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

Protocol v1.2 – 13/07/2022

Training slides v5.0 – 22/07/2022

Website: https://stroke.nottingham.ac.uk/maps-2/

Overview

- ✓Contacts
- ✓Study objectives
- ✓Background & rationale
- ✓Inclusion & exclusion criteria
- ✓IMP & Drug administration
- ✓Study design
- ✓Consent process
- ✓Randomisation & Blinding
- ✓eCRF overview
- ✓SAE reporting
- ✓Continuous monitoring & remote monitoring (checking consent forms/delegated consent/etc)
- ✓ISF -> documents (del/training log) stored on site

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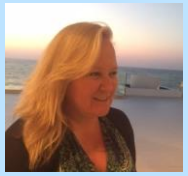

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Aims

- To investigate whether metoclopramide reduces mortality in stroke patients with dysphagia

- To investigate whether metoclopramide reduces pneumonia and improve patient's neurological recovery at day 14

- To investigate whether metoclopramide improves long-term (6-months) outcomes for patients

- To assess the cost-effectiveness of metoclopramide

Background - Stroke

- Stroke:

➢Second most common cause of death worldwide

➢Fourth most common cause of death in the UK

➢Most common cause of disability in the UK

- Pneumonia causes more deaths after stroke than neurological damage, increases the length of hospital stay and significantly increases NHS costs of treatment.

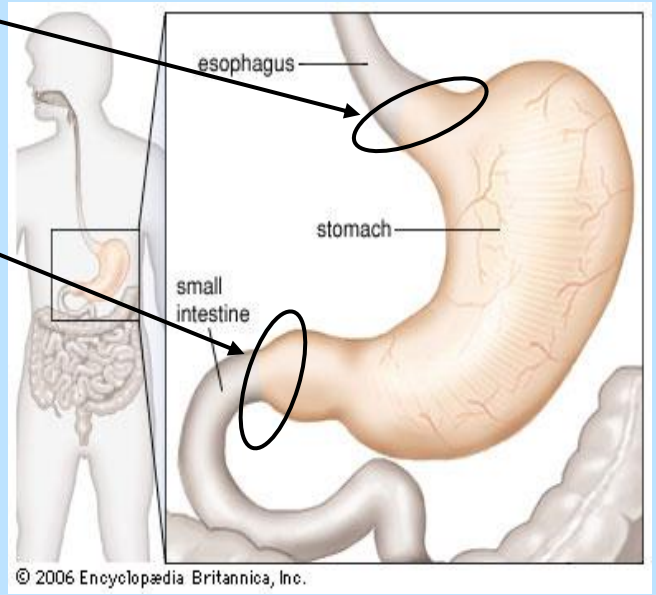
Website: https://stroke.nottingham.ac.uk/maps-2/

Background - SAP

- Stroke-associated pneumonia (SAP) is the most common complication from stroke and responsible for over one-third of deaths.
- SAP occurs in 12% of unselected stroke patients and in approximately 44-69% of stroke patients fed via a nasogastric tube.
- SAP is also associated with a 2-6x increase in mortality and a longer length of hospital stay and an increase in long-term disability.
- SAP most common in patients with severe strokes and dysphagia
- Patients that require feeding via nasogastric tube are at great risk of developing SAP.

Metoclopramide

- Dopamine antagonist with both central antiemetic and gastric prokinetic effects.
- Prevents vomiting by blocking dopamine receptors in the Chemoreceptor trigger zone in the brain.
- Increases **lower oesophageal sphincter pressure** and forward peristalsis.
- Decreases **pyloric sphincter pressure**
- Accelerates gastric emptying process
- Reduces vomiting and regurgitation
- Well established safety profile
- Cheap and widely available



Rationale

- MAPS pilot study found a significant reduction in SAP in 60 patients fed metoclopramide via nasogastric tubes compared to placebo.
- Other findings: metoclopramide use associated with lower mortality rate, fewer episodes of food aspiration, faster return to normal oral intake and less hypoxia.
- Larger study is required to confirm whether metoclopramide can reduce pneumonia and mortality in patients with severe strokes & dysphagia.

Inclusion Criteria

1. Adults (18 years and over) with a clinical diagnosis of acute stroke (WHO definition excluding duration);

2. Within 9 hours of symptom onset (in wake-up stroke the onset is defined as the time the patient awoke or was found);

3. Either of the two below criteria:

a) Moderate to severe neurological impairment (NIHSS Score ≥ 10), or

b) NIHSS Score ≥ 6 **and** dysphagia: unable to take normal unmodified oral diet or fluids because:

(i) Too drowsy to be assessed formally or

(ii) Failed bedside assessment of swallowing

Exclusion Criteria (1)

1. Definite or probable pneumonia
   a. abnormal CXR suggestive of pneumonia or
   b. focal chest signs with fever ≥38°C, or
   c. receiving antibiotic treatment at time of presentation

2. Contraindications to metoclopramide:

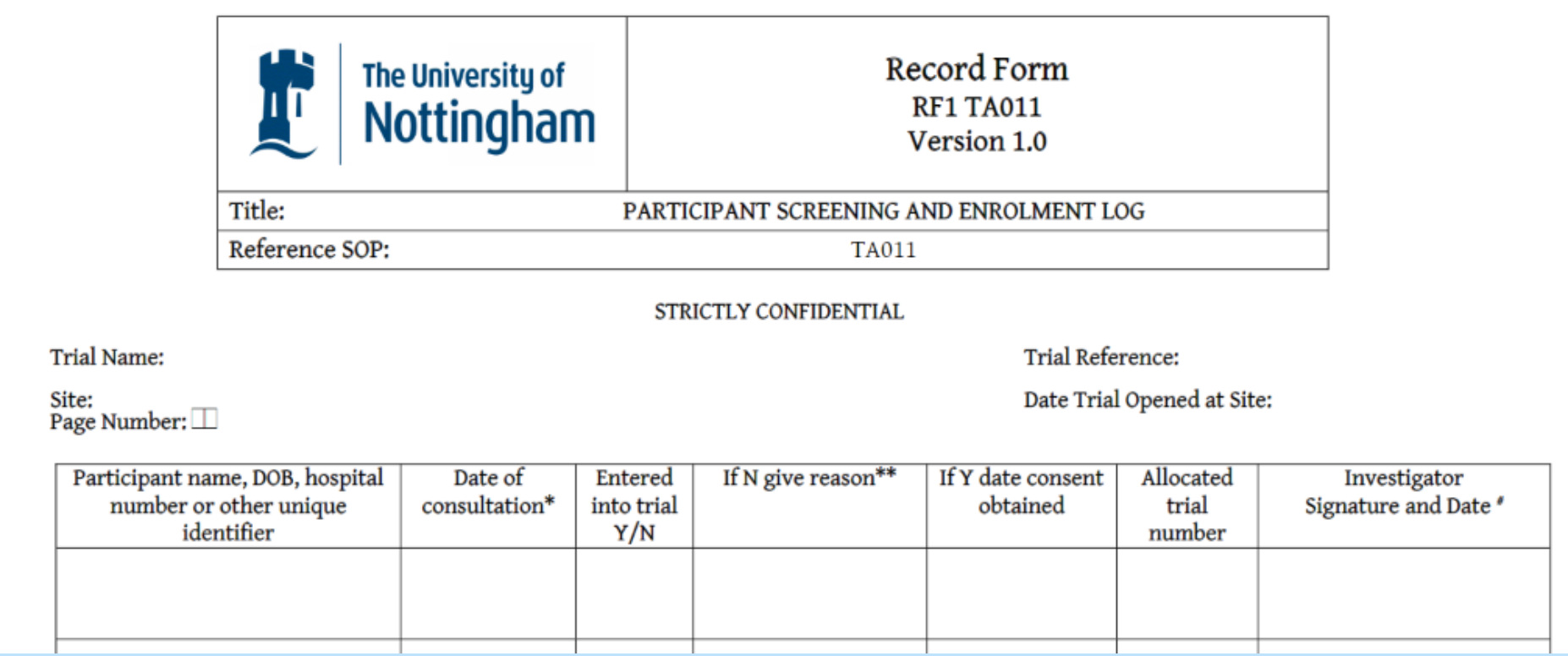
(a) hypersensitivity to metoclopramide
(b) epilepsy
(c) gastrointestinal obstruction, perforation, or haemorrhage
(d) gastrointestinal surgery within the last week
(e) Parkinson's disease
(f) treatment with levodopa or dopaminergic agonists
(g) phaeochromocytoma
(h) neuroleptic malignant syndrome
(i) history of neuroleptic or metoclopramide-induced tardive dyskinesia
(j) known history of methaemoglobinaemia with metoclopramide or of NADH cytochrome –b5 deficiency

Exclusion Criteria (2)

3. Participant has existing clinical indication for regular antiemetic treatment
4. Known cirrhosis of the liver
5. Known severe renal dysfunction (eGFR< 30 ml/min)
6. Pregnant or breast feeding
7. Moribund (expected to die within the next 48 hours)
8. Co-morbid conditions with life expectancy <3 months
9. Inability to gain consent (patient or legal representative) **OR** consent declined
10. Participants must not be taking part in or be co-enrolled into another CTIMP, device or interventional trial during the trial and follow-up period, **other than** the TICH-3 and RECAST-3 trials sponsored by the University of Nottingham.

Participant Screening

- All patients should be screened using the inclusion and exclusion criteria.
- Both recruited participants **and** screen failures should be recorded and signed off on the Participant Screening and Enrolment Log (RF1 TA011).



The University of Nottingham

Record Form
RF1 TA011
Version 1.0

Title:	PARTICIPANT SCREENING AND ENROLMENT LOG
Reference SOP:	TA011

STRICTLY CONFIDENTIAL

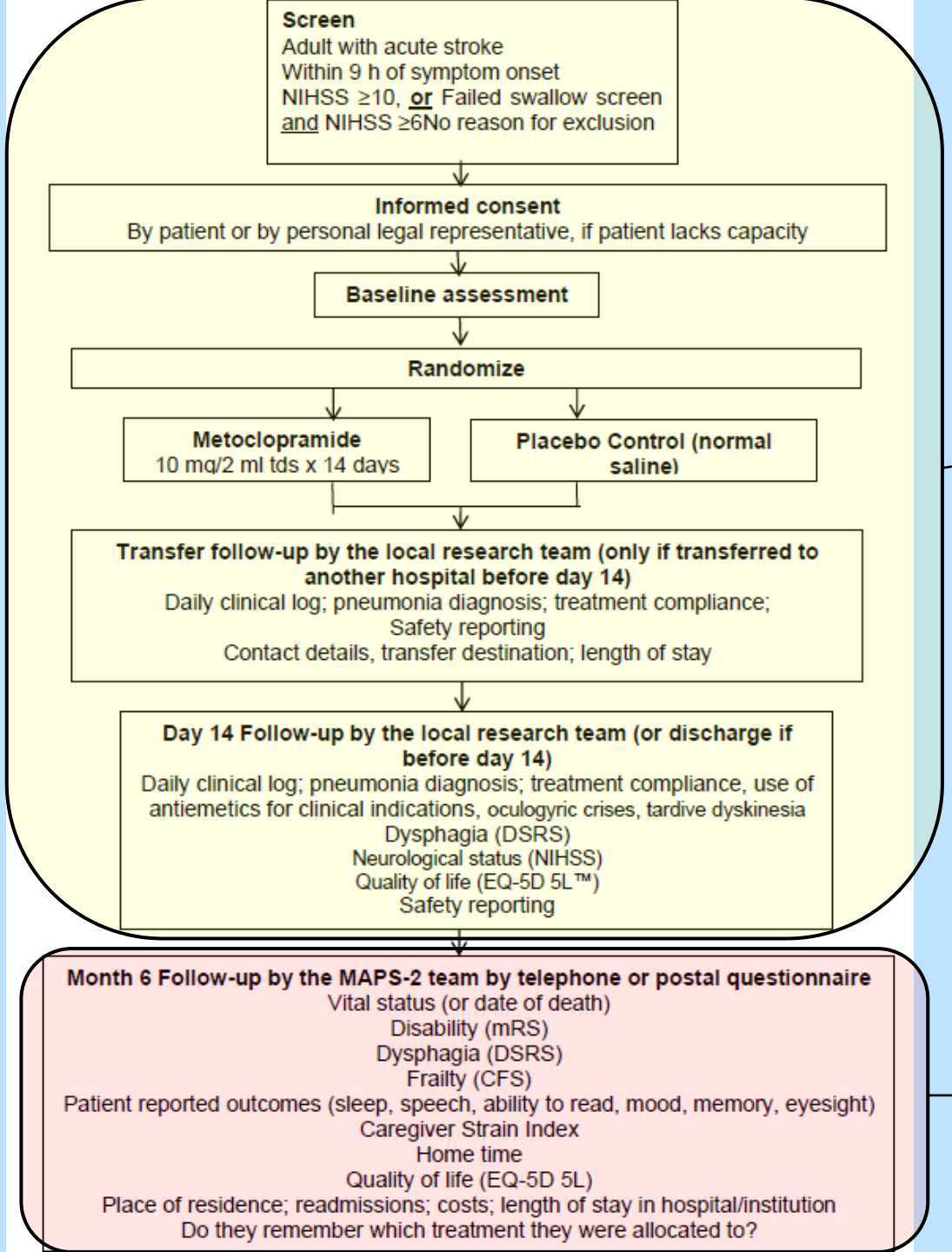
Trial Name:

Trial Reference:

Site:
Page Number:

Date Trial Opened at Site:

Participant name, DOB, hospital number or other unique identifier	Date of consultation*	Entered into trial Y/N	If N give reason**	If Y date consent obtained	Allocated trial number	Investigator Signature and Date



To be completed by sites

NOT to be completed by sites. Completed by Nottingham STU coordinator

Baseline

- Participant initials, date of birth, inclusion and exclusion criteria met, mode of consent, and baseline clinical (mRS, CFS, NIHSS & GCS score) and demographic details.

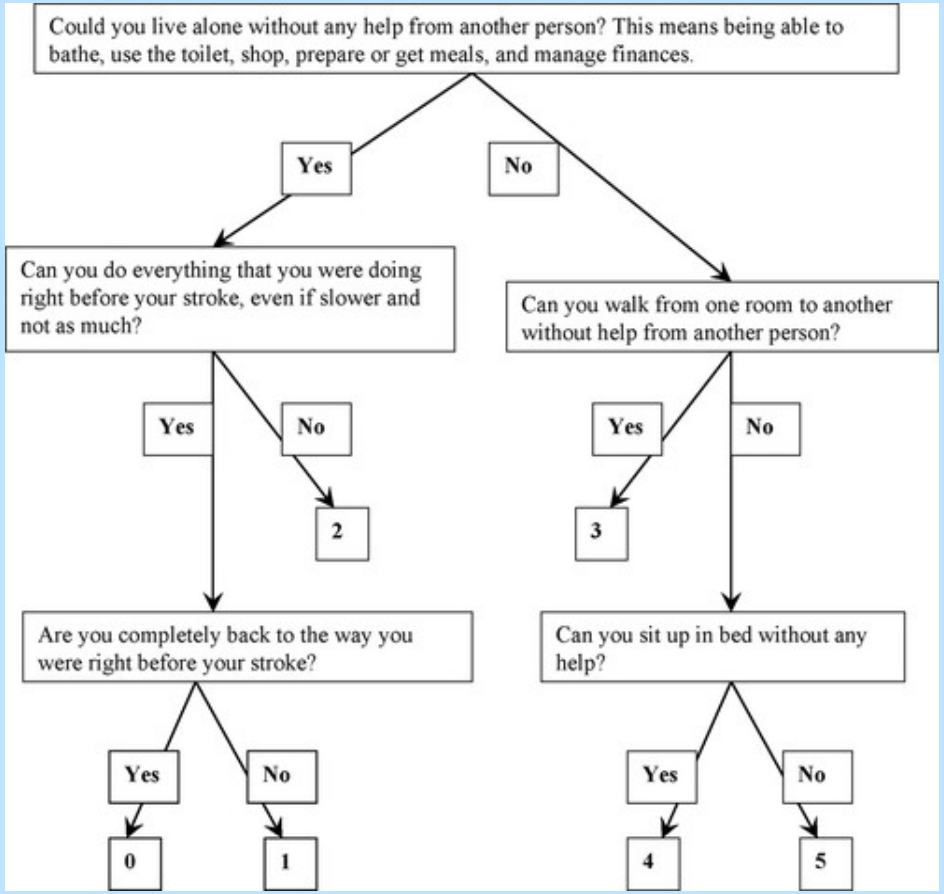
- Record contact details from patient / legal representative in secure vault database - this is required to contact them for 6-month follow-up.

- Consider taking more than one contact number, an email address, and address of someone who does not live with the participant, if available.

- Central team will monitor contact details uploaded to secure vault early in the participant's duration in the study.

- Send GP letter to participant's GP once consent has been gained!

Modified Rankin Scale (mRS)



C6. Modified Rankin Scale (pre-stroke)
view detail
* must provide value

- ○ 0- No symptoms at all
- ○ 1- No significant disability despite symptoms
- ○ 2- Slight disability
- ○ 3- Moderate disability
- ○ 4- Moderately severe disability
- ○ 5- Severe disability

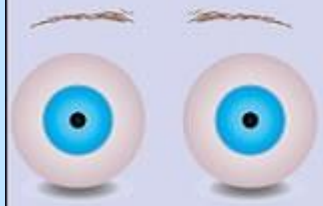
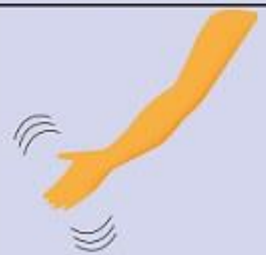
reset

NIHSS

1a—Level of consciousness	0 = Alert; keenly responsive 1 = Not alert, but arousable by minor stimulation 2 = Not alert; requires repeated stimulation 3 = Unresponsive or responds only with reflex
1b—Level of consciousness questions: What is your age? What is the month?	0 = Answers two questions correctly 1 = Answers one question correctly 2 = Answers neither questions correctly
1c—Level of consciousness commands: Open and close your eyes Grip and release your hand	0 = Performs both tasks correctly 1 = Performs one task correctly 2 = Performs neither task correctly
2—Best gaze	0 = Normal 1 = Partial gaze palsy 2 = Forced deviation
3—Visual	0 = No visual lost 1 = Partial hemianopia 2 = Complete hemianopia 3 = Bilateral hemianopia
4—Facial palsy	0 = Normal symmetric movements 1 = Minor paralysis 2 = Partial paralysis 3 = Complete paralysis of one or both sides
5—Motor arm Left arm Right arm	0 = No drift 1 = Drift 2 = Some effort against gravity 3 = No effort against gravity 4 = No movement
6—Motor leg Left leg Right leg	0 = No drift 1 = Drift 2 = Some effort against gravity 3 = No effort against gravity 4 = No movement
7—Limb ataxia	0 = Absent 1 = Present in one limb 2 = Present in two limbs
8—Sensory	0 = Normal; no sensory loss 1 = Mild-to-moderate sensory loss 2 = Severe-to-total sensory loss
9—Best language	0 = No aphasia; normal 1 = Mild-to-moderate aphasia 2 = Severe aphasia 3 = Mute; global aphasia
10—Dysarthria	0 = Normal 1 = Mild-to-moderate dysarthria 2 = Severe dysarthria
11—Extinction and inattention	0 = No abnormality 1 = Visual, tactile, auditory, spatial, or personal inattention 2 = Profound hemi-inattention or extinction
Score = 0–42	

Website: https://stroke.nottingham.ac.uk/maps-2/

Glasgow Coma Scale (GCS)

Behaviour	Response
 Eye Opening Response	4. Spontaneously 3. To speech 2. To pain 1. No response
 Verbal Response	5. Oriented to time, person and place 4. Confused 3. Inappropriate words 2. Incomprehensible sounds 1. No response
 Motor Response	6. Obeys command 5. Moves to localised pain 4. Flex to withdraw from pain 3. Abnormal flexion 2. Abnormal extension 1. No response

Clinical Frailty Scale (CFS)

Clinical Frailty Scale*

1 **Very Fit** – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 **Well** – People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g. seasonally.

3 **Managing Well** – People whose **medical problems are well controlled,** but are **not regularly active** beyond routine walking.

4 **Vulnerable** – While **not dependent** on others for daily help, often **symptoms limit activities.** A common complaint is being "slowed up", and/or being tired during the day.

5 **Mildly Frail** – These people often have **more evident slowing,** and need help in **high order IADLs** (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 **Moderately Frail** – People need help with **all outside activities** and with **keeping house**. Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.

7 **Severely Frail** – **Completely dependent for personal care**, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8 **Very Severely Frail** – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9. **Terminally Ill** - Approaching the end of life. This category applies to people with **a life expectancy <6 months**, who are **not otherwise evidently frail.**

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia**, they cannot do personal care without help.

* 1. Canadian Study on Health & Aging. Revised 2008.
2. K. Rockwood et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-495.

DALHOUSIE UNIVERSITY *Inspiring Minds*

Website: https://stroke.nottingham.ac.uk/maps-2/

Trial IMP – days 1-14

- Dispensed from local pharmacies/ward stock at both recruiting sites **and** repatriation sites.

- No trial-specific labelling. All medical record entries should identify the treatment (metoclopramide vs saline).

- IMP should be prescribed as “MAPS-2 trial drug (metoclopramide)” and “MAPS-2 trial drug (sodium chloride 0.9%)” on the **drug chart**, and referred to as “MAPS-2 trial drug” in communication with participants and their families.

- The drug chart should be passed to repatriation sites in order for participants to continue their treatment regimen at their repatriation site.

Trial IMP – days 1-14 (cont.)

- Metoclopramide and 0.9% saline are clear, colourless liquids.

- IMP will be dispensed in ampoules of the same volume. Should be stored as per the local pharmacy guidelines.

- Recruiting sites may transfer IMP to their repatriation sites with the participant, if the repatriation site is unable to dispense the IMP. Normal processes when transferring IMP between sites should be followed.

IMP Administration (1)

- IMP will be administered via nasogastric tube (NG) or intravenous injection (IV):
- 10mg/2ml metoclopramide 3x per day for 14 days, **or**
- 2ml normal saline 3x per day for 14 days

- IMP dose can be reduced to 1 ml/5mg if body weight < 60 kg

- First IMP dose should be given via slow IV injection over 3 minutes, with all other doses being administered via NG (preferred, if in place). If no NG tube is in place then all other doses should be administered via slow IV injection over 3 minutes.

IMP Administration (2)

- If the NG tube is removed during the fourteen-day regimen then participants may receive the IMP via slow IV injection instead.

- If participants initially have the IMP administered via slow IV injection and are then required to have a nasogastric tube inserted then the IMP may be administered via this route thereafter.

- Contemporaneous IMP delivery / administration will be collected throughout days 1-14 in the eCRF.

Administration Videos

- A video showing the metoclopramide administration via NG tube is available on our website:

https://stroke.nottingham.ac.uk/maps-2/docs/public.php

- A second video of an alternative administration method is also show, however this is not the preferred option of administration!

Safety Outcomes (Day 14 or discharge)

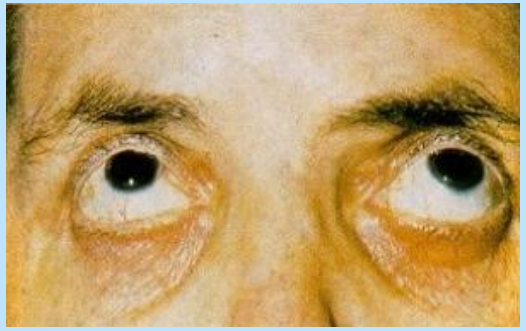
- Metoclopramide can induce acute dystonic reactions involving facial and skeletal muscle spasms, and oculogyric crises.
- More common in young women and the elderly/frail.
- These can usually occur shortly after starting treatment with metoclopramide

- Safety outcomes at this timepoint to be recorded by <u>local research team</u> include:

1. Oculogyric crises **(extremely rare)**
2. Tardive dyskinesia **(extremely rare)**
3. Adverse events
4. Any study discontinuations due to adverse events

Oculogyric Crises

- Prolonged involuntary upward deviation of the eyes.
- The eyes may converge, deviate upward and laterally, or deviate downward.
- Commonly coincides with backwards and lateral flexion of the neck, widely opened mouth, tongue protrusion, and ocular pain.



Tardive Dyskinesia

- Involuntary repetitive movements of the mouth, tongue, eyes, face, trunk, and extremities.
- I.e, lip-smacking, limb/torso twitching, rapid eye blinking
- Commonly coincides with a difficulty in breathing, difficulty in swallowing and difficulty speaking.
- Triggered by long-term use of dopamine-receptor-blocking medications, including metoclopramide.

These adverse events can be halted by injections of antiparkinsonian agents, such as procyclidine, or subside spontaneously within 24 hours after discontinuation.

Transfer to repatriation sites

- Some MAPS-2 patients may need to be transferred (as part of a standard of care) to a registered repatriation site.

- These repatriation sites will be trained on the study but will not recruit patients into MAPS-2.

- Recruiting sites are expected to deliver a comprehensive handover to their designated repatriation site when transferring the participant.

- Outcomes to be measured by recruiting site prior to repatriation:

Daily clinical log; pneumonia diagnosis; treatment compliance, safety reporting, contact details, transfer destination, length of stay

Follow-up (Day 14 or discharge)

- Data including metoclopramide compliance, safety reporting and pneumonia diagnosis will be collected from each participant up to and including day 14 **or** discharge day.

- Patients that have been repatriated will still be followed-up on day 14 in person and/or through consultation of medical records and hospital information systems by the local research team at that site.

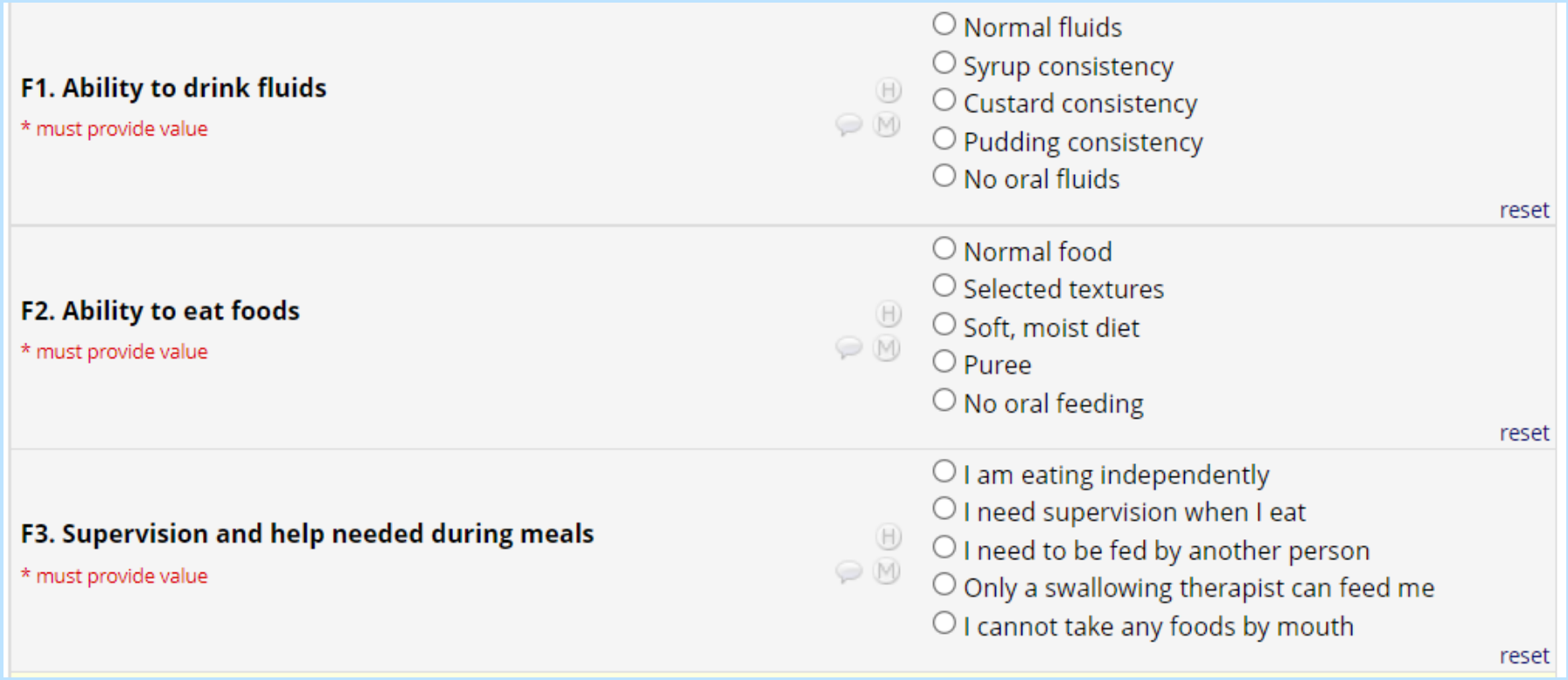
- Repatriation site staff should download data-collection CRFs from MAPS-2 website, complete and scan/email them to the central team at Nottingham: **MAPS-2@nottingham.ac.uk**

Follow-up (Day 14 or discharge) (cont.)

- Outcomes to be measured at 14 days by local research team:

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

Dysphagia Severity Rating Scale Score: DSRS



F1. Ability to drink fluids

* must provide value

- ○ Normal fluids
- ○ Syrup consistency
- ○ Custard consistency
- ○ Pudding consistency
- ○ No oral fluids

reset

F2. Ability to eat foods

* must provide value

- ○ Normal food
- ○ Selected textures
- ○ Soft, moist diet
- ○ Puree
- ○ No oral feeding

reset

F3. Supervision and help needed during meals

* must provide value

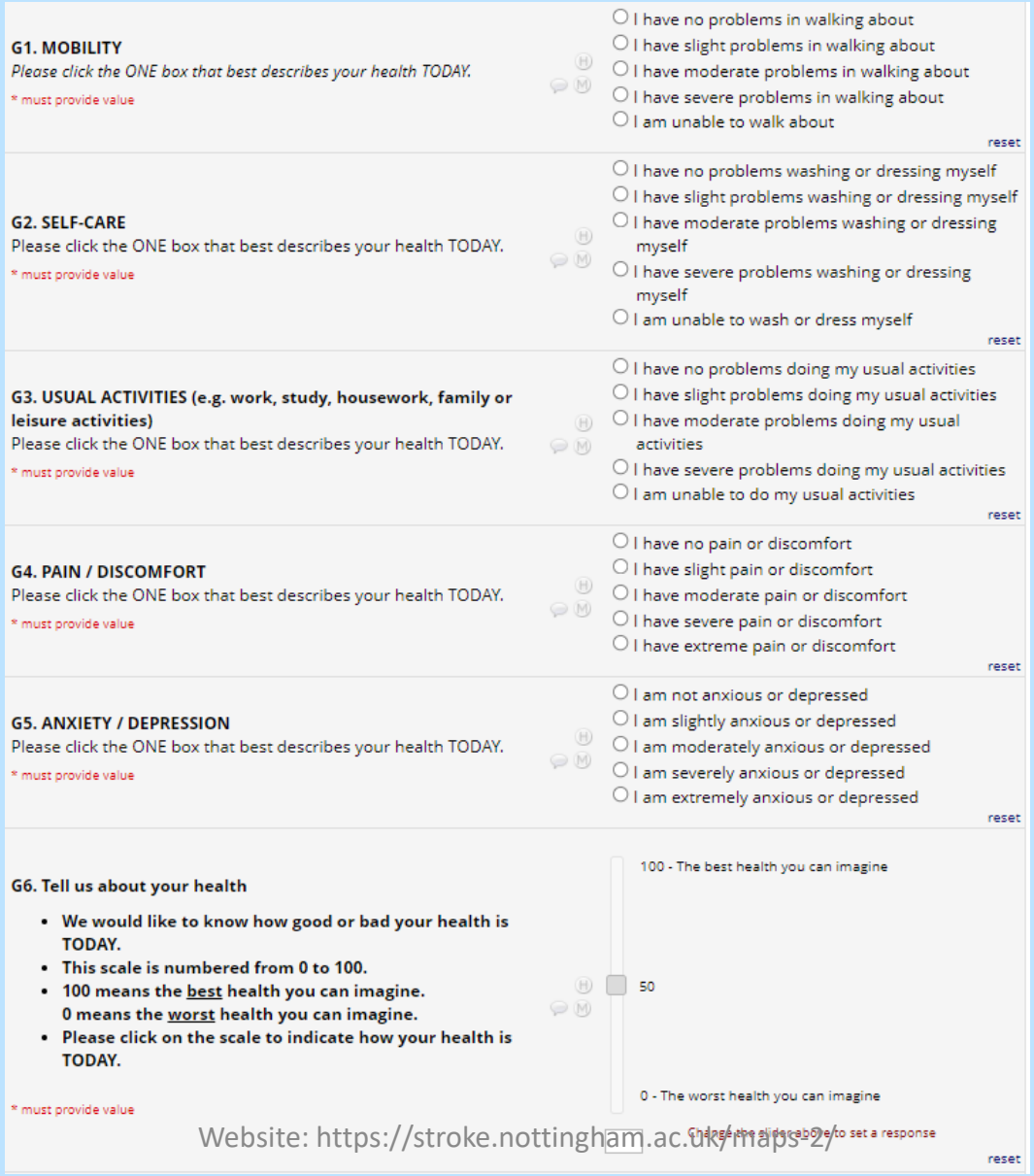
- ○ I am eating independently
- ○ I need supervision when I eat
- ○ I need to be fed by another person
- ○ Only a swallowing therapist can feed me
- ○ I cannot take any foods by mouth

reset

Does not need to be completed by a Speech & Language Therapist!

Website: https://stroke.nottingham.ac.uk/maps-2/

Quality of life (EQ-5D 5L)



G1. MOBILITY
Please click the ONE box that best describes your health TODAY.
* must provide value

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

reset

G2. SELF-CARE
Please click the ONE box that best describes your health TODAY.
* must provide value

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

reset

G3. USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)
Please click the ONE box that best describes your health TODAY.
* must provide value

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

reset

G4. PAIN / DISCOMFORT
Please click the ONE box that best describes your health TODAY.
* must provide value

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

reset

G5. ANXIETY / DEPRESSION
Please click the ONE box that best describes your health TODAY.
* must provide value

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

reset

G6. Tell us about your health

- **We would like to know how good or bad your health is TODAY.**
- **This scale is numbered from 0 to 100.**
- **100 means the best health you can imagine.**
  0 means the worst health you can imagine.
- **Please click on the scale to indicate how your health is TODAY.**

* must provide value

100 - The best health you can imagine

50

0 - The worst health you can imagine

Click/tap slider above to set a response

reset

Website: https://stroke.nottingham.ac.uk/maps-2/

Exploratory Outcomes (Day 14 or discharge)

- Recorded by local research team in database include:

1. Stroke diagnosis (infarct or haemorrhage)
2. Reperfusion therapies (thrombolysis and/or mechanical thrombectomy)
3. Viral pneumonia (influenza, Covid-19)
4. Other infections
5. Antiemetic use for clinical indications
6. Urinary catheterization

Informed Consent

- Participants must be consented by the Principal Investigator ***or*** delegated investigator.

- Non-medics *can* take consent in MAPS-2. Eligibility screening must be completed by a medic. Consenting investigators must discuss the trial with patients in-depth beforehand and should answer any questions.

- For independent physician consent, medics at registrar level and above may take consent. Junior / foundation doctors and house officers cannot take this consent.

- Patients will be excluded from the study if informed consent, or proxy consent, cannot be obtained.

Informed Consent – Long PIS

- Patients will provide informed consent once they have reviewed the ***Participant Information Sheet***, understand the purpose/design of the trial and have enough time to ask questions to the research team.

- It is important to remind participants that they have the right to withdraw from the trial at any point, but data collected up until the point of withdrawal may still be used for analysis.

- For patients that are deemed as having capacity to consent themselves, they will be required to sign and date the ***Participant Consent Form***. The consulting investigator must also sign this form.

Informed Consent – Short PIS

- A shorter, combined and pictorial, consent and information form is available for all patients to sign in MAPS-2: ***Participant Information and Consent Form.***

- Any participant may alternatively sign this consent form instead of the longer form, however it is suggested that this form only be signed if faced with significant time pressures.

- Participants that use this form to consent must also be provided with a copy of the ***Participant Information Sheet.***

Informed Consent – Independent Witnesses

- Participants that have capacity to consent themselves but physically unable to sign consent, **verbal** consent will be accepted providing this is witnessed and signed off by an **independent witness**.

- Alternatively, patients with physical impairments may ‘mark’ the consent form, but this must also be signed off by an **independent witness**.

- The independent witness must be an individual who is **not at all** affiliated with the MAPS-2 study, and is **not** on the electronic delegation log (e.g. a staff nurse in the ward).

Consent – Adults Lacking Capacity

- A large proportion of MAPS-2 trial participants may fall into this category.
- Participants with moderate/severe strokes may struggle to give full informed consent within the 9 hour recruitment window.
- If patients cannot consent themselves then every opportunity should be explored to gain written consent from a **personal** representative.
- If a patient is deemed to lack capacity to consent themselves, then this consent must be signed off by a medic.

Adults Lacking Capacity – Personal Reps (1)

- Personal representatives **must know, and can represent, the participant's wishes with regards to entering the trial.** This individual must be someone who the patient would trust with important decisions about their welfare.

- For English/Welsh/N. Irish sites, personal representatives **cannot** be a paid, professional carer for the participant.

- For Scottish sites, a welfare attorney/guardian would be sought initially, followed by the participant's nearest relative.

- These personal representatives should sign the ***Legal Representative Consent Form,*** after being provided with the ***Legal Representative Information Sheet***.

Adults Lacking Capacity – Personal Reps (2)

- Personal representatives may also be provided with a shorter, pictorial version of the information sheet/consent form, if faced with significant time pressures.

- Personal representatives must sign the ***Legal Representative Information and Consent Form,*** and must also be provided with a copy of the full ***Legal Representative Information Sheet*** to review after initial consent has been gained.

Telephone Consent

- Telephone consent may be used if a personal representative is identified but cannot attend the hospital to provide written consent.

- If telephone consent is used then the consenting medic and an **independent witness** must sign the ***Legal Representative Telephone Consent Form***.

- This personal representative must provide written consent on behalf of the participant when they next attend the hospital.

- All attempts at getting the personal representative to sign, at an appropriate opportunity, must be thoroughly documented in the participant's medical notes.

- Written consent must still be sought from the personal representative even if the participant is repatriated to a different hospital – **this instruction should be clearly written in the handover documentation between centres, if written consent is still outstanding**.

Independent Physician Consent

- Written consent from a **professional** representative (independent physician) must only be sought as a last resort.

- All attempts and opportunities to gain written / verbal consent from a personal representative must be explored before independent physician consent can be gained. **These attempts must all be documented in the patient's medical notes.**

- The independent physician should record the consent on ***Legal Representative Consent Form*** after reviewing the ***Legal Representative Information Sheet.***

- The independent physician cannot be connected to the research; they cannot be on the delegation log.

Participant Re-consent (1)

- Patients may be deemed to have regained capacity within the first fourteen days after a personal or professional legal representative has already provided consent on their behalf.

- If this occurs, patients must be provided with a copy of the following documents:

- ***MAPS-2 Participant Information Sheet***
- ***MAPS-2 Participant Re-consent***

- Participants must have enough time to review the information sheet and be provided with the opportunity to ask questions to the appropriate investigator. If re-consent is agreed, the participant and consenting investigator must sign the consent form.

Participant Re-consent (2)

- If participants regain capacity and are no longer happy to participate in MAPS-2, then they have the right to withdraw from the study without having to provide a reason for their decision.

- The data already collected from the participant up until the date of voluntary withdrawal cannot be erased, as consent was already in place at the time of data collection.

- Consent should be sought from participants to use this data in the final analysis. This whole process should be documented in the participant's medical notes.

Participant Re-consent (3)

- If participants lose mental capacity during the research after they have consented themselves, then:

- Their consent will still be valid from their initial consent form unless their personal / professional legal representative raises an objection to this. This is reflected in clause 9 in the ***MAPS-2 Participant Consent Form.***

- Participants who have lost capacity should still be informed about MAPS-2 to their level of understanding. They should **not** be forced to continue with the trial, or do anything which they have expressed, however they are able, they do not wish to.

Randomisation Overview

- Patients to be randomised by a member of their local research team within **9 hours** of stroke onset.

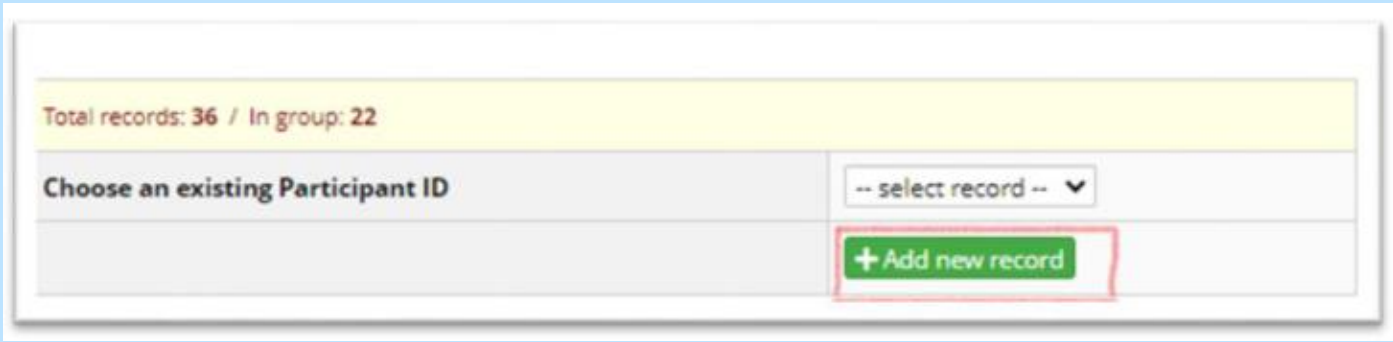
- Done via bespoke, secure web-based system. Maintained by the central Stroke Trials Unit in Nottingham.

- Randomisation video (within database demo video) is available on our website.

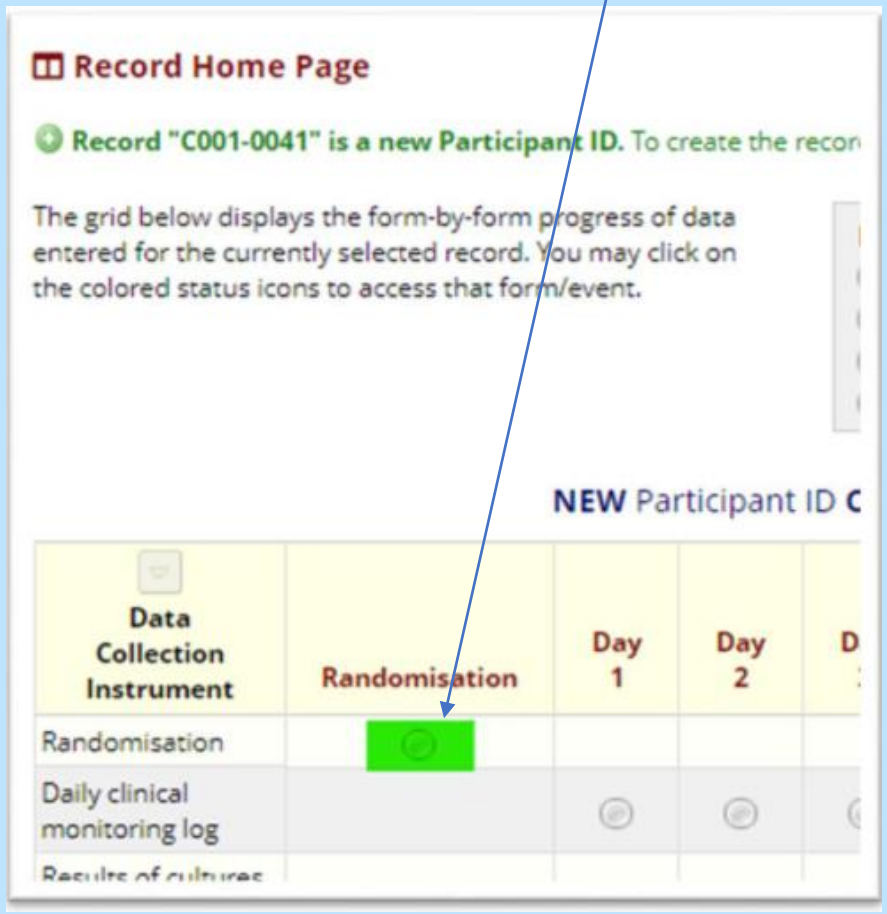
Randomisation Instructions

1. In RECAP, select ‘Add / Edit records’

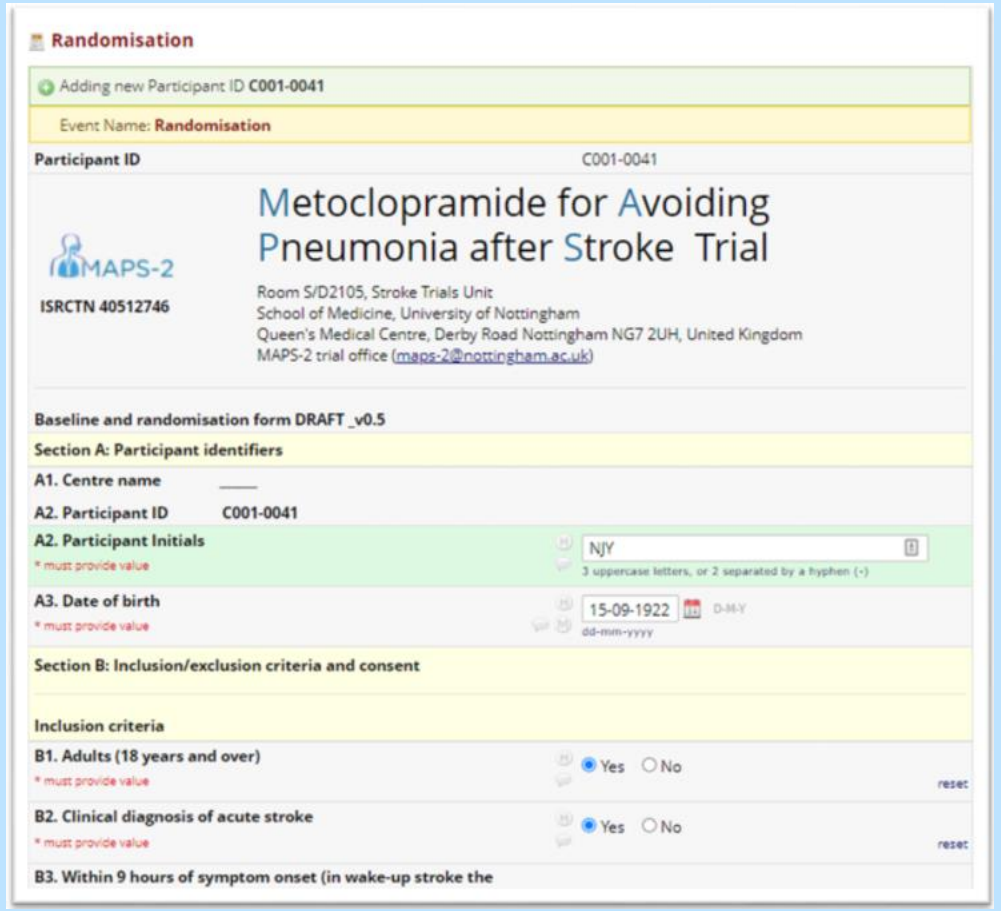
2. Add a new record



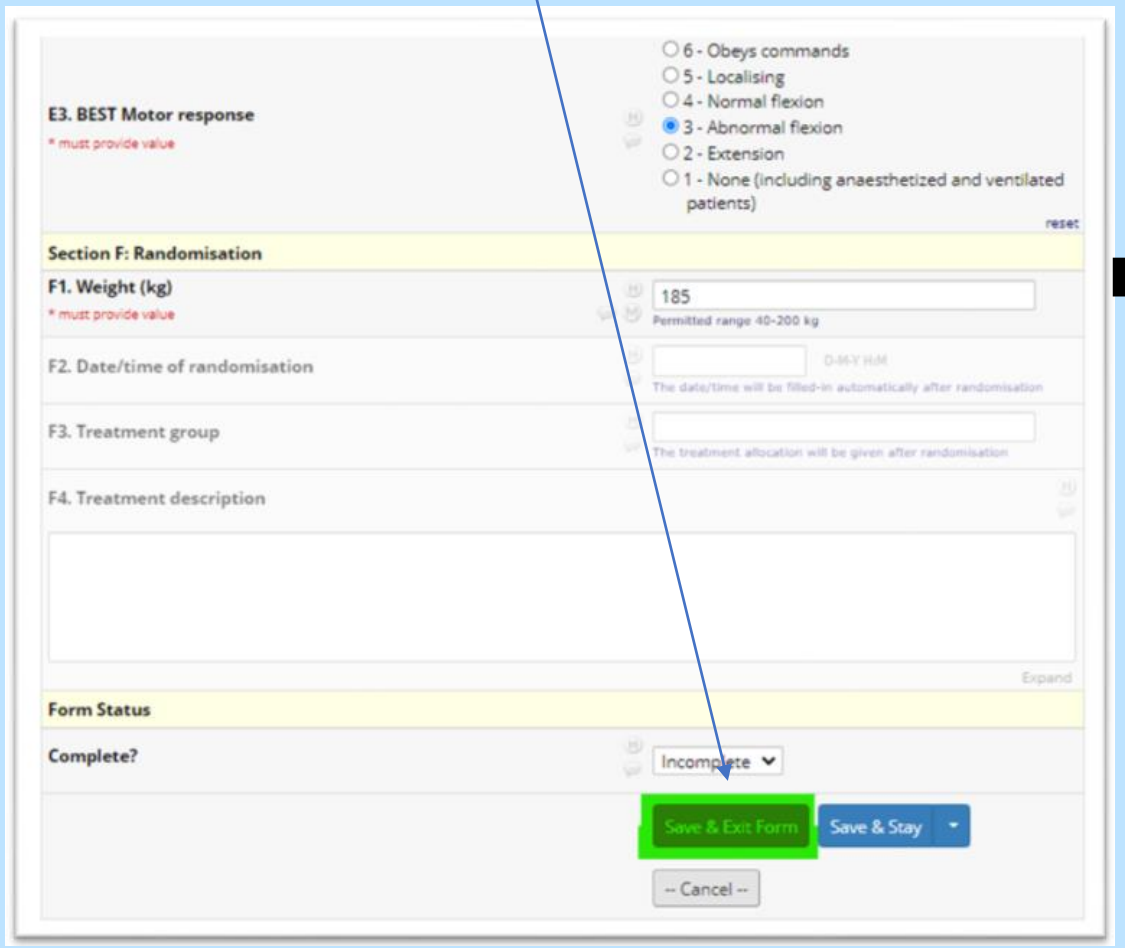
3. In the new data entry, select ‘Randomisation’



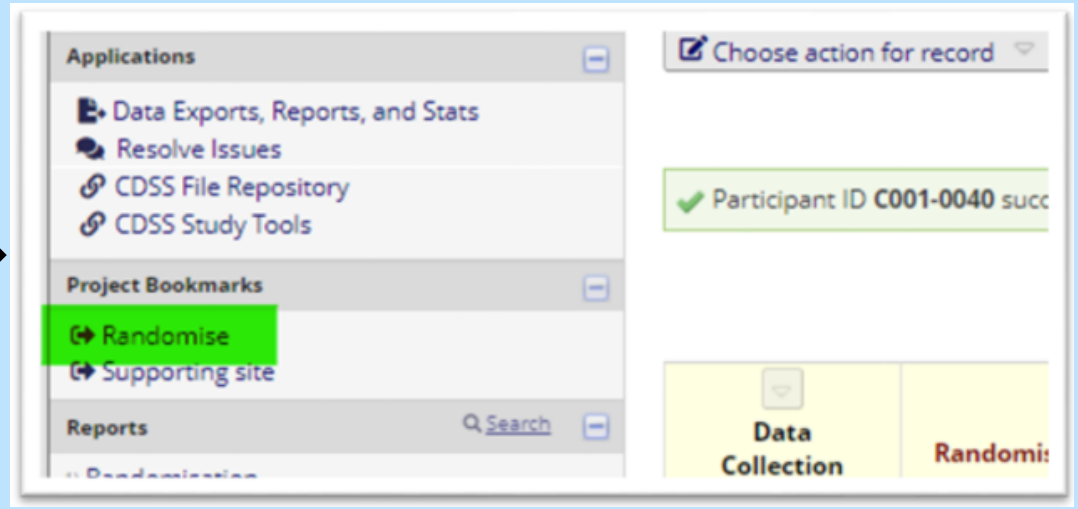
4. Complete the Randomisation form



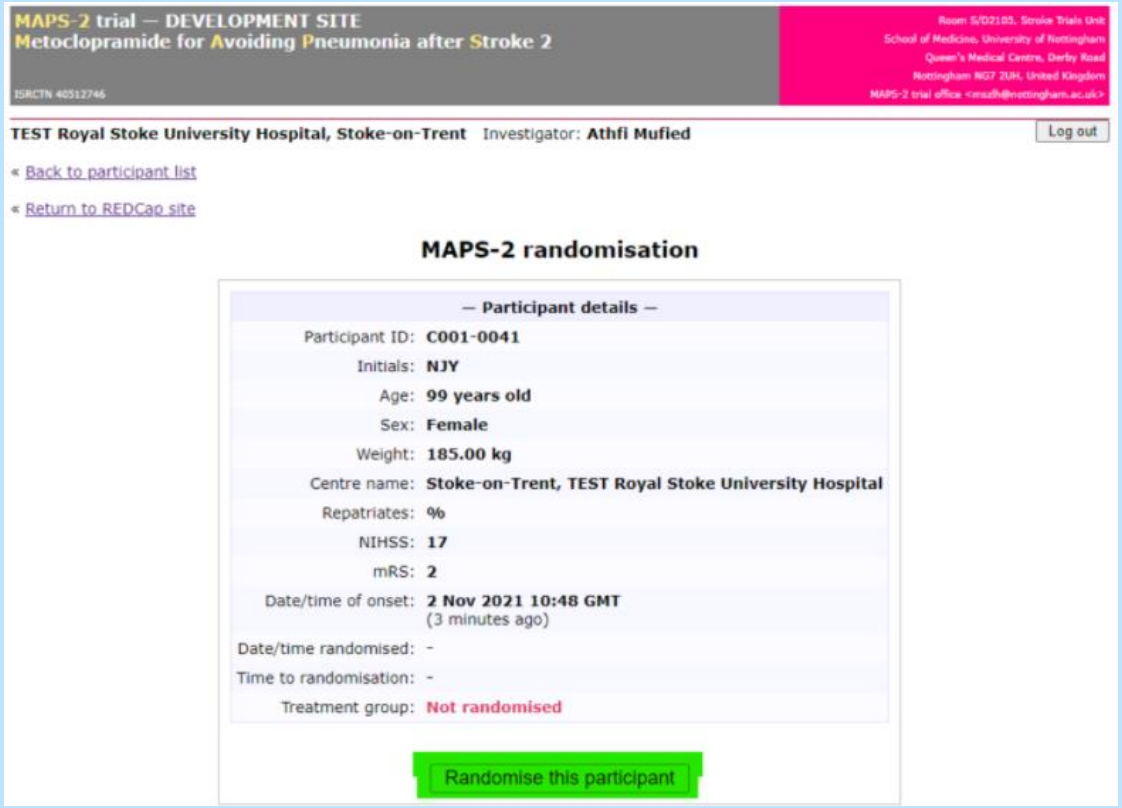
5. Once complete, click ‘save and exit form’.



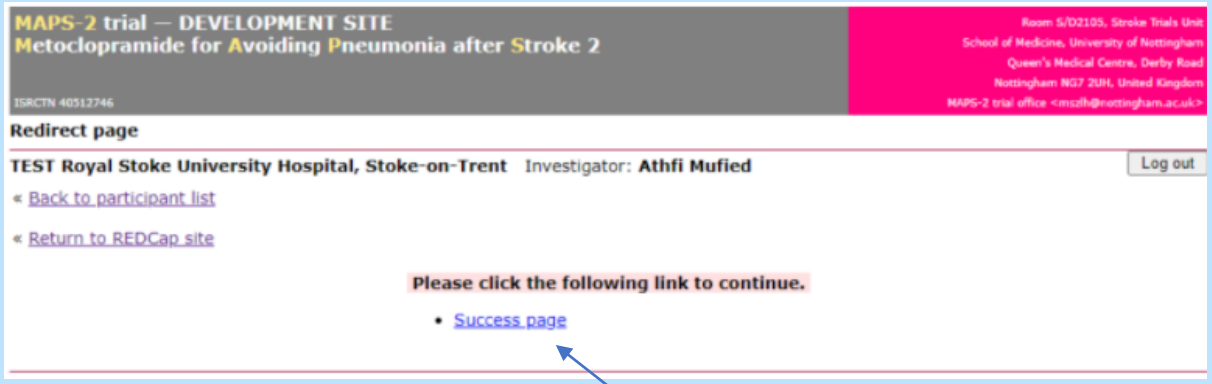
6. Click the ‘Randomise’ link under Project Bookmarks



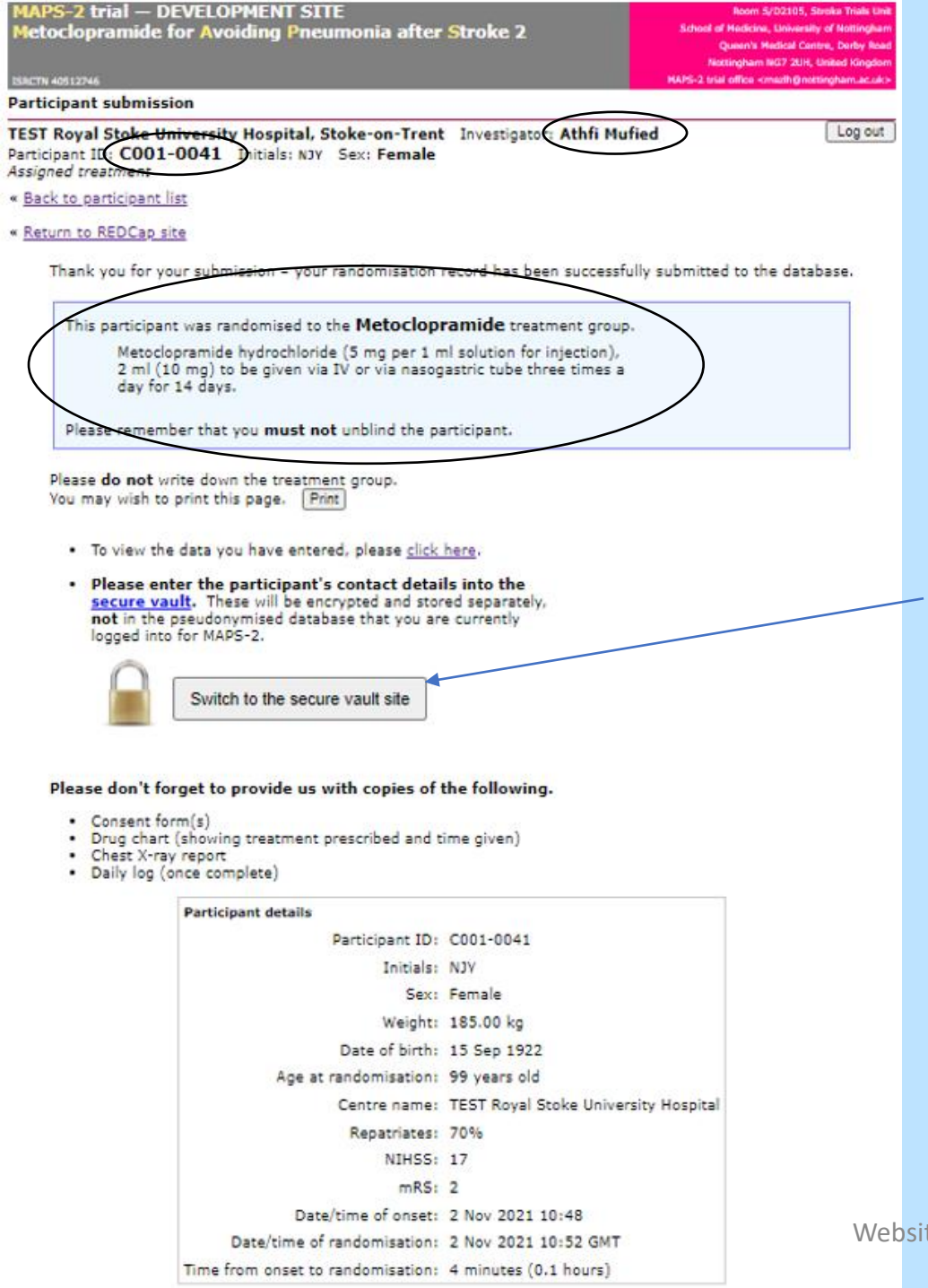
7. Check the information in the randomisation summary and then click ‘Randomise this participant’.



8. Once complete, the following page should appear:



9. Click the link to get to the ‘success page’.



10. The left page should be displayed, which shows a summary of all of the participant's randomisation information.

This shows:

- Participant's trial ID number
- The name of the randomising investigator
- Participant's their allocated treatment arm.

11. Click into the secure vault site to enter the participant's contact details, which will be required for follow-up.

12. Identifiable data will be kept separately in the secure vault, whereas all other data will be kept in the REDCap database.

Manual Randomisation

- In cases where sites are unable to randomise a patient and require a manual randomisation, contact the CI on the 24hr contact number: **07740 372 852.**

- CI will inform the site of the participant's allocated treatment.

- Sites should attempt to add the randomisation data to REDCap (as per slide 44-45). If sites cannot access REDCap, then the randomisation details may be entered by a programmer / trial manager at Nottingham STU.

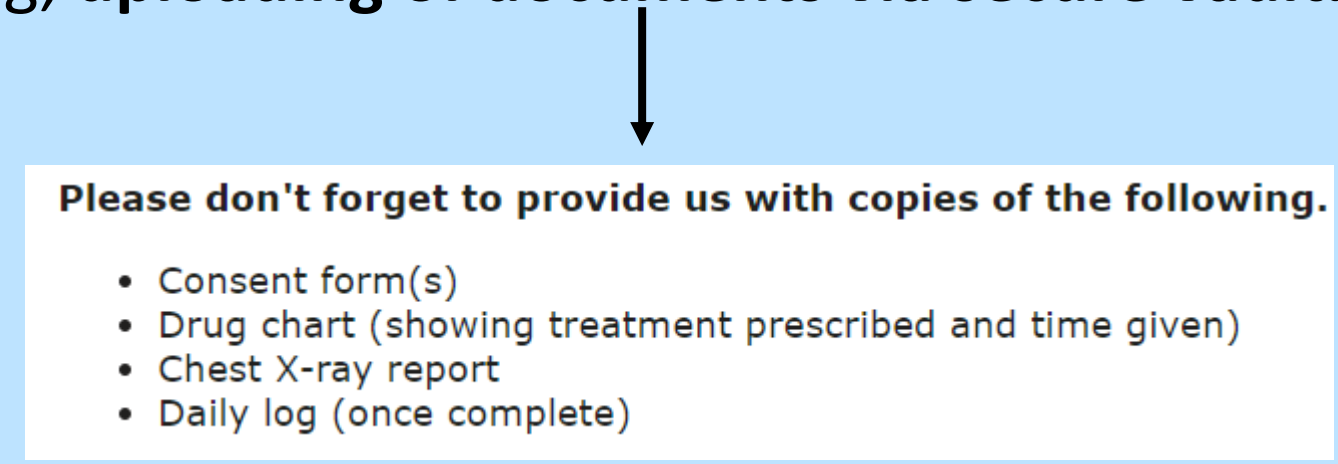
- Site investigators can add patient contact details via secure vault, once able to do so.

Databases

We are using two database systems in MAPS-2:

1. REDCap – basic data entry (daily clinical monitoring log, AEs, etc)

2. Bespoke system (synched to REDCap) – Randomisation, electronic delegation log, **uploading of documents via secure vault.**



Electronic Delegation Log

- Electronic delegation log to be used in MAPS-2.
- REDCap accounts will link through to the bespoke system. Nottingham will create/update the details of all site staff for the bespoke system.
- Activation email will be sent to all users from the bespoke system…
- (A Working Practice Document – WPD – is available to document the above!)

Example

Click link to activate account

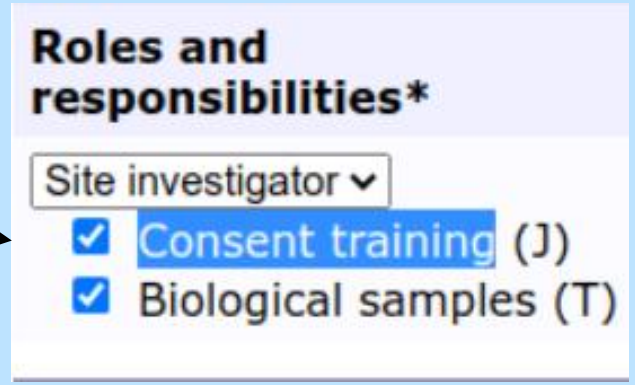
Dear XXX,

We invite you to participate in the MAPS-2 trial, which recruits acute stroke patients in hospital with dysphagia and aims to improve functional outcomes with metoclopramide.

Please **click here** to respond. This is a **necessary first step** before you can be authorised using the online delegation log relating to the following hospital.

- C00X: XXX Hospital
  You have been assigned as the XXX

Tick what you are trained to do



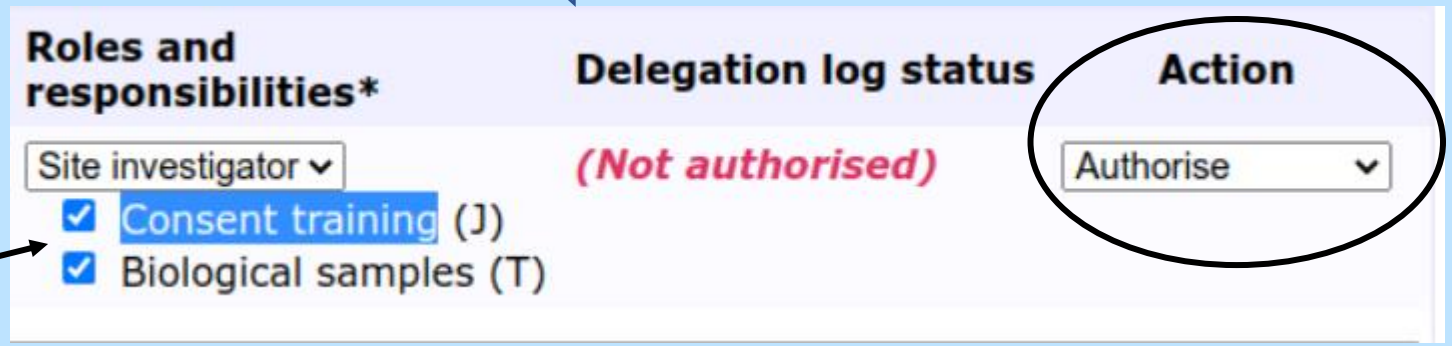
Electronic Delegation Log

- Once accounts are activated, they will appear on their electronic delegation log as ‘no authorised’:

Log ID	Investigator name/ID	Certificate/ date trained	Roles and responsibilities*	Delegation log status
-	XXX	*(Pending)*	Site Investigator	*(Not authorised)*

- The PI will prompted with an email to authorise each user in the bespoke system (i.e. they should click the link in the email)

***PIs should double check that the correct boxes are ticked before authorising their staff!**



Blinding

- Participants, their families, and the central follow-up coordinator performing the six-month follow-up will be **blinded** to the treatment allocation.

- The research team at the participant's local recruiting / repatriation site, pharmacist, clinical team and research staff performing the day-14 follow-up will be **unblinded** to the participant's treatment allocation.

- This is an **open-label** trial - all medical record entries will clearly identify the treatment allocated to the participant.

New Trial Personnel

- Investigators / research staff at sites must send Nottingham Stroke Trials Unit their signed training log
- Nottingham STU will send REDCap database credentials to all staff who need access.
- Nottingham STU will also send a link from our bespoke system (second database) that allows users to activate their accounts.
- Once accounts are activated in the bespoke system, they will appear on the site's electronic delegation log. PI must authorise all users, and will be prompted via email to do this.

Adverse Event Classification (1)

- Any unfavourable and unintended sign, symptom, syndrome or illness that develops or worsens during the period of observation in the study:

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

Adverse Event Classification (2)

- All AEs data should be collected in the eCRF, and will be reviewed by the Chief Investigator who will assess for expectedness against pre-existing IMP safety information.

- The following are **not** classified as AEs and do not require reporting:

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

Serious Adverse Event Reporting (SAE)

- Any AE occurring following study mandated procedures, having received the treatment, that results in any of the following outcomes:

1. Death

2. A life-threatening adverse event

3. Inpatient hospitalisation or prolongation of existing hospitalisation

4. A disability / incapacity

5. A congenital anomaly in the offspring of a participant

- Medical events that do not fall into the above criteria MAY still be classed as an SAE if they result in any of the five outcomes above, if left untreated.

AE / SAE Reporting (1)

- All AEs and SAEs will be assessed for causality using the following criteria:

1. **Not related / improbable** to IMP
2. **Possibly** related to IMP
3. **Probably** related to IMP
4. **Definitely** related to IMP

AE / SAE Reporting (2)

- Participants / persons looking after them must contact their sites immediately in the event of a possible SAE. Sites should collate the SAE information using the University of Nottingham ‘RF1 TA014 (v2.5)’ (SAE Reporting Form) and enter in the database.

- Data must be entered in REDCap **within 24 hours of knowledge** of the event.

- Any SAE entered in REDCap will trigger an email sent directly to the CI, who will review the event for causality and seriousness.

- Sites should record and monitor all AEs until resolution, stabilisation or until the AE has been found to **not** be caused by study treatment.

SUSARs

- A Suspected Unexpected Serious Adverse Reaction (SUSAR) is an SAE that is either:

a) Sudden in its onset (anaphylaxis);

b) Unexpected in its severity and seriousness; or

c) Not a known side effect of the IMP ***and*** related or suspected to be related to the IMP

- All SAEs that fall, or are suspected to fall, within this criteria shall be treated as a SUSAR until deemed otherwise.

- Sites should inform the Chief Investigator of the SAE within **24 hours of knowledge of the event.**

Withdrawal Due to AEs/SAEs

- Any participant who experiences an adverse event may be withdrawn temporarily or permanently from the study at the discretion of the Investigator.

- Wherever possible and acceptable, withdrawal will relate to the IMP only, with follow-up continued as per protocol.

Protocol Violations / Deviations

- All violations and deviations are to be reported to the Chief Investigator and Nottingham STU immediately via email.

- The CI will notify the Sponsor if a deviation or violation has an impact on participant safety or integrity of the trial data.

- The Sponsor will advise on appropriate measures to address the deviation / violation.

Investigator Site File (ISF)

- Must be stored in a secure room/office (if physically printed), and only accessible by the research team.

Must include:

- ✓ **Contacts sheet**
- ✓ **Trial development documentation**
- ✓ **MAPS-2 protocol (final & superseded)**
- ✓ **Regulatory approvals**
- ✓ **Training log, CVs & GCPs of trial personnel**
- ✓ **Amendments**
- ✓ **Pharmacy/IMP documents**
- ✓ **Approved and localised patient-facing documents (consent forms, PIS, GP letter)**
- ✓ **Signed clinical trial agreement (CTA)**
- ✓ **'wet ink' signed consent forms**
- ✓ **Signed SAE forms**
- ✓ **Site monitoring plan**

Trial Monitoring (1)

- All sites will be remotely monitored continuously by the Nottingham Stroke Trials Unit throughout the duration of the trial; this includes:

- Confirmation of informed consent

- Monitoring missing eCRF data

- ISF monitoring.

Trial Monitoring (2)

- Nottingham STU will complete a Investigator Site File checklist for sites throughout the duration of the trial. This will check, but not limited to:

1. Delegation & training logs in the ISF
2. Correct versions of patient-facing documents (PIS, RIS, GP letter, etc)
3. Ethical approval letters
4. Printed CRFs
5. SAE forms
6. Signed consent forms
7. CVs / GCPs

Trial Monitoring (3)

- Nottingham STU will complete a Patient File checklist for sites throughout the duration of the trial. This will check, but not limited to:

1. Randomisation result and eligibility
2. Consent form and GP letter
3. IMP chart / prescription
4. Baseline / follow-up scan reports
5. Adverse event log
6. Protocol violations affecting participant

Commonly Found Issues

- Amendment approvals (REC/HRA/MHRA) are hard to locate or are missing entirely from ISF.
- Incorrect ICF/PIS versions being provided to patients.
- SAEs not signed off by local PI.
- Screening log not kept up to date / not signed by Investigator.
- File notes missing which identify where documents are stored outside of the ISF (e.g., CVs and GCP certificates)
- Consent forms should be initialled, not ticked.

Trial Monitoring (4)

- Entries on the eCRF will be verified by inspection against the source data.

- On-site visits will *not* be permitted for the foreseeable future, so SDV will be done via:

1. Document uploading / sharing through secure vault.
2. Secure video conference screen sharing but not copying or recording.

- Any discrepancies identified in the eCRF will be clarified with the site and resolved.

Summary

- **Population:** Total 2100 participants; ≤ 9 hours of symptom onset; NIHSS Score ≥ 10, **OR** NIHSS Score ≥ 6 **AND** dysphagia. Patients with either ischaemic or haemorrhagic strokes are eligible.
- **Intervention:** Metoclopramide, administered via slow IV injection or nasogastric tube, 10mg/2ml three times per day for 14 days (or discharge).
- **Comparison:** Sodium chloride 0.9% solution, administered via slow IV injection or nasogastric tube, 2ml three times a day for 14 days (or discharge).
- **Outcome:** Mortality by 6 months *(primary).* Pneumonia diagnosis and neurological recovery at day 14; long-term disability outcome at 6 months; cost effectiveness of metoclopramide *(secondary).*

Clinical queries: 07740 372 852

Email: MAPS-2@nottingham.ac.uk

Green Light Checklist

✓Signed training log for all staff.

✓Signed SOP compliance form (for relevant SOPs)

✓CV & GCP for PI (and deputy-PI, if applicable).

✓Signed contract.

✓Confirmation of C&C from R&D.

✓Staff to be authorised by PI on electronic delegation log.

Questions?

Please complete and return a copy of the Investigator Training log (RF1 TA008) for all attendees who attended todays training!