially increase the risk of accidental mix-ups, putting patients at risk. It would also make providing the drug/ placebo and accounting for what was been given more difficult. To avoid this we initially considered giving metoclopramide intravenously throughout the 21-day period. However, cardiac arrhythmias are more likely with metoclopramide given intravenously than if given by the enteral route. Giving metoclopramide enterally, whenever possible, is therefore preferable. While no specific data on enteral tube administration are available for this formulation[86], there is no incompatibility between metoclopramide and its excipients (sodium chloride, citric acid monohydrate, sodium citrate, dilute hydrochloric acid, dilute sodium hydroxide, nitrogen, or water for injection) and the material of nasogastric tubes (rubber, polyurethane, silicon)[87].

8.2.2 - Selective oral decontaminant paste route of administration, dosage, regimen and treatment period

SOD paste will be applied in the same dosage, frequency and duration as in the pilot study[39]. 0.5 g of SOD paste (or placebo) will be applied to the oral mucosa four times a day at evenly spaced intervals. Treatment will start within 11 hours of onset (e.g. no longer than 2 hours after

randomisation) and continue until nasogastric feeding is no longer required or for a maximum of 21 days (whichever is earlier

8.3 - IMP Storage

IMP will be stored, temperature monitored and transferred between sites according to the medicines' management policies of the participating sites.

8.3.1 - Metoclopramide storage

The IMP will be stored below 25°C and protected from light as per medicines' management policies of the participating sites.

8.3.2 - Selective oral decontaminant paste storage

SOD paste and matching placebo must be stored between 2-8 C° according to the medicines' management policies of the participating sites. After dispensing, and in accordance with the stability studies carried out, prior to opening each tube can be stored outside of a refrigerator for up to seven days. Once in use, each tube can be stored outside of a refrigerator for up to 7 days.

8.4 - Packaging and Labelling

8.4.1 - Metoclopramide and placebo metoclopramide packaging and labelling

Metoclopramide ampoules will be labelled according to Annex 13[88] requirements and will contain the subject randomisation number. The head of the ampoules (top section) will also be labelled. The secondary packaging will contain 65 x 2ml ampoules. The secondary packaging label will contain the subject randomisation number.

Placebo metoclopramide (sodium chloride 0.9%) ampoules will be labelled according to Annex 13[88] requirements and will contain the subject randomisation number. The head of the ampoules (top section) will also be labelled for blinding purposes. The secondary packaging will contain 65 x 2ml ampoules. The secondary packaging label will contain the subject randomisation number.

8.4.2 - Selective oral decontaminant packaging and labelling

SOD paste and matching placebo will be packed in white aluminium tubes containing 15g of paste. Each tube will be labelled according to Annex 13[88] requirements and will contain the subject randomisation number. The secondary packaging will contain four x 15g SOD paste or matching placebo. The secondary packaging label will contain the subject randomisation number.

8.5 - Legal status of IMP

8.5.1 - Metoclopramide and placebo metoclopramide legal status

The trial is being carried out under a Clinical Trial Authorisation (CTA). The drug/placebo is therefore only to be used for the participants specified in this protocol, and within the trial.

8.5.2 - Selective oral decontaminant paste and placebo SOD paste legal status

The trial is being carried out under a Clinical Trial Authorisation (CTA). The drug/placebo is therefore only to be used for the participants specified in this protocol, and within the trial.

8.6 - Summary of Product Characteristics (SPC) or Investigator Brochure (IB)

8.6.1 - Metoclopramide SPC and sodium chloride SPC

The SPC (dated 15-SEP-2016) for metoclopramide[57] and the SPC (dated 04-FEB-2016) for sodium chloride 0.9%[89] can be found in Appendix 4.

8.6.2 - Selective oral decontaminant investigator brochure

SOD paste and matching placebo are unlicensed products and the product formulation, stability studies, manufacturing processes and labelling will be outlined in the Investigational Medicinal Product Dossier submitted to the MHRA for approval IB and IMP-D (dated 22-JUN-2017 provided as separate documents.

If during the trial period, the SPCs, IB and relevant safety information are updated, updates will be communicated to concerned investigators in a timely manner and substantial amendments will be undertaken as appropriate.

8.7 - Dosage modifications

8.7.1 - Metoclopramide dosage modifications

In participants weighing less than 60 kg the dose will be reduced from 10 mg tds to 5 mg tds[57]. Patients with severe hepatic dysfunction (cirrhosis) or severe kidney disease (eGFR<30 L/min) will not be included.

8.7.2 - Selective oral decontaminant dosage modifications

The standard dose used for SOD is 0.5 g four times daily to be applied to the oral mucosa. This will not be modified.

8.8 - Known drug reactions and interactions with other therapies

8.8.1 - Metoclopramide drug reactions and interactions with other therapies

These are the same as for regular clinical use of metoclopramide and are listed in the SPC (Appendix 4).

8.8.2 - Selective oral decontaminant drug reactions and interactions with other therapies

Both the SOD paste and matching placebo are unlicensed products. As a result, no evidence is available.

8.9 - Concomitant medications

1. Medications that are contraindicated or should be avoided in combination with metoclopramide:

Metoclopramide is contraindicated in patients taking levodopa or dopamine agonists. Patients taking these medications will be excluded from the trial. Combination with alcohol should be avoided. Participants in the MAPS-2 trial are hospital in-patients who cannot swallow safely. They will not be taking alcohol.

2. Both the SOD paste and matching placebo are unlicensed products. As a result, no evidence is available.

8.10 - Trial restrictions

None.

8.11 - Compliance with Treatment

The trial treatment is prescribed in the drug chart, and administration of each dose is recorded as per normal clinical practice. At the end of the intervention period the remaining treatment doses will be collected and counted. The number of missed doses will be recorded.

9. PHARMOCOVIGILANCE

9.1 - Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that

	participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the summary of product characteristics (SPC) for that product • in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question

9.2 - Operational Definitions for (serious) adverse events

An adverse event (AE) is any unfavourable or unintended sign, symptom, abnormal laboratory finding or illness in a trial participant that develops or worsens during the period of observation in the trial.

This includes:

1. Exacerbation or increase in frequency of a pre-existing illness or symptom
2. A condition or illness identified after inclusion into the trial, even if this was present, but undetected, before trial entry.

Adverse events do not include:

1. A symptom or sign of the stroke that made the participant eligible for the trial, unless it is more severe than expected.
2. An illness or condition that was present at trial inclusion and remains stable.
3. A situation where an untoward medical event has not occurred (e.g. cosmetic surgery, hospital admission for social or convenience reasons).
4. A medical, diagnostic or surgical procedure (e.g. hip replacement, pacemaker insertion, hernia repair, endoscopy). However, the condition that led to the procedure is an AE unless the procedure was elective or pre-planned for a pre-existing condition not associated with any deterioration in conditions.
5. Hospitalisation for treatment or monitoring for stroke not associated with any deterioration in condition
6. Any admission to hospital or other institution for general care where there is no deterioration of condition.

Serious adverse events are common after acute stroke, especially in patients with severe neurological deficits and dysphagia. A list of expected adverse events that are considered a consequence of the stroke and are not subject to safety reporting are given in Appendix Six. These events are to be recorded in the hospital notes.

Breaking the blind at the site should only take place where information about the participant's trial treatment is clearly necessary for the appropriate medical management of the participant.

9.3 - Recording and reporting of (S)AEs and SUSARs

9.3.1 - Timescales for reporting adverse events

Adverse events are to be recorded from the time of consent.

The IMPs (metoclopramide or placebo and/or SOD or placebo) are given for a maximum of 21 days.

All non-serious and serious adverse events that the PI is aware of (unless they are an expected consequence of stroke as per appendix 6) will be collected from the time of patient enrolment until day 30. The rationale for this is that the metoclopramide half life is short and the paste is topical and not systemic and is therefore not expected to be absorbed into the blood stream. In addition the metoclopramide is not expected to have long-term effects administered over the short trial period.

All non-serious events (unless excluded as per appendix 6) must be recorded onto the adverse

event form of the CRF and sent to the trial team as part of the 30 day follow up.

All SAEs (unless non-fatal and excluded as per appendix 6) must be recorded on the SAE form of the CRF and emailed to the Sponsor (maps2.safety@nhs.net) and trial coordinating team (maps-2.uhns@nhs.net) as soon as possible and within 24 hours of the research staff becoming aware of the event. Once all resulting queries have been resolved, original documents are to be retained on site. Any change of condition or other follow-up information should be emailed to the Sponsor as soon as it is available or at least within 24 hours of the information becoming available.

All events will be followed up until the event has resolved, final outcome has been reached or end of the trial.

For each SAE the following information will be collected:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality (i.e. relatedness to trial drug/investigation), in the opinion of the investigator
- whether the event would be considered expected or unexpected.

All SAEs assigned by the PI or delegate (or following central review by CI or delegate) as both suspected to be related to IMP-treatment and unexpected will be classified as SUSARs and will be subject to expedited reporting to the Medicines and Healthcare Products Regulatory Agency (MHRA). The Sponsor will inform the MHRA and the REC of SUSARs within the required expedited reporting timescales

Any adverse events considered to be related to a study procedure are to be reported using the adverse events forms as per the timelines above.

Any adverse events considered to be related to an excipient of any IMP are to be reported using the adverse event forms and timelines as described above. Please use the free text field to clearly indicate that the event is considered to be related to an excipient.

9.3.2 - Causality:

Causality is defined as follows for notification purposes:

Not related or unlikely: An AE with a temporal relationship to trial treatment administration that makes a causal relationship incompatible or for which other drugs, chemicals or disease provide a plausible explanation**.**

Possible: An AE with a 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.

Probable: An AE with a 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.

Definite: An AE with a temporal relationship to trial treatment administration that makes a causal relationship a reasonable possibility, and which can definitely not be attributed to other causes.

An AE whose causal relationship to the study IMP is assessed by the principal investigator or delegated physician as possible, probable or definite is an adverse reaction.

With regard to the criteria above, medical and scientific judgment shall be used in deciding whether prompt reporting is appropriate. The Sponsor cannot downgrade the PI's assessment of causality but can upgrade it.

9.3.3 - Expectedness

An unexpected adverse reaction is an adverse reaction where the nature and severity is not consistent with the information about the trial drug set out in the summary of product characteristics for metoclopramide and in the investigational medical product dossier for selective oral decontamination paste.

9.3.4 - Intensity

The assessment of intensity will be based on the local Investigator's clinical judgement using the following definitions:

- Mild – An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
- Moderate – An event that is sufficiently discomforting to interfere with normal everyday activities.
- Severe – An event that prevents normal everyday activities.

The term severity is often used to describe the intensity (severity) of a specific event. This is not the

same as ‘seriousness’, which is based on patient/event outcome or action criteria as described above.

9.4 - Responsibilities

9.4.1 - Principal Investigator:

- Checking for AEs and ARs at each follow-up assessment within the timelines specified above.
- Using medical judgement in assigning seriousness, causality and expectedness and using the Reference Safety Information approved for the trial.
- Ensuring that all SAEs and SARs (including SUSARs) are recorded and reported to the Sponsor and trial coordinating centre within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs and SARs (including SUSARs) are chased with Sponsor if a record of receipt is not received within 2 working days of initial reporting.
- Ensuring that AEs and ARs are recorded and reported to the Sponsor in line with the requirements of the protocol.

9.4.2 - Chief Investigator/delegate or Independent Medical Expert (where indicated):

- Clinical oversight of the safety of participants in the trial, including an ongoing review of the risk/benefit.
- Using medical judgement in assigning seriousness, causality and expectedness of SAEs where it has not been possible to obtain local medical assessment.
- Immediate review of all SUSARs up to the point where unblinding is required for regulatory reporting, thereafter an Independent Medical Expert will review.
- Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan which includes providing a causality and expectedness assessment.
- Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs and SARs[90].
- Preparing the clinical sections and final sign off of the Development Safety Update Report (DSUR).

9.4.3 - Sponsor

- Central data collection and verification of AEs, ARs, SAEs, SARs and SUSARs according to the trial protocol onto a MACRO database.

- Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk/benefit according to the Trial Monitoring Plan.
- Reporting safety information to the independent oversight committees identified for the trial (Data Monitoring Committee (DMC) and/or Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.
- Expedited reporting of SUSARs to the Competent Authority (MHRA in UK) and REC within required timelines.
- Notifying Investigators of SUSARs that occur within the trial.
- The unblinding of a participant for the purpose of expedited SUSAR reporting [For double blind trials only].
- Checking for (annually) and notifying PIs of updates to the Reference Safety Information for the trial.
- Preparing standard tables and other relevant information for the DSUR in collaboration with the CI or independent medical expert (if unblinded) and ensuring timely submission to the MHRA and REC.

9.4.4 - Trial Steering Committee (TSC):

In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data and liaising with the DMC regarding safety issues.

9.4.5 - Data Monitoring Committee (DMC):

In accordance with the Trial Terms of Reference for the DMC, periodically reviewing unblinded overall safety data to determine patterns and trends of events, or to identify safety issues, that would not be apparent on an individual case basis.

9.5 - Notification of deaths

Deaths occurring during the safety reporting period (up to 30 days) will be reported as SAEs, regardless of cause. This report will be as soon as possible and within 24 hours.

Note that death is also reported as a primary outcome and will be collected as part of the trial data until day 90 or end of the trial. Deaths occurring after the end of the safety reporting period do not need to be reported as SAEs unless the local PI considers the event to be related to the IMP or study procedures. Deaths occurring up to day 90 will be recorded on the CRF.

Only deaths that are assessed to be caused by the IMPs will be reported to the Sponsor by the CI or delegated individual as an SUSAR up to day 90. This report will be immediate.

9.6 - Pregnancy

As per the exclusion criteria, pregnancy is excluded. However in the event of the enrolment of a female participant with an undetected pregnancy, or in the event of a pregnancy occurring in a trial participant or the partner of a trial participant up to day 30, these are to be reported to the Sponsor using the trial specific pregnancy form.

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

The pregnancy will be followed up for outcome, and the outcome reported to the Sponsor. Where it is the partner of a trial participant consent will be obtained for this observation from both the partner and her medical practitioner.

9.7 - Overdose and Medication Errors

Overdose is considered to be any dose over and above the trial specified administration.

Occurrence of overdose and/or medication errors of either IMP with or without any associated adverse events are to be reported to the trial centre using the serious adverse event forms as per the timelines above in addition to following any local procedures.

9.8 - Reporting Urgent Safety Measures

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures.

10. STATISTICAL ANALYSIS

A separate Statistical Analysis Plan will be published for this trial.

10.1 - Sample Size

The primary outcome for this trial is mortality. In the MAPS trial mortality at 30 days was 8/30 (27%) in the metoclopramide group and 12/30 (40%) in the control group (OR 0.68), 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. The mortality rate in the MAPS control group appears high at 40%, but the trial did include high-risk participants with severe neurological disability and nasogastric feeding. Mortality for severe strokes (total anterior circulation syndrome) in the Oxfordshire Community Stroke project was 39%[91] and 14%, 32%, and

54% for stroke patients with NIHSS 8-13, 32% 14-21, 54%>21 respectively in a more recent study of American Medicare beneficiaries[92].

The hazard ratio to be estimated in this trial is based on an estimated 90-day mortality of 32% in the control group (based on data from the Stroke Oxygen Study for control patients with an NIHSS score of greater than 10) and an assumed reduction of 6 percentage points (to 26%; a reduction of just under 19% of the control mortality rate) in the treatment group. This gives a hazard ratio of 0.78. Death from reasons other than pneumonia constitute a competing risk (i.e. a risk that may 'compete' with pneumonia mortality to be the event). It is estimated that the competing risk will be 10% (in each group). Assuming 1:1 allocation, a 5% two-tailed significance level, 90% power, an accrual period of two years and a further 90 days' follow-up for participants recruited at the end of this period of accrual, 1044 participants (522 in each group) would need to be recruited to provide a required minimum of 658 events across the duration of the trial in order to detect a hazard ratio ≤ 0.78 (assuming proportional hazards) in the presence of the above rate of competing risks. Allowing for 10% loss to follow-up, the target recruitment would be at least 1160. As the assumed control event rate determines the number of participants required, this will be checked at the end of the internal pilot. The trial size and duration of follow-up might be revised in the light of accumulating data (blinded to allocation) to take into account a higher or lower survival than expected in both groups.

10.2 - Statistical Analysis

No formal unblinded interim analysis will be conducted unless requested by the Data Monitoring Committee. Analyses will estimate the effects of the two factors (metoclopramide and selective oral decontamination) in the factorial design. It is assumed that there is no interaction between these factors and the corresponding interaction term will therefore not be included in the statistical models.

Analysis will be according to the intention-to-treat principle, using methods that take appropriate account of missing values. Both adjusted and unadjusted analyses will be done. Appropriate pre-specified sensitivity analyses will also be carried out.

The main outcome, mortality, will be compared between treatment and control using competing risks survival analysis[93 94]. Covariates will include: age, sex, and the minimisation factors (NIHSS, Glasgow Coma Scale, mRS before the stroke, Six Simple Variables risk index for 30-day survival, whether the stroke is due to a haemorrhage or not, whether the patient was thrombolysed or not, and time from stroke onset).

Secondary outcomes will be analysed using appropriate methods. For the adjusted analyses the same covariates will be used as the main outcome.

The assumptions of all analyses will be checked and appropriate steps taken (e.g. data transformation, use of alternative analyses) in the event of their not being satisfied. A detailed statistical analysis plan will be agreed and reviewed by the trial steering committee before data analysis starts.

10.2.1 - Subgroup Analyses

Subgroup analyses will be specified in the statistical analysis plan and published before unblinding of the data.

10.2.2 - Statistical Significance

A *p* value of ≤ 0.05 will be accepted as significant for the main and secondary outcomes. 95% confidence intervals will be presented for all estimates.

10.3 - Planned Recruitment Rate

Recruitment rate in the MAPS trial was 1 patient per month. The most common reason for exclusion in the MAPS trial was that potential participants already had pneumonia (202 out of 296 screened). In MAPS-2 we will be recruiting much earlier before pneumonia manifests, and will therefore be able to recruit at a higher rate. For a large stroke service (admitting more than 800 stroke patients per year) a recruitment of 2/month is therefore realistic, while a rate of 1/month is considered achievable in a smaller service.

10.4 - Trial Population

The primary analysis will be by intention to treat. This will include all participants as randomised. A per protocol sensitivity analyses will be conducted including all participants who received more than 80% of each of the two trial treatments in the first 14 days- Safety analyses and estimation of costs will include all dosed subjects (on treatment analysis).

10.5 - Data queries

10.5.1 - Missing Data

Missing outcome assessments will be re-requested from the local investigator. All data forms will be checked for completeness on arrival in the trial office. Missing items in returned data forms will be queried and completed, as soon as possible after receipt of the data form.

10.5.2 - Spurious Data

Data will be entered into the online data entry form as soon as possible after they arrive in the trial office. The MACRO database will have variable definitions that will generate queries when data outside the defined range are entered. Spurious data will be queried and verified with the local investigator.

10.6 - Reporting Deviation(s) From Original Statistical Plan

A detailed statistical analysis plan will be agreed before data analysis starts.

10.7 - Health Economics Analysis

The aim of the economic evaluation is to determine the cost-effectiveness of metoclopramide and/or selective oral decontamination in reducing mortality and longer term-recovery in patients with dysphagia after stroke and to establish the lifetime cost and outcomes associated with the interventions. The economic evaluation will assume no interactions between the treatment groups:

1. Metoclopramide and oral decontaminant paste
2. Metoclopramide and placebo paste
3. Metoclopramide placebo and oral decontaminant paste
4. Metoclopramide placebo and placebo paste

The health economic analysis, from an NHS perspective will consist of two distinct parts. The first part is a cost-effectiveness analysis conducted alongside the randomised clinical trial. The second part is a model-based cost-effectiveness analysis building on the trial-based analysis and using published data on long-term outcomes and costs. Although the trial-based analysis is important in determining costs, mortality, quality of life, and cost-effectiveness over the first 90 days after the stroke, the model-based analysis will provide the most useful information to decision makers in estimating the long-term impact on costs and patient outcomes.

11. DATA HANDLING

11.1 - Definition of Source Data and Documents

Source Data - ICH E6 section 1.51, defines source data as "All information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies)."

Source Documents - ICH E6 1.52, defines source documents as "Original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial)."

11.2 - Case Report Forms (CRF)

For this trial the CRF is a form on which individual patient data required by the trial protocol are recorded and is a printed document. The CRF data are used to perform statistical analysis for the trial. The CRF is considered a source document for those data that are entered directly onto to the CRF. At each stage of the trial i.e. screening and consent, randomisation and baseline, daily observation log and follow-up data the relevant section of the CRF will be emailed to the trial coordinating centre where the information is entered into a MACRO database via an automated electronic document capture computer system. The trial site will retain the original copy of the CRF for the duration of the trial.

11.3 - Data Handling and Record Keeping

The Chief Investigator is the data custodian for this trial.

The PI is responsible for the research site to keep records of all participating patients (sufficient information to link records e.g., CRFs, hospital records and samples), all original signed informed consent forms and copies of the CRF pages.

Anglia Ruskin University Clinical Trial Unit will design and produce the trial database using MACRO, which is hosted by Infermed/Elsevier. MACRO is designed to support compliance with the technical aspects of international regulations, including FDA 21 CRF Part 11 Scope and Application 2003 as supplemented by Computerised Systems Used in Clinical Investigations, May 2007, Note for Guidance on Good Clinical Practice ICH E6/CPMP/ICH/135/95, EU Clinical Trial Directive, and Medicines for Human Use (Clinical Trials} Regulations. The system is protected by a firewall and by anti-virus software, and offers an acceptable level of cyber security. There is an operating system and database back-up service in place for disaster recovery as per MACRO policy. Full daily and weekly backups are taken with each backup being recoverable for up to two weeks.

There will be no need for the individual research sites to hold any data electronically for this trial. Access will be restricted to members of the trial team with delegated responsibility using unique identifiers and passwords.

The Anglia-Ruskin University Clinical Trial Unit (CTU) can access the data directly from the MACRO system to enable preparation of DMC reports with regard to safety reporting. There will be no patient identifiable data within the data base. No patient-identifiable data will be transferred outside of the EEA. Anonymised data will be made available for systematic reviews and meta-analysis upon request of researchers in the UK and abroad.

The trial manager is responsible for data entry and quality, and the trial statistician is responsible for data analysis.

11.4 - Access to data

The CRF and all source documents, including progress notes and copies of laboratory and medical test results will be made be available at all times for review by the chief investigator, the sponsor, the trial monitor, the trial manager, clinical auditors and for inspection by relevant regulatory authorities (MHRA).

11.5 - Data protection

CRFs will be held securely in a locked room, or locked cupboard or cabinet. Access to the information will be limited to members of the patients' clinical team or the research team at the site. Representatives of the sponsor and of the regulatory authorities will access this information for monitoring, audit and inspection purposes.

All data transfer will be in accordance with the UK Data Protection Act 1998. Information about the trial in the participants' medical records/hospital notes will be treated confidentially in the same way as all other confidential medical information.

All data will be stored on a MACRO database, which has full weekly backups with daily differential backup all other days of the week. There is a 2 week off-site backup retention after which point the backup data is permanently destroyed. A unique centre number will be allocated to each centre. A trial number will be used to identify each patient's research data. This will be stored securely in the local centre and in the Anglia Ruskin Clinical Trials Unit. The trial number and patient identifiers (NHS identifier, name, date of birth) will also need to be shared with the Health and Social Care Information Centre, and with the Stroke Sentinel National Audit Programme (SSNAP) database to obtain hospital episodes statistics and health status information. Data on participant outcomes will

also be transferred from the research database to SSNAP in an electronic encrypted password protected file via a secure internet server.

11.6 - Participant identification

Each patient at the time of randomisation will be allocated a unique patient identification (PID) number which will be used throughout the remainder of the trial to identify that patient. The PID number, patient's name, contact details, NHS number, GP contact and date of birth will be entered on the patient contact CRF; this sheet will be not be entered into the trial database and kept in a secure folder with access restricted to authorised research staff on the trial delegation log, staff at the trial coordinating centre and trial monitors only.

11.7 - Data Archiving and Storage

Archiving will be authorised by the Sponsor following the submission of the end of trial report and in compliance with the ICH/GCP guidelines and regulations.

The sponsor will be responsible for archiving all documentation relating to the trial from the trial coordinating centre including the trial master file (TMF) and trial database.

Each research site will be responsible for archiving the CRFs, consent forms and any other trial documents or records regarding the conduct of the trial.

All essential documents will be archived for a minimum of 15 years after the completion of the trial.

At the end of the archiving period, destruction of all essential documents will require authorisation from the Sponsor.

12. MONITORING, AUDIT AND INSPECTION

A Trial Monitoring Plan will be developed and agreed by the TMG and TSC based on the trial risk assessment which will include some on site monitoring and remote monitoring using the trial management system. Initially all sites will receive an on-site monitoring visit and subsequently conducted using a risk based approach.

Research sites will be expected to host site visits and/or provide information for remote monitoring.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1 - Research Ethics Committee Review and Reports

Before the start of the trial, approval will be sought from a REC for the trial protocol, informed consent forms and other relevant documents.

Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion. Amendments may also be reviewed and accepted by the MHRA and NHS R&D departments before they can be implemented in practice at the research sites.

All correspondence with the REC will be retained in the Trial Master File/Investigator Site File.

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. It is the CI's responsibility to produce the annual reports as required and to notify the REC of the end of the trial. If the trial is ended prematurely, the CI will notify the REC, including the reasons for the premature termination. Within one year after the end of the trial, the CI will submit a final report with the results, including any publications/abstracts, to the REC

13.2 - Peer Review

The trial has been externally peer reviewed as part of the NIHR HTA application process.

13.3 - Patient and Public Involvement

A patient pledge has been drawn up with the PPI lead detailing all the actions that the group will be completing during the life of the trial. Several meetings with members of the PPI group have taken place in preparation of the protocol. These addressed terms of reference and provided feedback on the case report form, the consent form, and the patient information sheet.

There will be a patient representative on both the TSC and TMG.

One of our patient representatives has written the following paragraph in support of the MAPS-2 trial: "The importance of the research project, the Metoclopramide for avoiding Pneumonia in after Stroke (MAPS-2) trial, cannot be overstated. For some considerable time now too many members of my peer group have suffered pneumonia as a consequence of their strokes. This research will hopefully resolve this intolerable and untenable situation and help with a faster more successful recovery from stroke thus reducing both mortality and morbidity."

13.4 - Regulatory Compliance

This protocol was designed according to the guidance set out in International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use (ICH) Good Clinical Practice (GCP) [ICH GCP E6] and the Health Research Authority (HRA). This protocol and the trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

The trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the MHRA.

Before any site can enrol patients into the trial, the PI will apply for NHS permission/confirmation of capacity and capability from the site's Research & Development (R&D) department.

13.5 - Protocol Compliance

Protocol deviations, non-compliances, or breaches are departures from the approved protocol.

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

Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.

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

13.6 - Notification of Serious Breaches to GCP and/or the Protocol

A serious breach is a breach of GCP or the protocol what is likely to affect the safety or physical or mental integrity of the subjects of the trial or the scientific value of the trial.

13.6.1 - Serious Breach Procedure

Identification, reporting and actions arising from a serious breach will be guided by the MHRA Serious Breach and Good Clinical Practice Reporting regulations[95]. Serious breaches will also be reported to the REC at the same time as the report to the MHRA.

13.7 - Indemnity

The UHNM NHS Trust will indemnify in accordance with the model agreement for non-commercial research in the health service.

In addition, the UHNM NHS Trust will issue Keele University staff associated with the Trial with honorary contracts to include indemnity arrangements in relation to those staffs' activities on the Trust's premises in fulfilling their role in managing and monitoring the Trial, auditing recruitment rates or Trial interventions and in relation to any activity associated with the conduct of this research (as per the Delegation of Sponsor responsibilities).

13.8 - Amendments

If the sponsor wishes to make a substantial amendment to the documents that supported the original application for REC and HRA approvals, the sponsor must submit a valid notice of amendment to the REC for consideration. It is the sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the REC.

Amendments also need to be notified to Health Research Authority and NHS R&D departments of participating sites to assess whether the amendment affects the NHS permission for that site. Note that some amendments that may be considered to be non-substantial for the purposes of REC may still need to be notified to NHS R&D. Centres should ensure amendment history for most recent trial documents are recorded and tracked in accordance with local SOP.

13.8.1 - Version numbering

The first draft version of any trial -related document will be 0.1 increasing to 0.2 for the next version of the draft and so on. Once the document is ready for submission, for this particular trial, it will become version 2.0. Non-substantial amendments to the documents will be in 0.1 increments e.g. 2.1 for the first non-substantial amendment of the first version. A substantial amendment to a document will result in a new version number being assigned e.g. a substantial amendment to the first version of a document will become version 3.0. All version numbers will be accompanied by a date and a log kept at the trial coordinating centre in the TMF.

13.9 - Access to the Final Trial Management System

The CI, trial coordinating team, health economics team and statistician will have access to the full, final trial management system. Database lock will occur once the final participant has completed follow-up.

Once analysis has been completed all participating centres will be informed of the outcomes at the same time as the main publication.

The trial will allow principal investigators access to the full anonymised trial management system if a formal request detailing the intended use of the data is made and reviewed by the TSC.

Anonymised data will be made available for research, systematic reviews and meta-analysis upon request of researchers in the UK and abroad. The CI will be responsible for managing such requests.

13.10 - Other Ethical Considerations

The key ethical issues related to this trial are:

1. Recruitment of patients without capacity to give informed consent. As stroke is a disorder of the brain, it frequently affects the patient's level of consciousness, their ability to concentrate sufficiently to take in the information, to understand language, to make reasoned judgments, and/or to communicate his/her views. Patients with swallowing problems tend to have more severe strokes, making fully informed consent even more likely. As the group of patients most likely to benefit from the treatment is also most likely to lack capacity, exclusion group of this group is not appropriate, as this could render results as invalid, as they are tested in the wrong population, and deprive the patients most likely to respond form a potentially effective treatment. We will therefore seek informed consent form a personal legal representative in this patient group.
2. Participants/personal legal representatives will have only a limited amount of time to read the participant information and make a decision whether or not to participate. In the pilot study we recruited patients within 72 hours of hospital admission. This allowed participants and their families sufficient time to consider and discuss the risks and benefits of participation. However, a large proportion of patients screened (202 out of 296) already had established pneumonia and therefore had to be excluded. Most pneumonias start soon after hospital admission. As time passes the risk of pneumonia is lower, reducing the potential of benefit. In this trial recruitment is therefore earlier, and time for decision making more limited.
3. Metoclopramide is given longer than the maximum of 5 days currently recommended in the SPC for prevention of vomiting, but within the 30 days the SPC allows for the maximum duration of treatment. There is a very small risk of developing tardive dyskinesia, a potentially irreversible complication, but this is very unlikely before 30 days. In our pilot study metoclopramide was used for a maximum of 21 days. There were no adverse reactions in any of the 30 participants in the actively treated group. As dystonia is not life threatening and reversible, but the development of pneumonia potential fatal, we the potential benefits outweigh the potential risks.
4. Selective oral decontamination paste is an unlicensed product, but is used widely in intensive care units in the Netherlands, and has an established safety profile with data from

randomised controlled studies including over 10,000 patients. No safety concerns were identified in our pilot study.

14. DISSEMINATION

14.1 - Dissemination policy

The data arising from the trial will be owned by the CI.

On completion of the trial, the full statistical analysis as detailed in the separate Statistical Analysis Plan will be carried out and a final trial report prepared. This will be available from the MAPS-2 trial website and the journal in which the report is published.

The participating PIs will not have rights to publish any of the trial data without specific approval from the CI, sponsor and TSC.

Results will be made accessible in technical language and lay format on the MAPS-2 website. The final report will also be made available to the participants by the local research team if requested.

The trial protocol, Statistical Analysis Plan and final report will be published in a peer-reviewed academic journal.

All publications of the trial results will follow the CONSORT guidelines.

14.2 - Authorship eligibility guidelines

The International Committee of Medical Journal Editors (ICMJE) has recommended that authorship is based on the following four criteria:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND

2. Drafting the work or revising it critically for important intellectual content; AND

3. Final approval of the version to be published; AND

4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The CI and TMG are responsible for identifying who meets these criteria.

The CI will be corresponding author on all publications including the final report and a MAPS-2 collaborative group consisting of the statistical and health economics team, and the public and patient representatives will author the publications on behalf of the participating PIs and staff at each of the research sites who will be listed in the acknowledgments section (in accordance with ICJME recommendation).

14.3 - Other dissemination of trial outcomes

When the trial is complete summary findings will be disseminated via the NIHR Clinical Research Network, and posted on the Stroke in Stoke website. Findings will also be presented at conferences such as the UK Stroke Forum, the European Stroke Conference, or the World Stroke Congress.

If the results are positive and require a change in practice, national and international stroke guideline development organisations such as the Royal College of Physicians in the UK, the European Stroke Organisation, the Karolinska Institute, and the American Heart Association will be alerted to the findings. The CI will also utilise the large network of clinical collaborators established via the Stroke Oxygen Study to rapidly disseminate clinically relevant findings.

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16. APPENDICES

16.1 - APPENDIX ONE - Risk Assessment

Research Risk Assessment Form					Version 2.0
This form should be completed by the CI/PI for all CTIMPs sponsored by UHNM in conjunction with the Research Project support team. The completed form will be reviewed by the R&D manager and discussed at the R&D sponsorship meeting. Following review and completion of any amendments this form will be signed by the CI/PI and sponsor.					
Full study title:	The Metoclopramide and selective oral decontamination for Avoiding Pneumonia after Stroke (MAPS-2): a 2x2 double-blind, randomised controlled trial of metoclopramide and selective oral decontamination for the prevention of pneumonia in patients with dysphagia after an acute stroke			**EudraCT:**	2016-003406-14
Short study title:	Metoclopramide and selective oral decontamination for Avoiding Pneumonia after Stroke (MAPS-2) Trial			**Acronym:**	MAPS-2
Protocol version number reviewed:	2.0	**Date of risk assessment:**	19th December 2016	**Risk assessment conducted by:**	Professor Christine Roffe
Sponsor:	University Hospital of North Midlands			**Proposed co-sponsors:**	
Chief Investigator:	Professor Christine Roffe			**Principal investigator:**	

Section 1 - Study synopsis			
Type of study:	Randomised controlled trial (CTIMP)	**Study design:**	
Type of control:	prospective, double-blind 2x2 factorial placebo-controlled trial	**Location:**	Multiple NHS hospitals in England
Test products:	(1) Metoclopramide and (2) selective oral decontamination paste (2% tobramycin, amphoteracin B and colistin in Orabase paste)	**Route of administration :**	(1)Metoclopramide solution is via a nasogastric tube (2) Oral decontaminant paste is topical to mucous membranes
Dosage regimen:	Metoclopramide 10mgs solution three times a day . Selective oral decontaminant paste is four times a day	**Duration of treatment:**	21 days or until the patient nasogastric tube no longer needed o until the patient is able to swallow normally
Study objectives :	To conduct a phase 3 multi-centre prosepctive double-blind, randomised, 2x2 factorial placebo-controlled trial to answer if early treatment with metoclopramide or selective oropharyngeal decontamination reduce mortality after stroke.		
Study intervention(s):	(1) Metoclopramide and (2) selective oral decontamination		
Details of follow-up:	Daily logs for 14 daysFollow-up @ 7 and 14 days for SAEs, diagnosis, antibiotic treatmentFollow-up @ 30 days for neurological assessment, wbc, crp, SAEs, antibiotics use and antibiotic resistant organisms.Follow-up @ 90 days for quality of life assessment, current location and total hospital time.Follow-up @ end of trial for vital status. (Primary outcome measure)		

Inclusion criteria:	(1) Adult patients with a clinical diagnosis of acute stroke (as defined by the World Health Organisation, excluding the requirement of a duration of 24 hr or more). (2) within 9 hours of stroke onset (in wake up stroke the onset is defined as the time the patient awoke or was found unless this is more than 12 hours from last known well). (3) Moderate to severe neurological impairment with a NIHSS score ≥ 10 (4) Unable to take a normal diet or fluids because (a) too drowsy to be assessed formally or (b) failed bdside assessment of swallowing	**Exclusion criteria:**	(1) Evidence of vomiting since stroke onset (2) Pre-existing swallowing problems (3) Known oesophageal pathology that might interfere with placement of a nasogastric tube (eg. malignancy, achalasia, pharyngeal pouch or web) (4) Probable or definite pneumonia (abnormal chest exam or pyrexia >37.7°C, or receiving antibiotic treatment at time of presentation) (5) Contraindications to metoclopramide (hypersensitivity to metoclopramide or any of the excipients (sodium metabisulphite, sodium chloride, dilute hydrochloric acid, or water for injection), epilepsy, gastrointestinal obstruction, perforation, or haemorrhage, gastrointstinal surgery within the last week, Parkinson's disease, treatment with levodopa or dopaminergic agonists, phaeochromocytoma or neuroleptic malignant syndrome or tardive dyskinesia or methamoglobinaemia or NADH cytochrome-b5 deficiency) (6) Patients with severe liver disease (cirrhosis) or severe kidney disease (eGFR <30 L/mim) (7) Known allergy to colistin (ploymyxin E), tobramycin, aminoglycosides in general, or amphotericin B (8) Pregnant or breat feeding (9) Other co-morbid conditions with a life expectancy of less than 3 months at the discretion of the clinical treating team

			(10) Inability to gain consent from the patient or a legal representative or refusal of consent.

Primary endpoints:	Mortality up to the end of the study	**Secondary endpoints:**	(1) Diagnosis of pneumonia up to day 14 using daily log and standard definition of pneumonia: pneumonia will be defined as fulfilment of 3/6 diagnostic criteria (fever, productive cough, abnormal chest examination, abnormal chest radiograph, arterial hypoxaemia, positive microbiology), based on the Mann criteria for the diagnosis of stroke associated pneumonia. See Appendix Two for detail. (2) Any new diagnosis of pneumonia up to day 15-30 using clinician diagnosis and antibiotic prescription data. (3) Antibiotic use: number of days of antibiotic treatment for pneumonia within the first 30 days. (4) Neurological recovery: Change in NIHSS between admission and day 30 (5) Functional recovery: modified Rankin Scale (mRS) score at 90 days with an additional category [6] added to include patients who died (6) Quality of life (EQ-5D™)
Sample-size calculation:	Assuming 1:1 allocation, a 5% two-tailed significance level, 90% power, an accrual period of two years and a further 90 days follow-up for patients recruited at the end of this period of accrual, 1044 patients (522 in each group) would need to be recruited to provide a required minimum of 658 events across the duration of the study in order to detect a hazard ratio ≤ 0.78 (assuming proportional hazards) in the presence of the above rate of competing risks. Allowing for 10% loss to follow-up, the target recruitment would be at least 1160.		

Primary statistical analysis:	The main outcome, mortality, will be compared between treatment and control using competing risks survival analysis. For an adjusted analysis, the covariates to be included are: age, sex, in addition to the minimisation factors (NIHSS, Glasgow Coma Scale, Six Simple Variables risk index for 30 day survival, whether the stroke is due to a haemorrhage or not, whether the patient was thrombolysed or not, and time from stroke onset).
Secondary statistical analyses:	Ordinal variables (e.g. mRS) will be analysed by ordinal logistic regression; count variables (e.g. days of antibiotic treatment) will be analysed by Poisson regression or negative binomial regression, as appropriate. Continuous variables (e.g. NIHSS) will be analysed by analysis of covariance, and binary outcomes (e.g. diagnosis of pneumonia) will be analysed by logistic regression.

Section 2 - Study sponsorship and research governance risk assessment

	1	2	3	4	5	SCORE	COMMENT
Scale of Research	0-20	21-50	51-100	101-250	>250	5	
Study Phase	None	IV	III	II	I	3	
Patient Population	No research involvement of human subject groups.	Subject group not considered vulnerable – able to give informed consent, may benefit from taking part.	Patients with potential limited capacity to consent e.g. early stages of cognitive impairment, limited English.	Patients with severely compromised capacity to consent – unconscious, cognitively impaired.	Any study where side effects of the intervention have a realistic chance of being fatal or causing serious harm (more than 30%).	4	

		Subjects are NHS staff rather than patients.	Specialist clinical areas with limited treatment options. Areas with high/rapid turnover of patients. Healthy volunteers in studies with moderate risk attached to the intervention. Patients with poorly controlled / complex illnesses.	Patients with poor prognosis / terminal disease & patients not likely to gain any benefit from taking part. Healthy volunteers in studies with high risk attached to the intervention.	Studies involving a target group of pregnant women, or women of childbearing age.		
Intervention	Non invasive procedures	Minor intervention e.g. taking blood or skin samples	Involves a clinical intervention which represents only a slight deviation from normal treatment and / or basic safety and efficacy testing has been carried out e.g. Phase III or IV trials. Treatment is licensed for this indication.	Involves a clinical intervention which represents a significant change from standard care or withholding of all /	Significant risk derived from single highly invasive clinical intervention or combination of interventions – e.g. surgical techniques, radiotherapy,	4	

				elements of standard care	cytotoxic drugs or combinations of the above. Significant numbers of adverse events expected.		
	Questionnaire / interview or survey research on non contentious subjects	Questionnaire/ interview or survey work on sensitive subjects e.g. sexual behaviour		Basic safety and efficacy data not yet available for the investigational product e.g. Phase I and II trials			
Assessment measures	Non-invasive	Minor intervention e.g. taking additional blood samples	Additional tests which represent a slight deviation from normal practice, i.e. additional outpatient visits, series blood sampling	Fully justified additional radiation or additional invasive tests that would not usually be part of patient care	Additional radiation or additional invasive tests with insufficient justification	1	

Follow-up	One-off intervention with no follow up	May be more than one intervention, no follow up	Follow up in line with / similar to clinical practice	Additional follow-up to standard care, may be for extended period	Extended follow-up for many years, may include ONS flagging, GP or relatives	5	
Investigator	No local investigator, or minimal involvement, e.g. recruitment only	Experienced Principal / Chief Investigator supported by well trained and experienced team	Limited experience of leading a study	No prior experience of leading a study	Previously investigated for fraud/misconduct or there is evidence to suggest the team is dysfunctional.	2	
		Study team have up to date training in GCP / governance	May have small research team / limited support from collaborators, sponsors	Inexperienced / stretched team			
			Some awareness of governance issues	No evidence of governance / GCP awareness			
Adverse Event reporting	Very low risk project - Not required	Few adverse events anticipated, reporting to CI within local team	Formalised system in place for reporting adverse events	Full pharmocovigilence and safety reporting mechanism	High risk intervention with likely numbers of SUSARs / SAEs requiring frequent review.	4	Investigators will receive blinded SUSAR reports quarterly.

				required			
Information / Personal Data	No personal data being used	Data anonymised or pseudonymised No data sent outside EU Data stored in secure site	Poorly defined processes of data recording and storage. Poorly defined result dissemination. Data to be stored in open environment. No clear process for un-blinding subjects. Sensitive data being collected.	Data to be sent to sites outside EU Discrepancy between ethics application, patient information, consent and/or protocol/trial information. Potential for fabrication, falsification, distortion/omission or corruption of research data. No limits on data access.	Previous breaches of data protection / confidentiality	2	Data is being shared with Stroke Sentinel. Personal data will also need to be released to HSCIC to share routinely collected HES data

			Personal identifiers associated with data.	No provision for result dissemination.			
Protocol Design	Minor or insignificant patient involvement with clear rationale and scientific justification. Simple, relevant eligibilty criteria.	Clear complete rationale and scientific justification. A properly generated randomisation schedule and randomisation method. Clearly defined proposal. Independent expert and peer review with written summary.	Some rationale and scientific justification. Protocol is unclear on first reading, potential ambiguity Independent statistical review	Limited scientific background for study intervention. Incomplete / draft protocol requiring additional work Poor/no documentation of review process.	New/experimental treatment without clear scientific background. Complex protocol or invasive procedure. No independent, expert review.	2	

		Clear developmental background for investigational drug or device.	Some developmental background / rationale				
Protocol Deviation	Straight forward study with low risk of non-adherence to protocol	Clear guidance for protocol violation	Poor guidance for potential protocol deviations or errors.	Potential for deviation from protocol No protocol violation contingency defined. Research to be conducted out of hours	Major potential for deviation from protocol, which may result in harm to study subject. Previous instances of inappropriate / unauthorised deviation from protocol.	2	There will be clear guidance for protocol deviations within relevant SOPs. Comprehensive training will be provided to research teams at site initiation and SOPs will provided a clear procedural structure.

Consent	Consent not necessary / REC approval to go ahead without it	Clearly defined process for informed consent with named designation of responsibility.	Assent process in place	Consent does not cover all aspects of research.	Prior instances of poor consenting procedures.	3	
		Clear defined recruitment process.	Consent from vunerable groups	Multiple consents for a single study			
		Patient given sufficient time to consider taking part	Patients given limited time (less than 48 hours) to consider taking part.	Unclear process for recording consent.			
		Clear consent form and PIS		No explanation of recruitment process.			
		Clearly identified risk and benefits.	Patients likely to lack capacity to give fully informed consent e.g. severe pain, language difficulties, cognitive impairment.	Patient required to consent same day (i.e. no time to reflect)			

				Complex patient information sheet. Potential for consent to be taken by someone who may not be entirely familiar with the trial e.g. A&E staff.			
Finance	No cost ramifications/ minor implications implications (<10K) Fully funded research costed by R&D with contract in place	Unfunded research with costs of £10-35k Partially funded research with division picking up the excess	Under-costed Partially funded unclear - who is picking up the remainder? No divisional support	Not costed by R&D office No defined contract with or between research . organisations	Previously identified issues of poor costing or use of funds Previous instances of PI signing off contract without R&D	1	The sponsor is reviewing costs for CTU oversight of data management

Low Score 0-28	Moderate Score 29-40	High Score 41-54	Extreme Score 55-65			
No action required	Efforts should be made to reduce risks by completing the Risk Management Plan.		Escalate to R&D Director to consider whether risks can be managed; or whether Trust should not support	SCORE:		38

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Trial Management Group required?	YES	☑
	NO	☐
Trial Steering Committee required?	YES	☑
	NO	☐
Independent Data Monitoring Committee required?	YES	☑
	NO	☐

To determine whether IDMC is required (consider if 1 'YES', mandatory if 2 or more 'YES':

1. Is the trial intended to provide definitive information about effectiveness and/or safety of a medical intervention? ☑ ☐

	YES NO		
2. Is there prior data to suggest that the intervention being studied has the potential to induce potentially unacceptable toxicity?	YES NO	☐	☑
3. Is the trial evaluating mortality or another major endpoint such that inferiority of one treatment arm has safety as well as effectiveness implications?	YES NO	☑	☐
4. Would it be ethically important for the trial to stop early if the primary question addressed has been definitively answered, even if secondary questions or complete safety information were not fully addressed?	YES NO	☑	☐

Section 3 - study specific Issues								
Area	Particular Issue Identified		Concerns	Mitagation or adaption	Monitoring Methods to Address			

For CTIMPS :IMP Management	Patient Safety	Drug manufacturers update the Summary of Product Characteristics periodically. As Sponsor we need to ensure we check regularly for updates and amend study documentation as appropriate to ensure patients have the latest information.	Checks will be conducted by R&D following local SOPs every 6 months	Record will be kept in R&D
Selective oral decontamination	The is no reference safety data available	The interactions between both IMPS are unknown.	Record all adverse events on case report forms. Serious adverse event reporting process and SOP in	Onsite source data verification of participant records. Inventory of all adverse events collated by sponsor office. Review of adverse events serious and non-serious by IDMC

			place	

Section 4 - Risks to participant safety associated with the trial IMP/intervention(s)

Type A	**Comparable to the risk of standard medical care:**	**Justification:**	1. Metoclopramide - licensed indications for metoclopramide are prevention of vomiting (to be given for a maxium of 5 days) and treatment of gastroparesis (up to 3 months). In MAPS-2 metoclopramide will be used for 21 days which is longer than recommended for the this specific indication but within the licensed treatment duration for diabetic gastroparesis. There is a risk of tardive dyskinesia hence the limitaion of 3 months use. The risk is less for up to 21 days. Intravenous injections of metoclopramide are associated with risk of cardiac arrhythmias (bradycardia, heart block, asystole). Metoclopramide will be given by NG tube once in place to mitigate this risk. Where given IV it wil be slowly over 3 minutes. As metoclopramide solution for IV use will be used via the naso gastric route there is the small possibility of small glass particles mixing with the drug when opening the glass ampoule. A needle will be used to draw the solution from the ampoule to void glss splinters entering the tube.
Type B	**Somewhat higher than the risk of medical care:**		
Type C	**Markedly higher than the risk of standard medical care:**		

			2. Selective oral decontamination- the paste has no product license or SPC. It is used regularly in Dutch stroke units and a similar product using the same antibiotics was shown to be safe in a pilot study. The active ingredients are licensed for use independently.

IMP / Intervention	Body system	Hazard	Likelihood (Low, Medium, High)	Mitigation	Comments
Metoclopramide	**Blood and lymphatic system disorders**	Methaemoglobinaemia, which could be related to NADH cytochrome b5 reductase deficiency, particularly in neonates Sulfhaemoglobinaemia, mainly with concomitant administration of high doses of sulfur-releasing medicinal products	Low		
Metoclopramide	**Cardiac disorders**	Bradycardia, particularly with intravenous formulation	Medium	Formulation given by NG tube as soon as NG tube is in place.	

Metoclopramide	**Cardiac disorders**	Cardiac arrest, occurring shortly after injectable use, and which can be subsequent to bradycardia; Atrioventricular block, Sinus arrest particularly with intravenous formulation; Electrocardiogram QT prolonged; Torsade de Pointes;	Low	Formulation given by NG tube as soon as NG tube is in place.	
Metoclopramide	**Endocrine disorders - Associated with prolonged use only**	Amenorrhoea, Hyperprolactinaemia,	Low		
Metoclopramide	**Endocrine disorders - Associated with prolonged use only**	Galactorrhoea	Low		
Metoclopramide	**Endocrine disorders - Associated with prolonged use only**	Gynaecomastia	Low		
Metoclopramide	**Gastrointestinal disorders**	Diarrhoea	High		
Metoclopramide	**General disorders and administration site conditions**	Asthenia	High		

Metoclopramide	**General disorders and administration site conditions**	Injection site inflammation and local phlebitis	Low		
Metoclopramide	**Immune system disorders**	Hypersensitivity	Medium		
Metoclopramide	**Immune system disorders**	Anaphylactic reaction (including anaphylactic shock) particularly with intravenous formulation	Low	Formulation given by NG tube as soon as NG tube is in place.	
Metoclopramide	**Nervous system disorders**	Somnolence	High		
Metoclopramide	**Nervous system disorders**	Extrapyramidal disorders (particularly in children and young adults and/or when the recommended dose is exceeded, even following administration of a single dose of the drug), Parkinsonism, Akathisia	High		
Metoclopramide	**Nervous system disorders**	Dystonia, Dyskinesia, Depressed level of consciousness	Medium		

Metoclopramide	**Nervous system disorders**	Convulsion especially in epileptic patients	Low		
Metoclopramide	**Nervous system disorders**	Tardive dyskinesia which may be persistent, during or after prolonged treatment, particularly in elderly patients, Neuroleptic malignant syndrome	Low		
Metoclopramide	**Psychiatric disorders**	Depression	High		
Metoclopramide	**Psychiatric disorders**	Hallucination	Medium		
Metoclopramide	**Psychiatric disorders**	Confusional state	Low		
Metoclopramide	**Vascular disorder**	Hypotension, particularly with intravenous formulation	High	Formulation given by NG tube as soon as NG tube is in place.	

Metoclopramide	**Vascular disorder**	Shock, syncope after injectable use. Acute hypertension in patients with phaeochromocytoma. Transient increase in blood pressure	Low		
Metoclopramide	**Skin disorder**	Skin reactions such as rash, pruritus, angioedema and urticaria+	Low		
Metoclopramide	**Gastrointestinal**	Glass splinters from ampoule	Low	Use of a needle to withdraw metoclopramide from ampoule	This is normal practice
Selective oral decontamination	**Gastrointestinal**	Antibiotic resistance or antibiotic associated diarrhoea	Low	All positive sputum cultures and resistant organisms will be recorded at 30 days.	Treatment is topical not systemic and none of the active substances are absorbed orally.

Section 5 - Signatures

Signature of chief investigator:		**Date: 05/01/2017**	
Signature of R&D manager:		**Date: 05/01/2017**	

This risk assessment is to be reviewed prior to the study commencing and then regularly throughout the project.

16.2 - APPENDIX TWO - Diagnostic criteria for 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 <3,000/ml* ***or*** *C-reactive protein > 65 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.

1. Mann G, Hankey GJ, Cameron D. Swallowing disorders following acute stroke: prevalence and diagnostic accuracy. Cerebrovasc Dis. 2000 Sep-Oct;10(5):380-6.
2. Warusevitane A, Karuntilake D, Lally F, Sim J, Roffe C. The safety and effect of metoclopramide to prevent pneumonia in stroke patients fed via nasogastric tubes (MAPS Trial). Stroke 2015;46:454-60.
3. Warusevitane A, Karunatilake D, Sim J, Smith C, Roffe C. Early Diagnosis of Pneumonia in Severe Stroke: Clinical Features and the Diagnostic Role of C-Reactive Protein. PlosOne 2016;1-11. March 3, 2016 . DOI: 10.1371/journal.pone.0150269
4. Vargas M, Horcajada JP, Obach V, Revilla M, Cervera A, Torres F, Planas AM, Mensa J, Chamorro A. Clinical consequences of infection in patients with acute stroke: is it prime time for further antibiotic trials? Stroke 2006; 37:461-5.

5. Harms H, Hoffmann S, Malzahn U, Ohlraun S, Heuschmann P, Meisel A. Decision-making in the diagnosis and treatment of stroke-associated pneumonia. J Neurol Neurosurg Psychiatry. 2012; 83:1225-30.

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).

1. Horan TC, Andrus M, Dudeck MA.CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. American Journal of Infection Control.2008;36:309-332.
2. Smith CJ, Kishore AK, Vail A, Chamorro A, Garau J, Hopkins SJ, Di Napoli M, Kalra L, Langhorne P, Montaner J, Roffe C, Rudd AG, Tyrrell PJ, van de Beek D, Woodhead M, Meisel A. Diagnosis of stroke-associated pneumonia. Recommendations from the Pneumonia in Stroke Consensus Group. Stroke 2015;46:2335-2340

16.3 - APPENDIX THREE - Schedule of Events

	Randomisation Day			Trial Days – Post Randomisation																							
	Screening	Baseline	Randomisation	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	30 or discharge if sooner	Discharge	90
Discuss trial	X																											
Eligibility and screening	X																											
Informed consent	X																											
Baseline assessment		X																										
Randomisation			X																									
Trial IMPs/placebos				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Daily clinical log				X	X	X	X	X	X	X	X	X	X	X	X	X	X											
Safety reporting				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		
Chest X-Ray		R		•	•	•	•	•	•	•	•	•	•	•	•	•	•											
NIHSS	X																									X		
mRS		X																								X		X
EQ-5D		X																										X
Sputum culture		•		•	•	•	•	•	•	•	•	•	•	•	•	•	•											
MRSA swab		R		•	•	•	•	•	•	•	•	•	•	•	•	•	•											
C. difficile culture/toxin				•	•	•	•	•	•	•	•	•	•	•	•	•	•											
Length of stay																											X	
Discharge destination																											X	
Report to coordinating centre	X	X	X								X							X								X		X
CRF Completion	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

R = routine clinical care • = if patient temperature >38°C urine, blood, sputum culture expected as part of normal clinical practice, and C. difficile is usually done in patients with diarrhoea, but left to clinical judgement

16.4 - APPENDIX FOUR - Summary of Product Characteristics

16.4.1 - Metoclopramide SPC

Metoclopramide 5 mg/ml Injection

Last Updated on eMC 15-Sep-2016 | hameln pharmaceuticals ltd

1. Name of the medicinal product

Metoclopramide 5 mg/ml Injection.

2. Qualitative and quantitative composition

Each 2 ml contains metoclopramide hydrochloride BP equivalent to 10 mg of anhydrous metoclopramide hydrochloride.

Each 20 ml contains metoclopramide hydrochloride BP equivalent to 100 mg of anhydrous metoclopramide hydrochloride.

3. Pharmaceutical form

Sterile injection or infusion.

4. Clinical particulars

4.1 Therapeutic indications

Paediatric population:

Metoclopramide 5 mg/ml Injection is indicated in children (1 – 18 years) for:

• Prevention of delayed chemotherapy induced nausea and vomiting (CINV) as a second line option

• Treatment of established post-operative nausea and vomiting (PONV) as a second line option

For other indications, the use in the paediatric population is not recommended.

Adult population:

Metoclopramide 5 mg/ml Injection is indicated in adults for:

• Prevention of post-operative nausea and vomiting (PONV)

• Symptomatic treatment of nausea and vomiting, including acute migraine induced nausea and vomiting

• Prevention of radiotherapy induced nausea and vomiting (RINV)

4.2 Posology and method of administration

The solution can be administered intravenously or intramuscularly.

Intravenous doses should be administered as a slow bolus (at least over 3 minutes).

All indications (paediatric patients aged 1-18 years)

The recommended dose is 0.1 to 0.15 mg/kg body weight, repeated up to three times daily by intravenous route. The maximum dose in 24 hours is 0.5 mg/kg body weight.

A minimal interval of 6 hours between two administrations is to be respected, even in case of vomiting or rejection of the dose (see section 4.4).

Dosing table

Age	Body Weight	Dose	Frequency
1-3 years	10-14kg	1 mg	Up to 3 times daily
3-5 years	15-19 kg	2 mg	Up to 3 times daily
5-9 years	20-29 kg	2.5 mg	Up to 3 times daily
9-18 years	30-60 kg	5 mg	Up to 3 times daily
15-18 years	Over 60 kg	10 mg	Up to 3 times daily

The maximum treatment duration is 48 hours for treatment of established post-operative nausea and vomiting (PONV).

The maximum treatment duration is 5 days for prevention of delayed chemotherapy induced nausea and vomiting (CINV).

All indications (*adult patients)*

For prevention of PONV a single dose of 10mg is recommended.For the symptomatic treatment of nausea and vomiting, including acute migraine induced nausea and vomiting and for the prevention of radiotherapy induced nausea and vomiting (RINV): the recommended single dose is 10 mg, repeated up to three times daily

The maximum recommended daily dose is 30 mg or 0.5mg/kg body weight.

The injectable treatment duration should be as short as possible and transfer to oral or rectal treatment should be made as soon as possible.

The maximum recommended treatment duration is 5 days.

Special population

Elderly

In elderly patients a dose reduction should be considered, based on renal and hepatic function and overall frailty.

Renal impairment

In patients with end stage renal disease (Creatinine clearance ≤ 15 ml/min), the daily dose should be reduced by 75%.

In patients with moderate to severe renal impairment (Creatinine clearance 15-60 ml/min), the dose should be reduced by 50% (see section 5.2).

Hepatic impairment

In patients with severe hepatic impairment, the dose should be reduced by 50% (see section 5.2)

Paediatric population

Metoclopramide is contraindicated in children aged less than 1 year (see section 4.3)

4.3 Contraindications

• Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

• Gastrointestinal haemorrhage, mechanical obstruction or gastro-intestinal perforation for which the stimulation of gastrointestinal motility constitutes a risk

• Confirmed or suspected phaeochromocytoma, due to the risk of severe hypertension episodes

• History of neuroleptic or metoclopramide-induced tardive dyskinesia

• Epilepsy (increased crises frequency and intensity)

• Parkinson's disease

• Combination with levodopa or dopaminergic agonists (see section 4.5)

• Known history of methaemoglobinaemia with metoclopramide or of NADH cytochrome-b5 deficiency.

• Use in children less than 1 year of age due to an increased risk of extrapyramidal disorders (see section 4.4)

4.4 Special warnings and precautions for use

Neurological Disorders

Extrapyramidal disorders may occur, particularly in children and young adults, and/or when high doses are used. These reactions occur usually at the beginning of the treatment and can occur after a single administration. Metoclopramide should be discontinued immediately in the event of extrapyramidal symptoms. These effects are generally completely reversible after treatment discontinuation, but may require a symptomatic treatment (benzodiazepines in children and/or anticholinergic anti-Parkinsonian medicinal products in adults).

The time interval of at least 6 hours specified in the section 4.2 should be respected between each metoclopramide administration, even in case of vomiting and rejection of the dose, in order to avoid overdose.

Prolonged treatment with metoclopramide may cause tardive dyskinesia, potentially irreversible, especially in the elderly. Treatment should not exceed 3 months because of the risk of tardive dyskinesia (see section 4.8). Treatment must be discontinued if clinical signs of tardive dyskinesia appear.

Neuroleptic malignant syndrome has been reported with metoclopramide in combination with neuroleptics as well as with metoclopramide monotherapy (see section 4.8). Metoclopramide should be discontinued immediately in the event of symptoms of neuroleptic malignant syndrome and appropriate treatment should be initiated.

Special care should be exercised in patients with underlying neurological conditions and in patients being treated with other centrally-acting drugs (see section 4.3)

Symptoms of Parkinson's disease may also be exacerbated by metoclopramide.

Methaemoglobinaemia

Methaemoglobinaemia which could be related to NADH cytochrome b5 reductase deficiency has been reported. In such cases, metoclopramide should be immediately and permanently discontinued and appropriate measures initiated (such as treatment with methylene blue).

Cardiac Disorders

There have been reports of serious cardiovascular undesirable effects including cases of circulatory collapse, severe bradycardia, cardiac arrest and QT prolongation following administration of metoclopramide by injection, particularly via the intravenous route (see section 4.8).

Special care should be taken when administering metoclopramide, particularly via the intravenous route to the elderly population, to patients with cardiac conduction disturbances (including QT prolongation), patients with uncorrected electrolyte imbalance, bradycardia and those taking other drugs known to prolong QT interval.

Intravenous doses should be administered as a slow bolus (at least over 3 minutes) in order to reduce the risk of adverse effects (e.g. hypotension, akathisia).

Renal and Hepatic Impairment

In patients with renal impairment or with severe hepatic impairment, a dose reduction is recommended (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

Contraindicated combination

Levodopa or dopaminergic agonists and metoclopramide have a mutual antagonism (see section 4.3).

Combination to be avoided

Alcohol potentiates the sedative effect of metoclopramide.

Combination to be taken into account

Due to the prokinetic effect of metoclopramide, the absorption of certain drugs may be modified.

Anticholinergics and morphine derivatives

Anticholinergics and morphine derivatives may both have a mutual antagonism with metoclopramide on the digestive tract motility.

Central nervous system depressants (morphine derivatives, anxiolytics, sedative H1 antihistamines, sedative antidepressants, barbiturates, clonidine and related)

Sedative effects of Central Nervous System depressants and metoclopramide are potentiated.

Neuroleptics

Metoclopramide may have an additive effect with other neuroleptics on the occurrence of extrapyramidal disorders.

Serotonergic drugs

The use of metoclopramide with serotonergic drugs such as SSRIs may increase the risk of serotonin syndrome.

Digoxin

Metoclopramide may decrease digoxin bioavailability. Careful monitoring of digoxin plasma concentration is required.

Cyclosporine

Metoclopramide increases cyclosporine bioavailability (Cmax by 46% and exposure by 22%). Careful monitoring of cyclosporine plasma concentration is required. The clinical consequence is uncertain.

Mivacurium and suxamethonium

Metoclopramide injection may prolong the duration of neuromuscular block (through inhibition of plasma cholinesterase).

Strong CYP2D6 inhibitors

Metoclopramide exposure levels are increased when co-administered with strong CYP2D6 inhibitors such as fluoxetine and paroxetine. Although the clinical significance is uncertain, patients should be monitored for adverse reactions.

4.6 Fertility, pregnancy and lactation

Pregnancy

A large amount of data on pregnant women (more than 1000 exposed outcomes) indicates no malformative toxicity nor foetotoxicity. Metoclopramide can be used during pregnancy if clinically needed. Due to pharmacological properties (as other neuroleptics), in case of metoclopramide administration at the end of pregnancy, extrapyramidal syndrome in the newborn cannot be excluded. Metoclopramide should be avoided at the end of pregnancy. If metoclopramide is used, neonatal monitoring should be undertaken.

Breastfeeding

Metoclopramide is excreted in breast milk at a low level. Adverse reactions in the breast-fed baby cannot be excluded. Therefore metoclopramide is not recommended during breastfeeding. Discontinuation of metoclopramide in breastfeeding women should be considered.

4.7 Effects on ability to drive and use machines

Metoclopramide may cause drowsiness, dizziness, dyskinesia and dystonias which could affect the vision and also interfere with the ability to drive and operate machinery.

4.8 Undesirable effects

Adverse reactions listed by System Organ Class. Frequencies are defined using the following convention: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10000, <1/1000), very rare (<1/10000), not known (cannot be estimated from the available data).

System Organ Class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders		
	Not known	Methaemoglobinaemia, which could be related to NADH cytochrome b5 reductase

		deficiency, particularly in neonates (see section 4.4) Sulfhaemoglobinaemia, mainly with concomitant administration of high doses of sulfur-releasing medicinal products
Cardiac disorders		
	Uncommon	Bradycardia, particularly with intravenous formulation
	Not known	Cardiac arrest, occurring shortly after injectable use, and which can be subsequent to bradycardia (see section 4.4); Atrioventricular block, Sinus arrest particularly with intravenous formulation; Electrocardiogram QT prolonged; Torsade de Pointes;
Endocrine disorders*		
	Uncommon	Amenorrhoea, Hyperprolactinaemia,
	Rare	Galactorrhoea
	Not known	Gynaecomastia
Gastrointestinal disorders		
	Common	Diarrhoea
General disorders and administration site conditions		
	Common	Asthenia
	Not Known	Injection site inflammation and local phlebitis
Immune system disorders		
	Uncommon	Hypersensitivity
	Not known	Anaphylactic reaction (including anaphylactic shock) particularly with intravenous formulation
Nervous system disorders		
	Very common	Somnolence
	Common	Extrapyramidal disorders (particularly in children and young adults and/or when the recommended dose is exceeded, even following administration of a single dose of the drug) (see section 4.4), Parkinsonism, Akathisia
	Uncommon	Dystonia, Dyskinesia, Depressed level of consciousness
	Rare	Convulsion especially in epileptic patients
	Not known	Tardive dyskinesia which may be persistent, during or after prolonged treatment, particularly in elderly patients (see section 4.4), Neuroleptic malignant syndrome (see section 4.4)
Psychiatric disorders		
	Common	Depression
	Uncommon	Hallucination
	Rare	Confusional state
Vascular disorder		

	Common:	Hypotension, particularly with intravenous formulation
	Not known	Shock, syncope after injectable use. Acute hypertension in patients with phaeochromocytoma (see section 4.3). Transient increase in blood pressure
Skin disorder		
	Not known	Skin reactions such as rash, pruritus, angioedema and urticaria

*Endocrine disorders during prolonged treatment in relation with hyperprolactinaemia (amenorrhoea, galactorrhoea, gynaecomastia).

The following reactions, sometimes associated, occur more frequently when high doses are used:

- Extrapyramidal symptoms: acute dystonia and dyskinesia, parkinsonian syndrome, akathisia, even following administration of a single dose of the medicinal product, particularly in children and young adults (see section 4.4).

- Drowsiness, decreased level of consciousness, confusion, hallucination.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at:www.mhra.gov.uk/yellowcard.

4.9 Overdose

Symptoms

Extrapyramidal disorders, drowsiness, a decreased level of consciousness, confusion, hallucination and cardio-respiratory arrest may occur.

Management

In case of extrapyramidal symptoms related or not to overdose, the treatment is only symptomatic (benzodiazepines in children and/or anticholinergic anti-parkinsonian medicinal products in adults).

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

5. Pharmacological properties

5.1 Pharmacodynamic properties

Metoclopramide as a dopamine antagonist stimulates gastric motility and gastric emptying and speeds small intestinal transit time by increasing gastric peristalsis and increasing the resting tone of the gastro oesophageal sphincter.

5.2 Pharmacokinetic properties

Renal impairment

The clearance of metoclopramide is reduced by up to 70% in patients with severe renal impairment, while the plasma elimination half-life is increased (approximately 10 hours for a creatinine clearance of 10-50 mL/minute and 15 hours for a creatinine clearance <10 mL/minute).

Hepatic impairment

In patients with cirrhosis of the liver, accumulation of metoclopramide has been observed, associated with a 50% reduction in plasma clearance.

5.3 Preclinical safety data

No further information other than that which is included in the Summary of Product Characteristics.

6. Pharmaceutical particulars

6.1 List of excipients

Sodium Chloride

Citric Acid Monohydrate

Sodium Citrate

Water for Injections

Hydrochloric acid

Sodium hydroxide

Nitrogen

6.2 Incompatibilities

Any dilutions of Metoclopramide 5 mg/ml Injection should be protected from light during infusion. Degradation is indicated by a yellow discoloration. Such solution must not be used.

6.3 Shelf life

36 months

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6.4 Special precautions for storage

Protect from light and store in a cool place.

6.5 Nature and contents of container

Type I clear glass ampoules 2 ml, 10 ml and 20 ml packed in cardboard cartons to contain 10 ampoules in each.

6.6 Special precautions for disposal and other handling

Metoclopramide Injection has been shown to be compatible with the following infusion solutions:

• Sodium chloride Intravenous infusion BP (0.9% w/v)

• Dextrose Intravenous Infusion BP (5% w/v)

• Sodium chloride and Dextrose Intravenous Infusion BP (Sodium chloride 0.18% w/v and Dextrose 4% w/v)

• Compound sodium lactate Intravenous Infusion BP (Ringer lactate solution, Hartman's solution)

7. Marketing authorisation holder

hameln pharmaceuticals ltd

Gloucester

UK

8. Marketing authorisation number(s)

PL 01502/0044

9. Date of first authorisation/renewal of the authorisation

16th August 1996

10. Date of revision of the text

12th September 2016

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Sodium Chloride Injection BP 0.9% w/v

Last Updated on eMC 04-Feb-2015 View changes | hameln pharmaceuticals ltd Contact details

1. Name of the medicinal product

Sodium Chloride Injection BP 0.9% w/v

2. Qualitative and quantitative composition

Each ml contains 0.9% Sodium Chloride in Water for Injections.

3. Pharmaceutical form

Sterile Injection.

4. Clinical particulars

4.1 Therapeutic indications

For use in prophylactic and replacement therapy, requiring the use of isotonic saline solution.
In the reconstitution, dilution and making up of certain drugs.
As a saline irrigant.
As a priming fluid for haemodialysis procedures and to initiate and terminate blood transfusions.

4.2 Posology and method of administration

In the prophylaxis or replacement therapy of extracellular fluid deficits, the dosage of sodium chloride injection BP 0.9% is dependent on the age, weight, clinical status and degree of deficiency, and must be determined on the individual basis.

4.3 Contraindications

There are no absolute contraindications to use of Sodium Chloride Injection BP 0.9% w/v.

4.4 Special warnings and precautions for use

Sodium Chloride Injection BP 0.9% w/v, should be administered with caution to patients with congestive cardiac failure, pre-eclampsia, impaired renal function or oedema with sodium retention. Care is also required with administering this solution to very young or to elderly patients.
Pseudohyponatraemia is a condition in which spuriously low concentrations of sodium are found when plasma sodium is measured by conventional methods. It may occur when there is an abnormally high concentration of large molecules and hence an abnormally low percentage of plasma water. This may occur in hyperlipaemia and hyperproteinaemia and has also been reported in patients with diabetes mellitus. Correct values may be obtained by referring the concentration to plasma water.
Before use, ensure that the container is undamaged and the contents clear in appearance. After use, discard any remaining solution.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration of other sodium salts, may contribute to the sodium load. Only use as a pharmaceutical diluent where indicated in the manufacturer's literature.

4.6 Pregnancy and lactation

The solution is physiological saline and may be used during pregnancy and lactation.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

Injudicious intravenous saline therapy (e.g. post-operative and in patients with impaired cardiac or renal function) may cause hypernatraemia. Osmotically induced water shift decreases intracellular

volume, resulting in dehydration of internal organs, especially the brain, which may lead to thrombosis and haemorrhage. General adverse effects of sodium chloride excess in the body include: nausea, vomiting, diarrhoea, abdominal cramps, thirst, reduced salivary and lachrymal secretions, sweating, fever, hypotension, tachycardia, renal failure, peripheral and pulmonary oedema, respiratory arrest, headache, dizziness, restlessness, irritability, weakness, muscular twitching and rigidity, convulsions, coma and death. Excess chloride in the body may cause a loss of bicarbonate, with an acidifying effect. With judicious use of intravenous saline therapy these side effects can be avoided. If administered sub-cutaneously, any addition to the isotonic solution could render it hypertonic and cause pain at the site of injection.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Injudicious intravenous saline therapy (e.g. post-operatively or in patients with impaired cardiac or renal function) may cause hypernatraemia. Osmotically induced water shift decreases intracellular volume, resulting in dehydration of internal organs, especially the brain, which may lead to thrombosis and haemorrhage. General adverse effects of sodium chloride excess in the body include: nausea, vomiting, diarrhoea, abdominal cramps, thirst, reduced salivary and lachrymal secretions, sweating, fever, hypotension, tachycardia, renal failure, peripheral and pulmonary oedema, respiratory arrest, headache, dizziness, restlessness, irritability, weakness, muscular twitching and rigidity, convulsions, coma and death. Excess chloride in the body may cause a loss of bicarbonate, with an acidifying effect. With judicious use of intravenous saline therapy these side effects can be avoided.

5. Pharmacological properties

5.1 Pharmacodynamic properties

The principal determinant of the effective osmolality of the extracellular fluids (and also of the intracellular fluids, since they remain in osmotic equilibrium with the extracellular fluids) is the extracellular fluid sodium concentration. The reason for this is that sodium is the most abundant positive ion of the extracellular fluid. Negative ion concentrations of the body fluids are adjusted to equal those of the positive ions by renal acid-base control mechanisms. Furthermore, glucose and urea, the most abundant of the non-ionic osmolar solutes in extracellular fluids, normally only represent about 3% of the total osmolality. Therefore, in effect, the extracellular fluid sodium ion concentration controls over 90% of the effective osmotic pressure of the extracellular fluid. Sodium Chloride remains the most important single salt for prophylaxis or replacement therapy of deficits of extracellular fluid. Volume contraction, whether isotonic, hypotonic or hypertonic, may seriously impair the circulation (cardiac output falls and microcirculation is compromised) and prompt infusion of isotonic sodium chloride solution is indicated.

5.2 Pharmacokinetic properties

The homeostatic mechanisms involved in maintaining constant ion concentrations are well described in standard text books of physiology and biochemistry and are not, therefore, included here.

5.3 Preclinical safety data

No further information other than that which is included in the Summary of Product Characteristics.

6. Pharmaceutical particulars

6.1 List of excipients

Water for Injections
Sodium Hydroxide
Hydrochloric Acid

6.2 Incompatibilities

The addition of sodium chloride to mannitol 20 or 25% may cause precipitation of the mannitol.

6.3 Shelf life

60 months for ampoules.
36 months for vials.

6.4 Special precautions for storage

Should be stored at room temperature and protected from excessive heat and freezing.

6.5 Nature and contents of container

Type I clear glass ampoules, 2ml, 5ml, 10ml and 20ml. Packed in cardboard cartons to contain 10 ampoules.
Type I clear glass vials 50ml with chlorbutyl rubber stopper, plastic outer cap and inner aluminium ring.
Type II clear glass vials (33ml, 100ml and 200ml) with bromobutyl rubber stopper, plastic outer cap and inner aluminium ring.

6.6 Special precautions for disposal and other handling

Use as directed by a physician.

Administrative data

7. Marketing authorisation holder

hameln pharmaceuticals ltd
Gloucester
UK

8. Marketing authorisation number(s)

01502 / 0006R

9. Date of first authorisation/renewal of the authorisation

30th August 1985/ 10th January 1995

10. Date of revision of the text

09/01/2015

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16.5 - APPENDIX FIVE - Data collection

16.5.1 - Baseline (before randomisation)

Data collection at baseline will include key patient and demographic details, clinical examination and laboratory results such as:

Eligibility criteria check
Consent form patient [yes/no]
Consent from a personal legal representative [yes/no]
Name
Hospital
Unit number
Date of birth
Sex
Date and time of onset of symptoms
Date and time of presentation at hospital
Usual place of abode [home alone/ home with others/ residential home/nursing home/ other institution/ other]
Modified Rankin Scale sore before the stroke
EQ-5D
Comorbid conditions and treatments:
- Heart failure [yes/no]
- Ischemic heart disease [yes/no]
- Chronic obstructive airways disease or asthma
- Other chronic lung problems [yes/no]
- Diabetes mellitus [yes/no]
- Prior stroke [yes/no]
- Wears dentures [yes/no]

Treatment before randomisation
- Metoclopramide [yes/no]
- Thrombolysis [yes/no]

Body temperature [C]
Oxygen saturation on air [%]
Heart rate [beats/minute]
NIHSS (full scale)
Glasgow Coma Scale (GCS) (full scale)
Simple Six Variables (SSV): *age*, *pre-stroke independence in activities of daily living, living alone*, (*normal verbal component of the GCS*, ability to lift both arms, ability to walk)
Weight [kg]
Randomisation date and time
Participant identification (PID) number
Kit information for SOD paste and metoclopramide

16.5.2 - Daily Clinical Monitoring Log

Each day's entry relates to 00:00 to 24:00 of the day before. Data collected will include information about the place of care, swallowing, feeding, symptoms and signs of pneumonia, treatments, complications, adverse events and laboratory results such as:

Day from inclusion [number (range 1-14)]
Current stay [ITU / Acute / Rehabilitation / Step-down / other (specify_____)]
Normal diet and fluids [Y/N]
Modified diet and or fluids [Y/N]
Nil by mouth [Y/N]
Nasogastric tube feeding [Y/N]
PEG tube feeding [Y/N]
Palliative care [Y/N]
Vomiting [Y/N]
Urinary catheter [Y/N]
Out of bed at least once in 24 h [Y/N]

Highest temperature in the last 24 hours [°C]
Highest respiratory rate in the last 24 hours [respirations/minute]
Highest heart rate in the last 24 hours [beats/minute]
Lowest heart rate in the last 24 hours [beats/minute]
Lowest oxygen saturation in the last 24 hours [%]

Temperature > 37.5°C on two occasions [Y/N]*
New confusion not present on admission and no other identifiable cause [Y/N]
Respiratory Rate>25/min [Y/N]*
Oxygen given [Y/N]*
New or increased cough [Y/N]*
New or increased respiratory secretions or sputum [Y/N]*

New infiltration on CXR [Y/N/ND]
Positive sputum culture [Y/N/ND]
Clinical diagnosis of pneumonia made today [Y/N]
Antibiotics given [Y/N]

White cell count [10^9/L] [number or ND for not done]
CRP [mg/L] [number or ND for not done]

Number of times metoclopramide/placebo given today via IV or NG (specifiy) [0-3]
Number of times oral decontaminant/placebo given today [0-4]
Lost or damaged doses: Number of vials of metoclopramide/placebo lost or damaged; Number of tubes of oral decontaminant/placebo lost or damaged.

Orofacial dyskinesia [Y/N]
Tardive dyskinesia [Y/N]
Diarrhoea (Bristol type 7) [Y/N]
Indication for antibiotics [Pneumonia, LRTI, UTI, Cellulitis, Other, specify_____]
Site ID

*if any of these is yes suspect chest infection and check with clinical team that CXR, blood and sputum culture, WBC and CRP are done.

16.5.3 - Day 7 (+ 3 days if no staff available over weekends/holidays)

Data collection at day 7 (+ 3 days) will include diagnosis, treatment, and adverse events and the daily log. Data will include items such as:

Diagnosis and treatment:
Mechanical thrombectomy (yes/no)
Decompressive hemicraniectomy (yes/no)
OCSP syndrome (TAC/PAC/LAC/POC)
CT diagnosis: cerebral infarct (visible infarct or ischemia, normal or non-specific changes), intracerebral haemorrhage, other (give detail)
Final (combined clinical and CT) Diagnosis (cerebral infarct/ intracerebral haemorrhage/ subdural haemorrhage/ subarachnoid haemorrhage/ transient ischaemic attack/ not a stroke)

Adverse Events:
- A further stroke (yes/no) If yes, give date and type (infarct/ haemorrhage/no imaging diagnosis). If yes, give date
- A collapse or cardiac/ respiratory arrest requiring resuscitation (yes/no) /- bradycardia/ torsade de pointes/ ventricular tachycardia/ asystole/ electromechanical dissociation/ hypotension/ haemorrhage/ respiratory arrest/ other. If yes, give date and complete SAE form
- Severe bradycardia requiring atropine or pacemaker insertion (yes/no).If yes, give date and complete SAE form
- Definite epileptic seizure (focal or generalized) If yes, give date and complete SAE form
- Orofacial dyskinesia (yes/no). If yes, give date and complete SAE form
- Tardive dyskinesia (yes/no) If yes, give date and complete SAE form
- A NEW diagnosis of Parkinson's disease (yes/no) If yes, give date and complete SAE form
- Any serious adverse event that is NOT a known complication of stroke

If there have been any SAEs complete the SAE report form. Remember that complications of the stroke as per appendix 6 should not be reported as SAEs.

Daily log day 1-7:
Ensure all WBC, CRP, CXR, and culture results done during the week for clinical reasons are recorded on the log.

Complete and scan and email daily log for this week.

16.5.4 - Day 14 (+ 3 days if no staff available over weekends/holidays)

Data collection will be the same as for day 7 except for items relating to diagnosis and treatment of the acute episode, which will not be repeated here. It will include safety outcome data (same as week 1, but relating to days 8-14) and the daily log for days 8-14.

Daily log day 8-14:
Ensure all WBC, CRP, CXR, and culture results done during the week for clinical reasons are recorded on the log.

Complete and scan and email daily log for this week.

16.5.5 – Day 21 (+ 3 days if no staff available over weekends/holidays)

Number of times metoclopramide/placebo given on Days 15-21 via IV or NG (specifiy) [0-3] (per day).
Number of times oral decontaminant/placebo given on days 15-21 [0-4] (per day).

Lost or damaged doses on Days 15-21: Number of vials of metoclopramide/placebo lost or damaged; Number of tubes of oral decontaminant/placebo lost or damaged.

16.5.6 - Day 30 (+ 3 days if no staff available over weekends/holidays)

This will include an examination of neurological and functional status, adverse events, infections, antibiotic use, transfer and/or discharge details such as:

Examination:
NIHSS
mRS

Adverse Events:
- A further stroke (yes/no) If yes, give date and type (infarct/ haemorrhage/no imaging diagnosis). If yes, give date
- A collapse or cardiac/ respiratory arrest requiring resuscitation (yes/no) /- bradycardia/ torsade de pointes/ ventricular tachycardia/ asystole/ electromechanical dissociation/ hypotension/ haemorrhage/ respiratory arrest/ other. If yes, give date and complete SAE form
- Severe bradycardia requiring atropine or pacemaker insertion (yes/no).If yes, give date and complete SAE form
- Definite epileptic seizure (focal or generalized) If yes, give date and complete SAE form
- Orofacial dyskinesia (yes/no). If yes, give date and complete SAE form
- Tardive dyskinesia (yes/no) If yes, give date and complete SAE form
- A NEW diagnosis of Parkinson's disease (yes/no) If yes, give date and complete SAE form
- Any serious adverse event that is NOT a known complication of stroke

Record new SAEs since the week 2 assessment and ensure all events/SAEs have been confirmed by the local investigator. Remember that complications of the stroke as per appendix 6 should not be reported as SAEs.

Investigations and treatment:

Record every course of antibiotics (antibiotic name, indication, start date, end date)

Transfer or discharge:

Transferred to another hospital? (yes/no) If yes, complete transfer form.

Discharged into the community? (yes/no) If yes, please complete discharge form.

16.5.7 - Day 90 (+ 8 days if not possible to review on day 90)

Source of information (participant/ family member or friend/ staff at care facility/ hospital staff/ GP or community support team/ SSNAP/ other)
Still in hospital (yes/no)
If yes:

Nasogastric tube still in place? (yes/no)
If no, date of nasogastric tube removal
PEG tube still in place? (yes/no)
If no, date of PEG tube removal:

If not in hospital any longer:
Date of discharge to the community:
Any readmissions?
If yes, give reason, name of hospital and dates of admission and discharge for each
Current residence (home / residential home / nursing home / other: specify)

For all:
mRS
EQ-5D

16.5.8 - Transfer to another hospital / repatriation

Participants repatriated or transferred to other hospitals must complete their trial treatment and assessments as per protocol.

Information collected will include:

Hospital and ward transferred to:
Trial contact at new hospital (name, email, phone)
Transfer date:
Number of days in intensive care from:
No of days on the acute stroke unit:
No of days on the stroke rehabilitation unit:
No of days on other ward (specify):

Review clinical and lab logs and ensure all are complete and emailed to the coordinating centre. Ensure all queries have been resolved.

16.5.9 - Discharge to the community

Information collected will include:

Any AEs / SAEs? If yes and before day 30 complete AE/SAE form

Discharge date into the community:
Discharge destination (home / residential home / nursing home / other: specify)
Number of days in intensive care
No of days on the acute stroke unit
No of days on the stroke rehabilitation unit
No of days on other ward (specify)

Complete discharge address and contact form. Review clinical and lab logs and ensure all are complete and emailed to the coordinating centre. Ensure all queries have been resolved.

16.5.10 - Vital status check/Notification of Death/Withdrawal

Information collected will include:

Alive/deceased/ withdrawn/ lost to follow-up
Date of death
Cause of death

16.6 - APPENDIX SIX - PHARMACOVIGILANCE

16.6.1 - Expected Serious Adverse Events that NOT to be reported

Complications of the original stroke

Extension of the initial stroke

Haemorrhagic transformation of the stroke

Malignant cerebral oedema

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 randomisation)

Headaches

Confusion

Falls

Fractures

Elective and diagnostic procedures (carotid endarterectomy, PEG insertion, endoscopy)

16.6.2 - Serious Adverse Events to be reported

Any adverse event that is serious as per the definitions of regulatory seriousness in section 9.1 and does not meet the exclusion criteria above should be reported.

16.7 - APPENDIX SEVEN - Trial management / responsibilities

16.7.1 - Patient registration/randomisation procedure

Randomisation will be using a secure centralised web-based IRT. This is an automated computer generated randomisation system provided by the Anglia Ruskin Clinical Trials Unit. Authorised

personnel at the trial site will be allocated personalised log in details by Anglia Ruskin CTU, in order to access the randomisation system via https://prod.tenalea.net/anglia/dm/ . A patient identification number will be assigned.

If the online allocation IRT system is unavailable a paper system will be used. All required details will be recorded in a paper form and a temporary patient identification number (tPID) assigned to the patient. Once the system is recovered, the details will be entered and a permanent patient identification number (PID) assigned, the assigned treatment will be overridden to match that which was allocated.

16.7.2 - Data management

Once the CRF is emailed to the trial coordinating centre, data will be entered into a trial specific MACRO database. This system has been designed to minimise human error in data entry, has built in validation rules and will highlight missing data so that any data queries can be sent back to the research site within 48 hours. Overall this should result in high quality, robust data.

16.7.3 - Preparation and submission of Annual Safety Report/Annual

The Sponsor Research and Development Department will appoint an independent medical expert to review safety reports and will take responsibility for submitting annual safety reports to the regulatory authorities.

16.7.4 - Data protection/confidentiality

CRFs will be held securely in a locked room, or locked cupboard or cabinet. Access to the information will be limited to members of the participants' clinical team or the research team at the site. All data transfer will be in accordance with the UK Data Protection Act 1998. Information about the trial in the participants' medical records/hospital notes will be treated confidentially in the same way as all other confidential medical information.

16.7.5 - Trial documentation and archiving

The archiving of trial data will be undertaken at each site following a close out procedure detailed by the co-ordinating centre at the end of the trial. The requirement of the HTA as funders will mean that sites will need to retain any documentation relating to the trial for a period of 15 years. Provision has been made in the payment when a patient is recruited for this service.

16.8 - APPENDIX EIGHT - Authorisation of participating sites

All sites will have completed a feasibility study which along with the statement of activities and schedule of events will ensure they are able to carry out the requirements of the trial. Prior to the

site initiation visit approval will need to have been received from the sponsor that the site are ready to commence. Contacts will need to be exchanged and financial arrangements set up. All training will be provided during the initiation visit where the delegation log will be signed and evidence of staff listed on it provided (Good Clinical Practice Certificates and Research Curriculum vitaes). As with all drug trials the Pharmacy department will need to incorporate the brochure provided into their SOPs.

16.8.1 - Procedure for initiating/opening a new site

Site initiation visits for each site will be carried out by the MAPS-2 trial team. These will include training on the protocol, provision of information relating to standard operating procedures, provision of access to training materials, the trial website, and the trial documentation. Following the completion of the site initiation visit the randomisation facility and once the approvals process has been completed and contacts have been signed the web randomisation and provision of the drugs for the site will be activated.

16.8.2 - Principal Investigator responsibilities

The PI's legal responsibilities are listed in the Participating Site Agreement. These will include attendance at the initiation meeting/teleconference, training of new members of the trial team in the protocol and its procedures, ensuring that the Investigator Site File is accurately maintained, dissemination of important safety or trial related information to all stakeholders within their site, and safety reporting within the timelines.

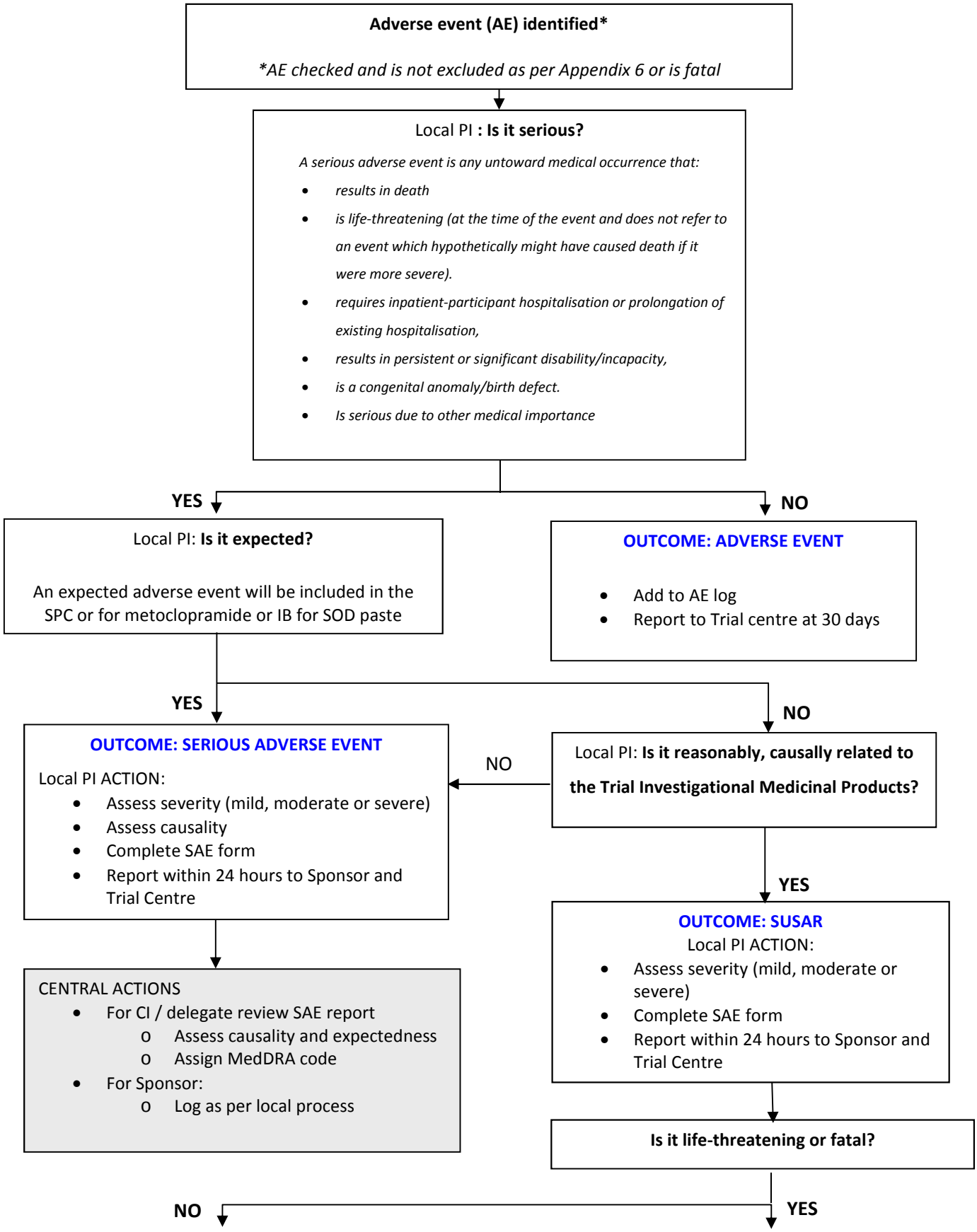
16.8.3 - Required documentation

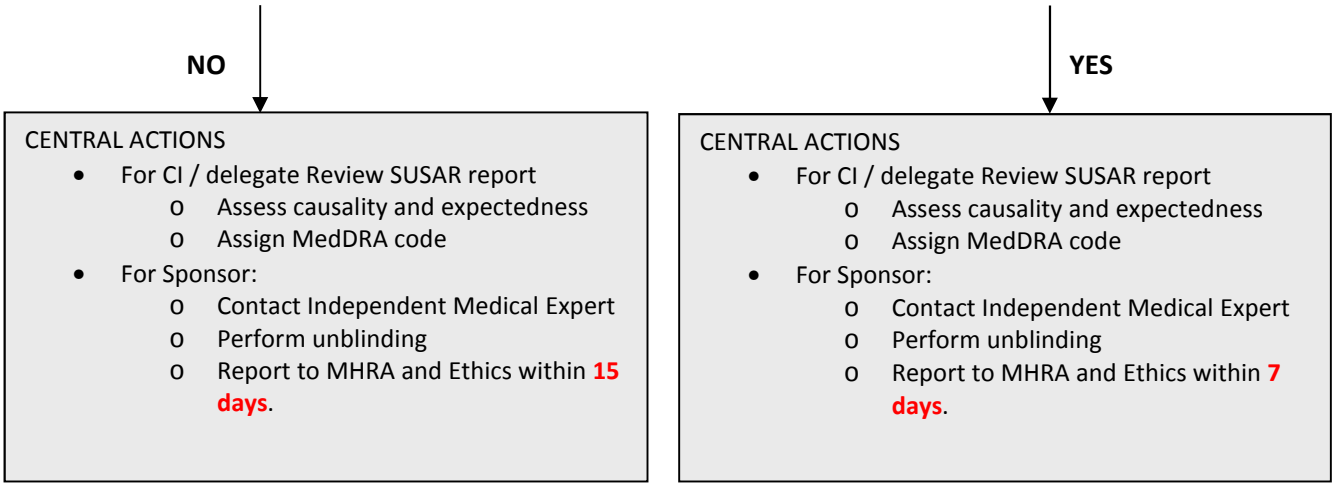
1. Identification of a PI for MAPS-2 at the site

2. Completed feasibility study

3. Evidence from the site R&D department that they are working on completing the necessary legal documentation e.g. CTA.

16.9 - APPENDIX NINE - Safety Reporting Flow Chart




NO
YES
CENTRAL ACTIONS
For CI / delegate Review SUSAR report
Assess causality and expectedness
Assign MedDRA code
For Sponsor:
Contact Independent Medical Expert
Perform unblinding
Report to MHRA and Ethics within 15 days.
CENTRAL ACTIONS
For CI / delegate Review SUSAR report
Assess causality and expectedness
Assign MedDRA code
For Sponsor:
Contact Independent Medical Expert
Perform unblinding
Report to MHRA and Ethics within 7 days.