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

Sponsor: University of Nottingham
Funder: NIHR HTA

NIHR | National Institute for Health Research

Protocol Training slides v6.0: 03/01/2023
Protocol v1.3: 08/11/2022

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

Overview

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- ✓IMP details and IMP administration
- ✓Trial design
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Trial Objectives

Primary

To investigate whether metoclopramide reduces mortality in stroke patients with dysphagia

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Secondary

1) To investigate whether metoclopramide reduces pneumonia and improves patients' neurological recovery at day 14

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

3) 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.

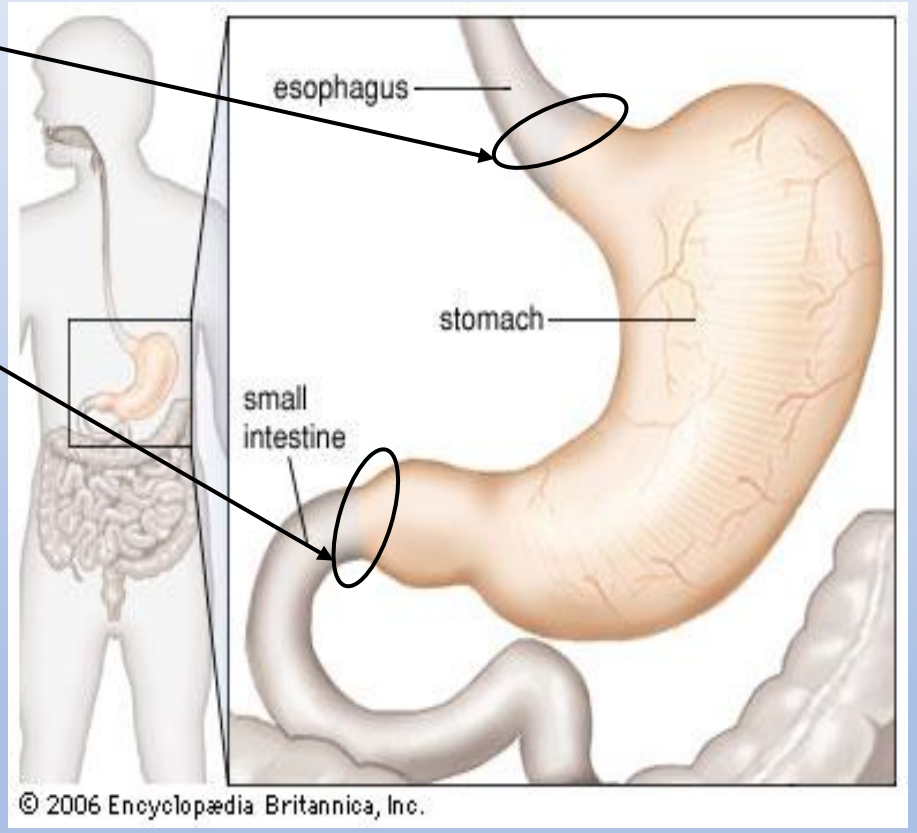
Stroke-associated Pneumonia

SAP:

1) Most common complication from stroke and responsible for over one-third of deaths
2) Occurs in 12% of unselected stroke patients and in approximately 44-69% of stroke patients fed via a nasogastric tube
3) Linked with a 2-6x increase in mortality, longer length of hospital stay, increase in long-term disability
4) Most common in patients with high NIHSS and dysphagia
5) Patients that require feeding via nasogastric tube are at greatest risk

Metoclopramide

- Commonly prescribed anti-sickness treatment
- Increases **lower oesophageal sphincter pressure**.
- Decreases **pyloric sphincter pressure**
- Accelerates gastric emptying process
- Inhibits and prevents vomiting/regurgitation
- Well established safety profile
- Cheap and widely available



Rationale

- MAPS-1 pilot trial (2016) 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.

- A larger trial is required to confirm whether metoclopramide can reduce pneumonia and mortality in patients with severe strokes & dysphagia.

Eligibility Criteria

Inclusion criteria

1. Adults with a clinical diagnosis of acute stroke;
2. Within 9 hours of symptom onset (or wake up);
3. **One** of the below:

3a) NIHSS Score ≥ 10

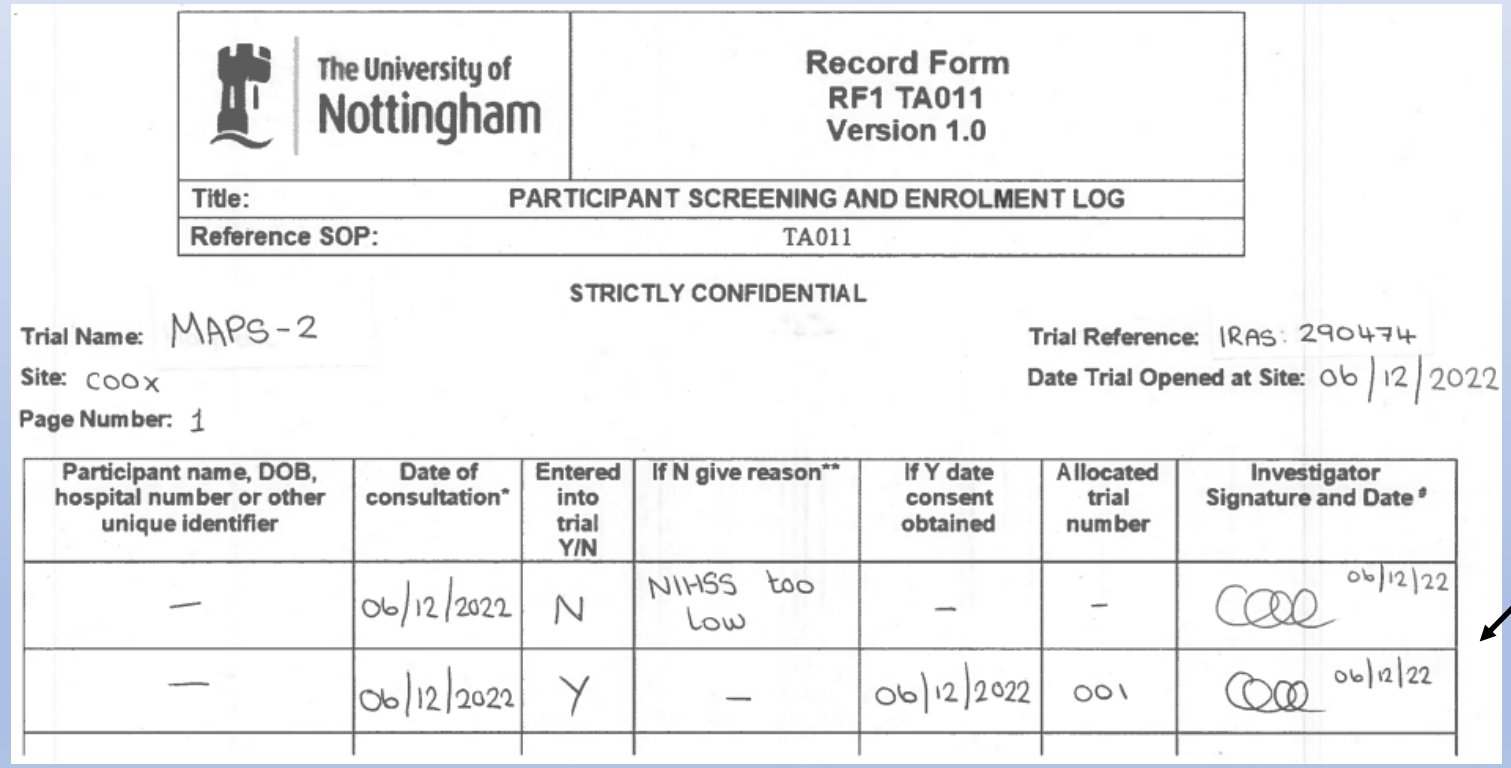
3b) NIHSS Score ≥ 6 **and** dysphagia

Exclusion criteria

1. Probable / confirmed pneumonia;
2. Contraindications to metoclopramide;
3. Clinical indication for regular antiemetic treatment;
4. Known severe liver disease (cirrhosis);
5. Known kidney disease (eGFR <30ml/min);
6. Pregnant or breast feeding;
7. Moribund (expected to die within 48 hours);
8. Other co-morbid conditions with a life expectancy of <3 months (e.g. cancer);
9. Inability to gain consent;
10. Participating in another trial **not** sponsored by University of Nottingham.

Patient 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 UoN Participant Screening and Enrolment Log (RF1 TA011). Example:



The University of Nottingham

Record Form
RF1 TA011
Version 1.0

Title:	PARTICIPANT SCREENING AND ENROLMENT LOG
Reference SOP:	TA011

STRICTLY CONFIDENTIAL

Trial Name: MAPS-2
Trial Reference: IRAS: 290474
Site: COOX
Date Trial Opened at Site: 06/12/2022
Page Number: 1

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 #
—	06/12/2022	N	NIHSS too low	—	—	06/12/22
—	06/12/2022	Y	—	06/12/2022	001	06/12/22

Must be signed off by a delegated investigator.

- Screening logs will be collected at the beginning of every month.

Trial Flow

Screen

Consent

Baseline Assessments:
Participant details and demographics; pre-stroke mRS; clinical frailty scale (CFS) score; NIHSS; Glasgow coma scale (GCS) score.

Randomise (Metoclopramide vs Placebo)

Treatment Period (days 1-14 / discharge):
Status & current stay; feeding status; vomiting; vital signs; pneumonia symptoms; lab results (if done); drug administration details.

Day-14 / Discharge Assessments:
Stroke details; reperfusion therapies; safety reporting (AEs & SAEs); NIHSS; mRS; dysphagia severity rating scale (DSRS); EQ-5D-5L & EQ-VAS; co-enrolment; pneumonia diagnoses.

Six-month Follow-up

To be completed by sites.

Not completed by sites.
Completed by UoN coordinator.

Baseline Assessments (Randomisation CRF)

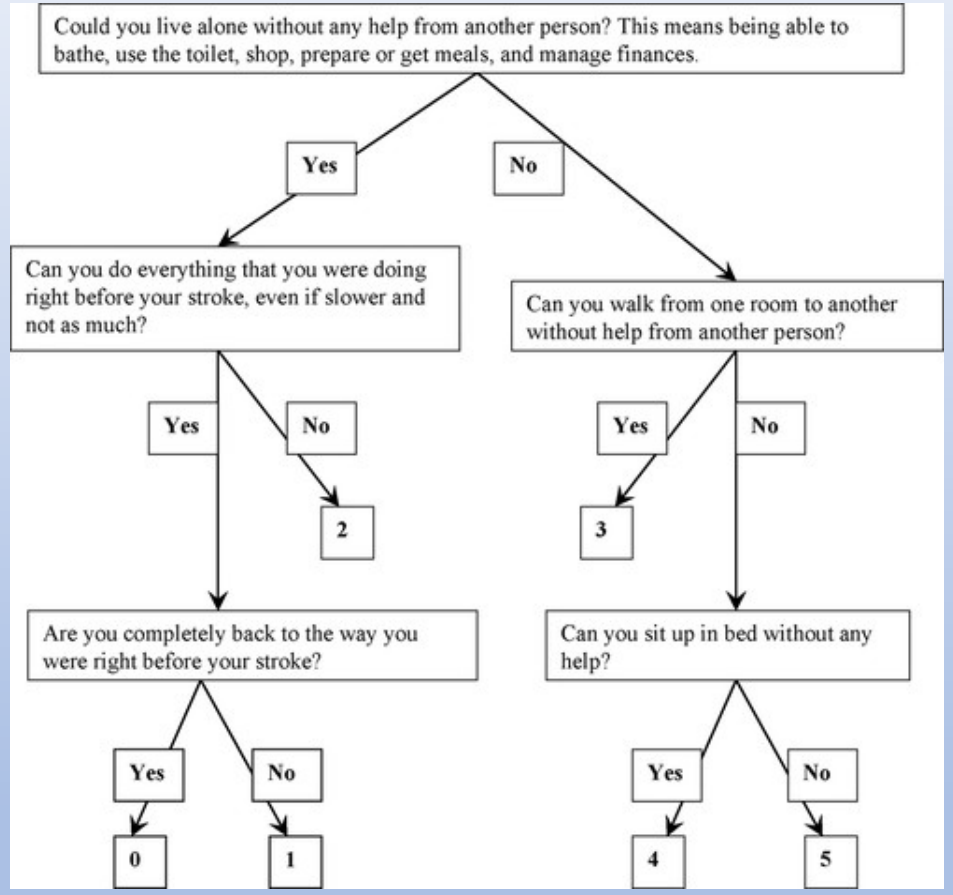
- ✓ Participant initials
- ✓ Date of birth
- ✓ Eligibility criteria met
- ✓ Mode of consent
- ✓ Baseline clinical assessments (mRS, CFS, NIHSS & GCS scores)
- ✓ Demographic details
- ✓ Associate PI involvement?

- Record contact details, including an alternative telephone number and address (if possible), from patient and legal representative. Upload to *secure vault* database.

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

Clinical Assessments (1) (Randomisation CRF)

Pre-Stroke 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

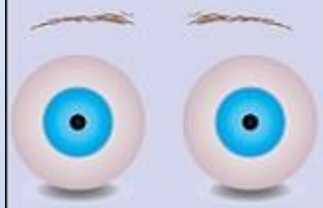
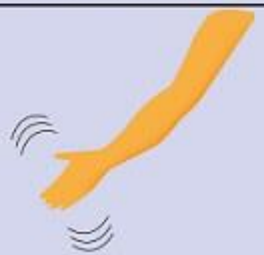
reset

Current 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	

Clinical Assessments (2) (Randomisation CRF)

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.

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Trial Treatment

- Metoclopramide 2ml/10 mg and 0.9% saline 2 ml prep are clear, colourless liquids.
- Trial treatment is the IV preparation of metoclopramide and saline. These can be given iv or via nasogastric tube.
- Dispensed from on-site pharmacy/ward stock.
- Minimal pharmacy involvement (no trial-specific labelling, no IWRS, no pharmacy monitoring visits, no protocol-specific storage requirements).
- Should be prescribed as “MAPS-2 trial drug (metoclopramide)” or “MAPS-2 trial drug (sodium chloride 0.9%)” on the drug chart, and should be referred to as “MAPS-2 trial drug” in communication with participants and their families.
- The drug chart may be passed to repatriation sites in order for participants to continue their treatment regimen at their repatriation site (usual processes should follow).

Prescription Template Example

Drug History ☐ Indication for starting	**MAPS-2 TRIAL DRUG**: Metoclopramide 10mg/2mL solution for injection			Duration: **14 days** *NOT FOR DISCHARGE*	Pharmacy:	
	Dose: **10mg/2ml**	Date:	Clinical trial: ***DO NOT UNBLIND PATIENT/CARER*** Lower dose if weight < 60kg (cross off as appropriate)		Dispensing:	Morning / Midday / Teatime / Bedtime
	Frequency: **TDS**	Route: **IV/NGT**	Prescriber's signature:	PRINT name and GMC No.:		

Drug History ☐ Indication for starting	**MAPS-2 TRIAL DRUG**: Sodium Chloride 0.9% injection			Duration: **14 days** *NOT FOR DISCHARGE*	Pharmacy:	
	Dose: **10mg/2ml**	Date:	Clinical trial: ***DO NOT UNBLIND PATIENT/CARER*** Lower dose if weight < 60kg (cross off as appropriate)		Dispensing:	Morning / Midday / Teatime / Bedtime
	Frequency: **TDS**	Route: **IV/NGT**	Prescriber's signature:	PRINT name and GMC No.:		

Treatment Administration

- IV prep should 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

- Metoclopramide / 0.9% saline oral prep should **not** be used. Only IV prep is permitted.

- 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.

- Method of administration may be changed during treatment window, if clinically indicated (e.g. NG → IV and IV → NG).

Blinding

Blinded	Unblinded
Participants	Nottingham Clinical Trial Managers
Participants' families	Chief Investigator
Central Follow-up Coordinator	Site staff (Principal Investigator, Research Team, Pharmacy)

Do not email MAPS-2@nottingham.ac.uk with details of participants' treatment allocations.

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!

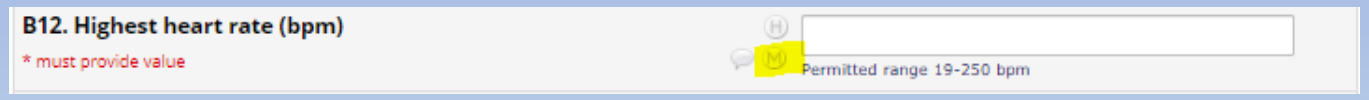
Daily Clinical Monitoring Log

- To be completed on days 1 to 14 (or discharge):

Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13		Day 14		
Daily clinical monitoring log	Daily clinical monitoring log	Daily clinical monitoring log	Daily clinical monitoring log	Daily clinical monitoring log	Daily clinical monitoring log	Daily clinical monitoring log	Daily clinical monitoring log	Daily clinical monitoring log	Daily clinical monitoring log	Daily clinical monitoring log	Daily clinical monitoring log	Daily clinical monitoring log	Daily clinical monitoring log	Microbiology results day 1-14	Antibiotic treatment day 1-14	Day 14 follow-up
○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○

- Day 1 = day of randomisation

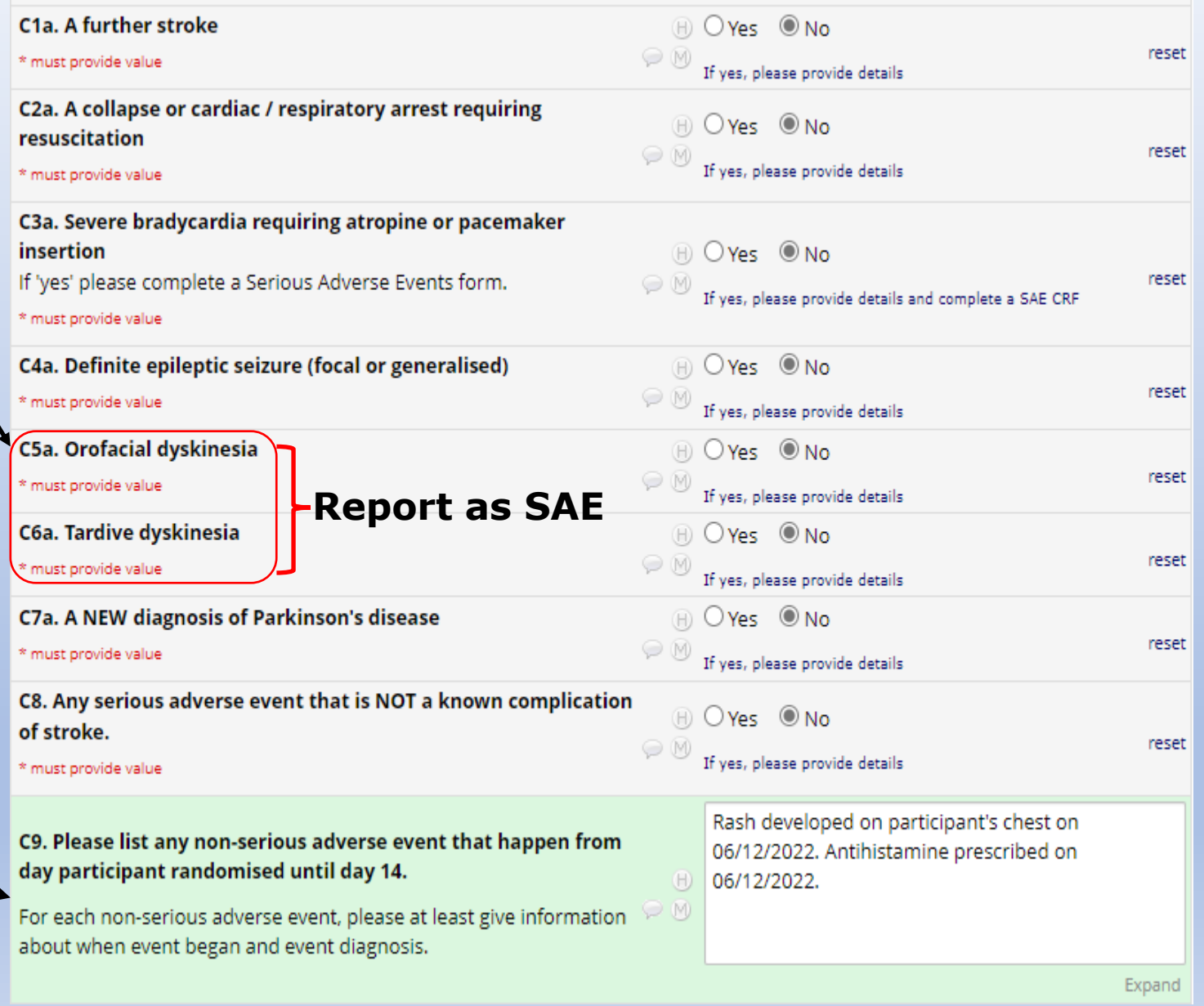
- Mark fields as 'not done' using **M** symbol next to field, e.g.:



- ✓Status & current stay
- ✓Feeding status
- ✓Vomiting
- ✓Vital signs
- ✓Pneumonia symptoms
- ✓Lab results (if done)
- ✓Drug administration details

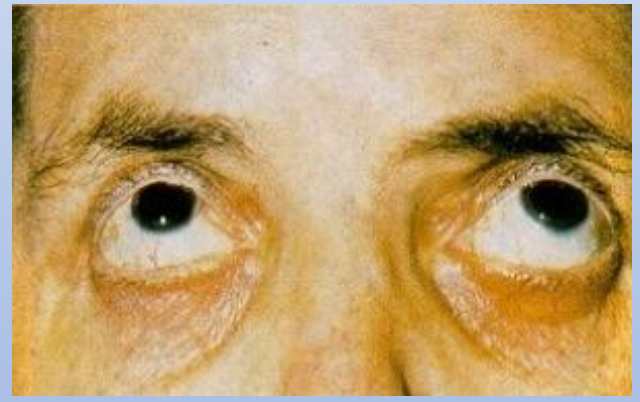
Safety Outcomes (Day 14 or discharge CRF)

- Adverse events should be recorded until <u>day-14 (or discharge).</u>
- Metoclopramide can induce acute dystonic reactions involving facial and skeletal muscle spasms, and oculogyric crises.
- Not all events need to be reported as an AE → check **Appendix 3** in protocol if unsure.
- Non-SAEs should be reported in the free text box.



Oculogyric Crises and Tardive Dyskinesia

- 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.



- Involuntary repetitive movements of the mouth, tongue, eyes, face, trunk, and extremities (e.g. 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 (e.g. procyclidine), or subside spontaneously within 24 hours after discontinuation.

Site Repatriations (1)

- Some MAPS-2 patients may need to be transferred (as part of a standard of care) to a registered repatriation site within the first 14 days.

- To ensure continuity and completion of trial treatment, patients should only be recruited if going to be transferred [with the treatment period] to:

1) other recruiting sites already set up in MAPS-2;
2) sites specifically set up as local repatriation sites.

- Repatriation sites will be trained on the study but will <u>not</u> recruit patients.

- Recruiting sites should deliver a comprehensive handover to their designated repatriation site when transferring the participant…

Handover Example

MAPS-2 Patient Transfer Form		
CI: Prof Christine Roffe **MAPS-2 Trial Office: 0115 823 1665 / 0115 823 1664** **Email: maps-2@nottingham.ac.uk** **Website: https://stroke.nottingham.ac.uk/maps-2/docs/public.php**		
Participant trial ID:		
Current centre name:		
Date & time of transfer:		
Reason for transfer:		
Name of researcher:		
Trial role:		
Date:		
Signature:		
Receiving centre name:		
Name of staff receiving:		
Role:		
Date & time of arrival:		
Date:		
Signature:		
CHECKLIST		
	Prescription	
	Drug chart- treatment compliance	
	Daily clinical logs (CRFs on website)	
	Day 14/Discharge assessment form	
	SAE reporting form	

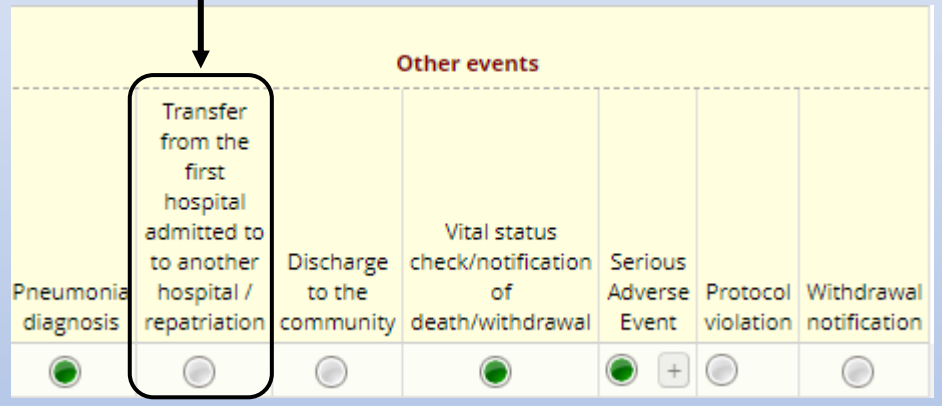
Guidance for MAPS-2 trial for transferring sites:

This patient is currently enrolled in a stroke clinical trial. Please read the below information carefully:

1. The patient being transferred is currently receiving the "MAPS-2 Trial Drug"(Placebo vs Metoclopramide).
2. As per the discharge letter, please prescribe the trial drug:
   a. IV preparation to be given through NG if patient has one, *or*
   b. IV via cannula
3. The MAPS-2 Trial drug should be given for 14 days **or** up until discharge (if before day-14)
4. Please complete daily logs for each day the patient is taking the medication up until day-14 / the day the patient is discharged from hospital if before day-14.
5. Please complete the day-14 follow up assessments on day-14 of the patient's treatment regimen, or on the day of discharge if this is before day-14.
6. Collect all information on the respective data forms. Once complete, scan and email these forms to the research team at the site where the patient was recruited, All data will be entered into the electronic database on your behalf.

Site Repatriations (2)

- Ensure Transfer / Repatriation CRF is completed when participants are repatriated.



- Repatriation site staff should download data-collection CRFs from MAPS-2 website, complete and scan/email them back to the research team at the recruiting site for input.

Section A: Participant details

A1	Centre name	[redacted]
A2	Participant ID	[redacted]
A3	Participant initials	[redacted]

A4. Date of data collection * must provide value — Today D-M-Y dd-mm-yyyy

Section B: Transfer details

B1. Hospital and ward transferred to * must provide value

B2. Trial contact at new hospital:

B2a. Name * must provide value

B2b. Email * must provide value

B2c. Phone number * must provide value

B3. Transfer date * must provide value — Today D-M-Y dd-mm-yyyy *(day _____)*

B4a. Admitted to intensive care * must provide value — Yes No reset If yes, please provide details

B5a. Admitted to acute stroke unit * must provide value — Yes No reset If yes, please provide details

B6a. Admitted to stroke rehabilitation unit. * must provide value — Yes No reset If yes, please provide details

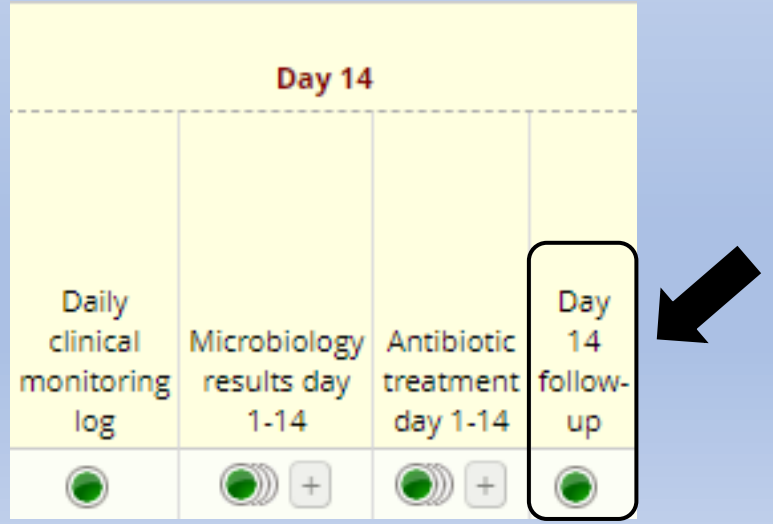
B7a. Admitted to other ward * must provide value — Yes No reset If yes, please provide details

Please review clinical and lab logs and ensure all are complete. Ensure all queries have been resolved.

Day-14 Assessments (1) (Day 14 or discharge CRF)

- To be completed on day-14 **or** day of discharge (if before day-14):

✓Stroke details
✓Reperfusion therapies;
✓Safety reporting (AEs & SAEs);
✓NIHSS (can be performed +/-3 days if day-14 falls on non-working day. If NIHSS not performed +/-3 days, any NIHSS score performed during treatment period can be used);
✓mRS;
✓Dysphagia Severity Rating Scale (DSRS);
✓EQ-5D-5L & EQ-VAS;
✓Co-enrolment;
✓Pneumonia diagnoses.



Dysphagia Severity Rating Scale (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

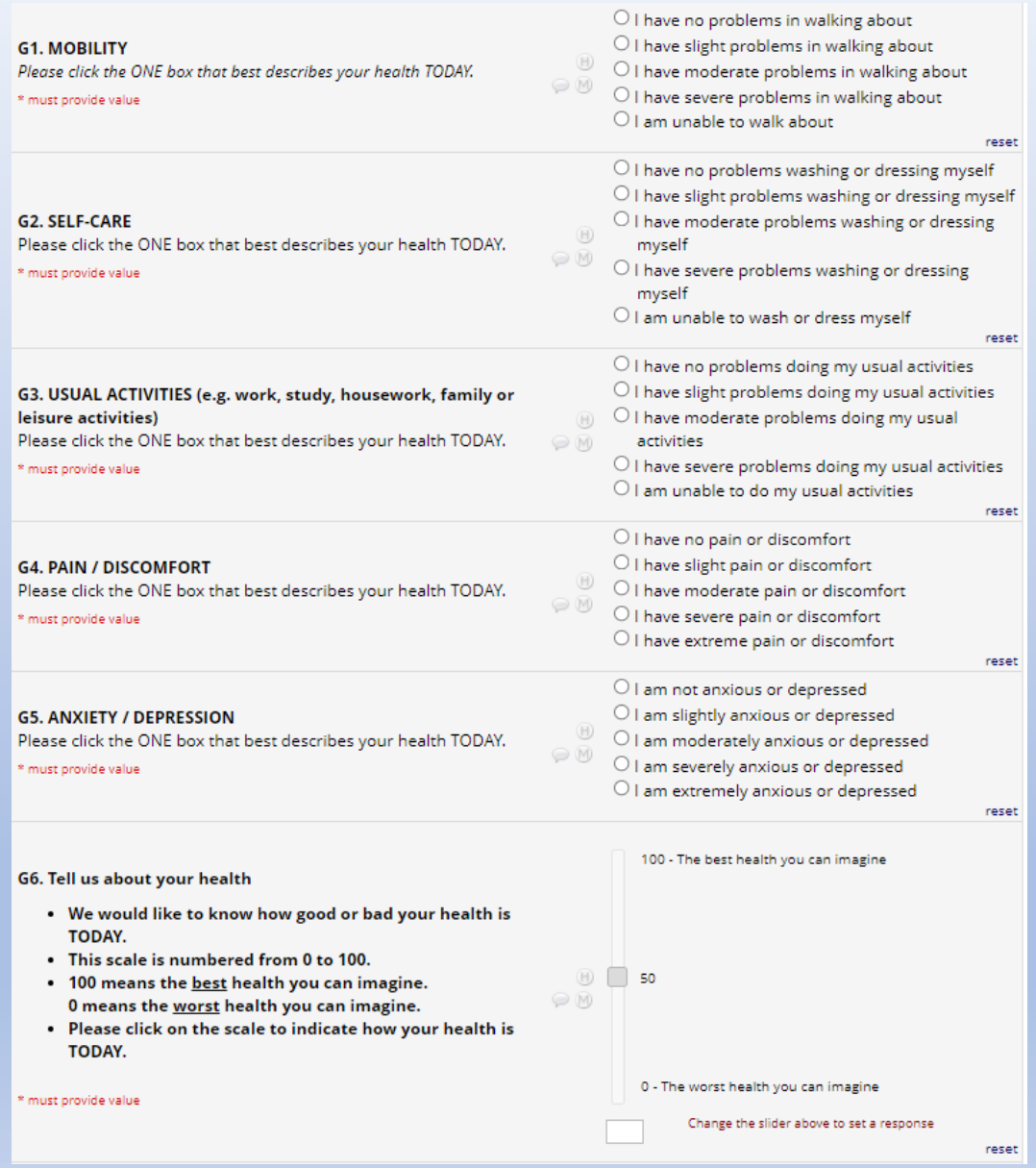
* must provide value

- ○ 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!

EQ-5D 5L & EQ-VAS



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

Change the slider above to set a response

reset

- If participant is unable to answer for themselves (i.e. unconscious), complete fields and scales from an observer's point of view.
- Select the worst possible outcomes for fields G4, G5.
- Mark G6 as '0'.

Day-14 Assessments (2)(Day 14 or discharge CRF)

- Other data to be collected up until day-14 (multiple forms can be added!):

Microbiology results:

Day 14

Microbiology results day 1-14

B1. Date of sample
* must provide value
Today D-M-Y
dd-mm-yyyy *(day _____)*

B2a. Type of sample
* must provide value
- Sputum
- Blood
- Urine
- Other

If other, please provide details
reset

B3. Result
If positive please specify organism
* must provide value
Negative Positive
If positive, please provide details
reset

B4a. Type of organism grown
(check as many as appropriate)
* must provide value
- Staphylococcus aureus
- Streptococcus pneumoniae
- Haemophilus
- E. coli
- Enterobacter
- Pseudomonas aeruginosa
- Klebsiella
- Bacteroides
- Methicillin-resistant staphylococcus aureus (MRSA)
- Extended Spectrum Beta-Lactamases (ESBL)
- Vancomycin-resistant Enterococci (VRE)
- Klebsiella pneumoniae carbapenemase (KPC)
- Clostridium difficile (Culture only positive)
- Clostridium difficile (Toxin only positive)
- Clostridium difficile (Culture and toxin positive)
- Covid-19 (PCR)
- Influenza
- Candida
- Other

If other, please provide details

B5. Any other culture
If yes, please fill another Microbiology results form
* must provide value
Yes No
If yes, please fill another Results of cultures form
reset

Antibiotic treatments:

Antibiotic treatment day 1-14

B1. Date of data collection
* must provide value
Today D-M-Y
dd-mm-yyyy *(day _____)*

B2a. Antibiotic name
* must provide value
- Amoxicillin
- Aztreonam
- Cefuroxime
- Clarythromycin
- Clindamycin
- Co-amoxiclav
- Doxicyclin
- Meropenem
- Metronidazole
- Nystatin (topical)
- Tazocin
- Trimethoprim
- Vancomicin oral/NG/PEG
- Vancomycin IV
- Other

If other, please provide details

B3a. Indication
* must provide value
- Pneumonia
- Lower respiratory tract infection
- Urinary tract infection
- Phlebitis
- Cellulitis
- Sepsis
- Other

If other, please provide details

B4. Start date
* must provide value
Today D-M-Y

B5a. Antibiotic status
* must provide value
- Treatment ongoing
- Course of treatment completed

Ongoing, no End date specified
reset

B5b. End date
* must provide value
Today D-M-Y

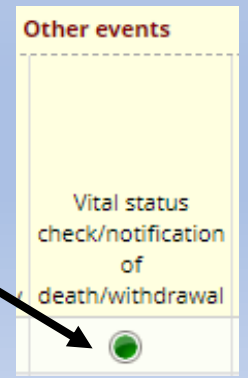
B6. Any other antibiotic
If yes, please fill another Antibiotic treatment form
* must provide value
Yes No
If yes, please fill another "Antibiotic treatment day 1-14" CRF
reset

Mortality Before Day-14 (Day 14 or discharge CRF)

- Day-14 or Discharge assessment should still be completed if the participant passes away before day-14:

1) Enter “date of data collection” as the date of death;
2) Complete section B and C with information from their medical records;
3) Section D can be marked as 'No'. No reason is required as they are deceased;
4) Section E can be marked as 6 – died;
5) Section F marked as 'No’;
6) Section G marked as 'No' Section G8 mark as 0;
7) Sections H, I, J complete as per medical records.

- Ensure the “notification of death” CRF is completed



Pneumonia Diagnoses (Pneumonia CRF)

Pneumonia diagnosis

B1. Clinical diagnosis of pneumonia or lower respiratory tract infection made by treating physician

Diagnosed _____ time(s) on daily logs. ○ Yes ○ No

On Day 14 / Discharge assessment: _____

reset

* must provide value

CDC and PISCES diagnosis

General signs (c-f)

(must be > 0 for CDC and PISCES)

View equation

Calculated

2. Respiratory symptoms or signs within 2 days before or after the diagnosis

Respiratory symptoms and signs (a-d)

(must be > 1 for CDC and PISCES)

View equation

Calculated

3. Abnormal chest radiograph (within 2 days before to 5 days after diagnosis)

Abnormal chest radiograph (a-c)

(must be > 0 for CDC)

View equation

Calculated

Section C: Calculated pneumonia diagnosis

Pneumonia	Calculated diagnosis
Clinician diagnosis	_____

Section D: Pneumonia diagnosis changed

Da. Pneumonia diagnosis changed ○ Yes ○ No

reset

If yes, please provide details

- Complete CRF for any diagnoses made during treatment period.
- Pneumonia diagnosis will automatically be calculated by database by using input data, e.g:

Pneumonia	Calculated diagnosis
Clinician diagnosis	Yes
* CDC diagnosis: definite pneumonia	Yes
** PISCES diagonsis: probable pneumonia	Yes
*** MAPS-2 diagnosis	Yes

- Correct day-14 CRF if pneumonia mis-diagnosed:

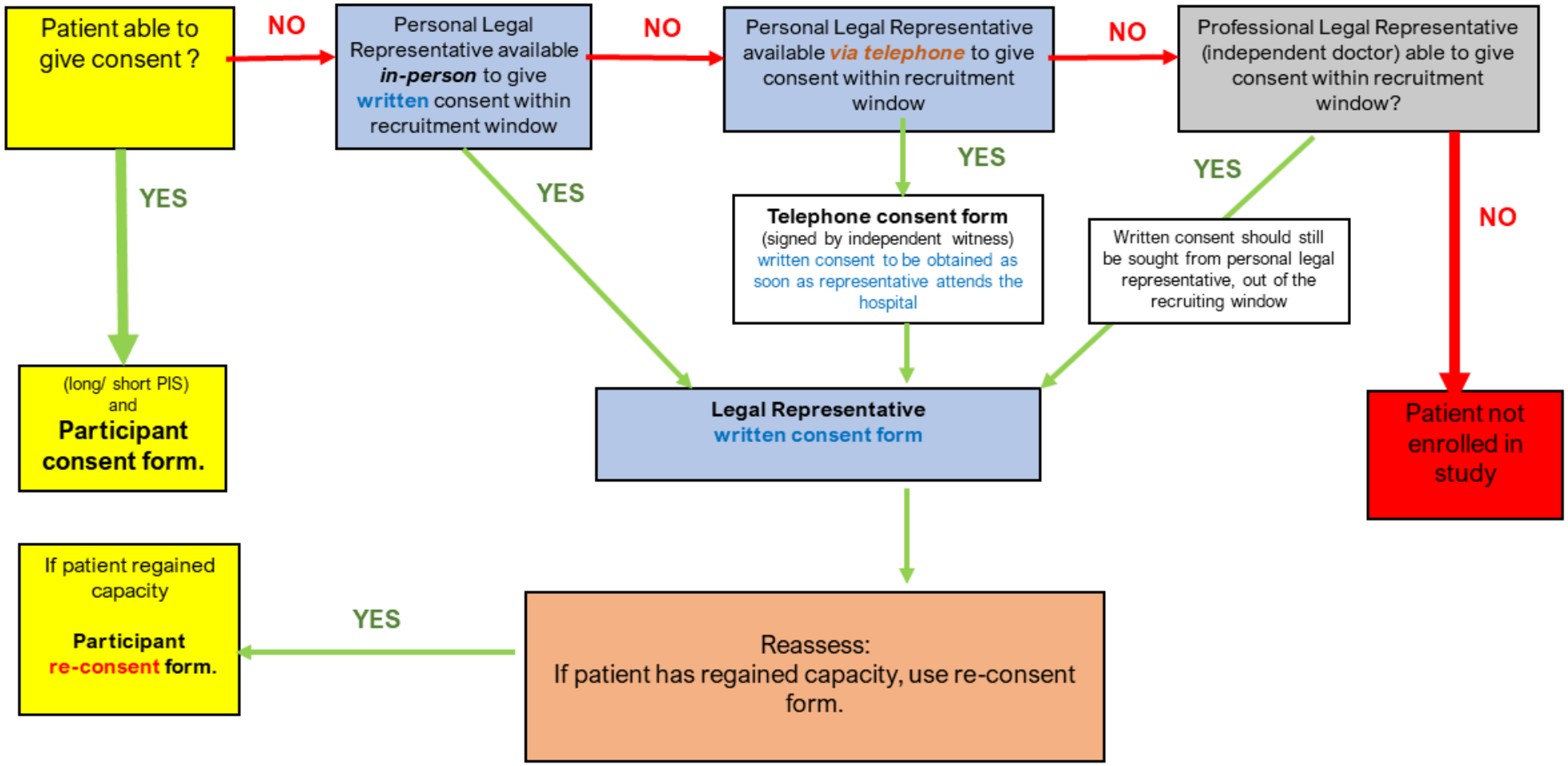
J1. Diagnosis of pneumonia made at any time during day 1-14

- Diagnosed x0 time on daily logs.

- Diagnosed on the pneumonia CRF: _____ on _____ (day _____)

○ No pneumonia
○ Pneumonia diagnosed
○ Pneumonia mis-diagnosed

Consent Flowchart



Informed Consent

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

- Non-medics may take the initial consent in MAPS-2 (if allowed by local NHS Trust policy).

- Consenting investigators must discuss the trial with patients in-depth beforehand and should answer any questions.

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

- Two separate consent forms are available:

❖'Long' Patient Information Sheet (PIS)

❖'Short' Patient Information Sheet (PIS)

Participant Information Sheet ('Long' PIS)

- Patients should review the ***1. Participant Information Sheet***, understand the purpose/design of the trial and have enough time to ask questions to the consenting investigator.

- Written informed consent should follow.

- Remind patients 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 are required to initial all boxes, sign and date the ***2. Participant Consent Form***. The consulting investigator must also sign this form.

- The participant's unique trial ID should be handwritten on the consent form.

Participant Consent Form

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MAPS-2

(Form to be printed on local headed paper)

PARTICIPANT CONSENT FORM
(Final version 1.0: 08/11/2021)

Title of Study: Metoclopramide for Avoiding Pneumonia after Stroke (MAPS-2) Trial

IRAS Project ID: 290474 **ISRCTN:40512756** **CTA ref : *03057/0075/001-0001***

Name of Researcher:

Name of Participant:

Please initial box

1. I, the above-named participant, confirm that I have read and understand the Patient Information Form version number 1.0 dated 08/11/2021 for the above study and have had the opportunity to ask questions. JS
2. I understand that I can withdraw from the study at any time, without giving any reason, and without my medical care or legal rights being affected. I understand that should I withdraw from the study then the information collected so far cannot be erased and that this information may still be used in the project analysis. JS
3. I understand that relevant sections of my medical records and data collected in the study may be looked at by authorised individuals from the University of Nottingham, the research group and regulatory authorities where it is relevant to me taking part in this study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential. JS
4. I understand that the information held and maintained by NHS Digital, EDRIS and other central UK NHS bodies may be used to help contact me or my named contact to provide information about my health status. JS
5. I agree to the information collected about me in this study being used to support other research in the future, and be shared anonymously with other researchers. JS
6. I agree to my GP being informed of my participation in this study and will be asked to provide information on my status before I am contacted for the 6 month follow up. JS
7. I agree to you sending me a letter/email with a summary of the results. Yes/No
8. I understand that pregnancy would exclude participation and agree that a pregnancy test can be performed if appropriate. JS
9. If I lose the capacity to make decisions for myself during the course of the study, I'd be happy to continue in the study unless my legal representative (relative, friend or independent physician acting on my behalf) raises an objection to this. JS

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10. I consent to take part in the above study. JS

John Smith	06/12/2022	
Name of Participant	Date	Signature
Max Stuart	06/12/2022	
Name of Person taking consent	Date	Signature
Name of Independent Witness (if necessary)	Date	Signature

Role of Independent Witness

3 copies: 1 for participant, 1 for the project notes and 1 for the medical notes

Combined PIS and Consent Form ('Short' PIS)

- Time pressures or emotional distractions may prevent patients from reading and processing the longer PIS and consent form.

- A shorter, combined and pictorial, consent and information form is available for all patients to sign: ***3. Participant Information and Consent Form.***

- Any participant may alternatively sign this combined consent form instead of the longer form.

- *However*, participants that use this form to consent must also be provided with a copy of the ***1. Participant Information Sheet.***

- Participants may sign the longer ***2. Participant Consent Form*** after consent has already been obtained on the combined form.

Combined PIS and Consent Form ('Short' PIS)

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(Form to be printed on local headed paper)

MAPS-2

Metoclopramide for Avoiding Pneumonia after Stroke (MAPS-2) study
Participant Information and Consent Form
(Final version 1.0: date: 08/11/2021)

	**What is this about?** • This study will test whether metoclopramide (an anti-sickness medicine) can prevent pneumonia and death in patients who have had a stroke.
	**Whilst you are in hospital:** • The doctor or nurse will ask you a few questions and will test your speech, swallowing, eyesight, head, arms and legs to find out how the stroke has affected you. • You may have a scan of your head and blood tests. • You will be given treatment for your stroke. • Research staff will discuss the study with you and can answer any questions you may have.
	**If you agree to take part in the study:** • If you are a woman of childbearing age and may be pregnant, with your permission we would do a pregnancy test. • You will then be assigned at random to take either the trial treatment or a dummy treatment. • You will be given the treatment 3 times a day for 2 weeks or until you are discharged.
	**2 weeks and 6 months after your stroke:** • For the first 2 weeks research staff will record details of your condition, your test results and what medication you are taking. A researcher will call you after 6 months to see how you are, whether you have had any problems and how well you have recovered.
	**Risks** • The side-effects are generally mild but include drowsiness, abnormal movements of the face and limbs, diarrhoea, low blood pressure and a feeling of weakness, all of which can be treated.
	**During the study:** • If you have any questions, then please ask. • You may decide you do not want to take part anymore. This will not affect any of your care now or in the future. All the information we hold about you will be kept in the strictest confidence.

Local header

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Metoclopramide for Avoiding Pneumonia after Stroke (MAPS-2) study

IRAS Project ID: 290474 **ISRCTN: 40512746** **CTA ref : 03057/0075/001-0001**

Name of Researcher: Florence Schmidt

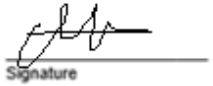
Name of Participant: John Smith

I confirm that I have been given a copy of the Patient Information Form (Version *1.0*) and I agree:

- I will take part in the MAPS-2 study.
- I will have a pregnancy test if deemed necessary because I am of a childbearing age.
- For my medical records to be accessed.
- To be followed up for 2 weeks and at 6 months.
- For my GP to be informed of my participation and to provide information on my status before the telephone follow up.
- For my contact details to be collected and used for the purpose of the study.
- My information held by NHS digital and other UK NHS bodies may be used to help contact me or provide information about my health.

I understand that I am free to withdraw myself from the study at any point without giving a reason.

Participant consent

John Smith Name of Participant	06/12/2022 Date	 Signature
Florence Schmidt Name of Person taking consent	06/12/2022 Date	 Signature
Name of Independent Witness (if necessary)	Date	Signature
Role of Independent Witness		

3 copies: 1 for participant, 1 for the project notes and 1 for the medical notes

Independent Witnesses

- Verbal consent is acceptable for patients who are capable of consenting themselves but physically unable to sign the consent form.
- Additionally, patients with physical impairments may 'mark' the consent form.
- In these two scenarios, the consent form must be signed off by an independent witness.
- The independent witness must be a family member or clinical member of staff who is **not** affiliated with the MAPS-2 study, and is **not** on the electronic delegation log (e.g. a staff nurse in the ward).
- Independent witnesses are **not** required for patients who are physically and mentally capable of providing consent *unless* the patient cannot write. They will witness the signature, and not the consent.

Independent Witnesses Example

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10. I consent to take part in the above study. ☑

John Smith	06/12/2022	
Name of Participant	Date	Signature
Henry Clive	06/12/2022	
Name of Person taking consent	Date	Signature
Jane Thompson	06/12/2022	
Name of Independent Witness (if necessary)	Date	Signature

Ward Nurse
Role of Independent Witness

3 copies: 1 for participant, 1 for the project notes and 1 for the medical notes

Adults Lacking Capacity

- If patients cannot consent themselves then every opportunity should be explored to gain written consent from a **personal** representative.

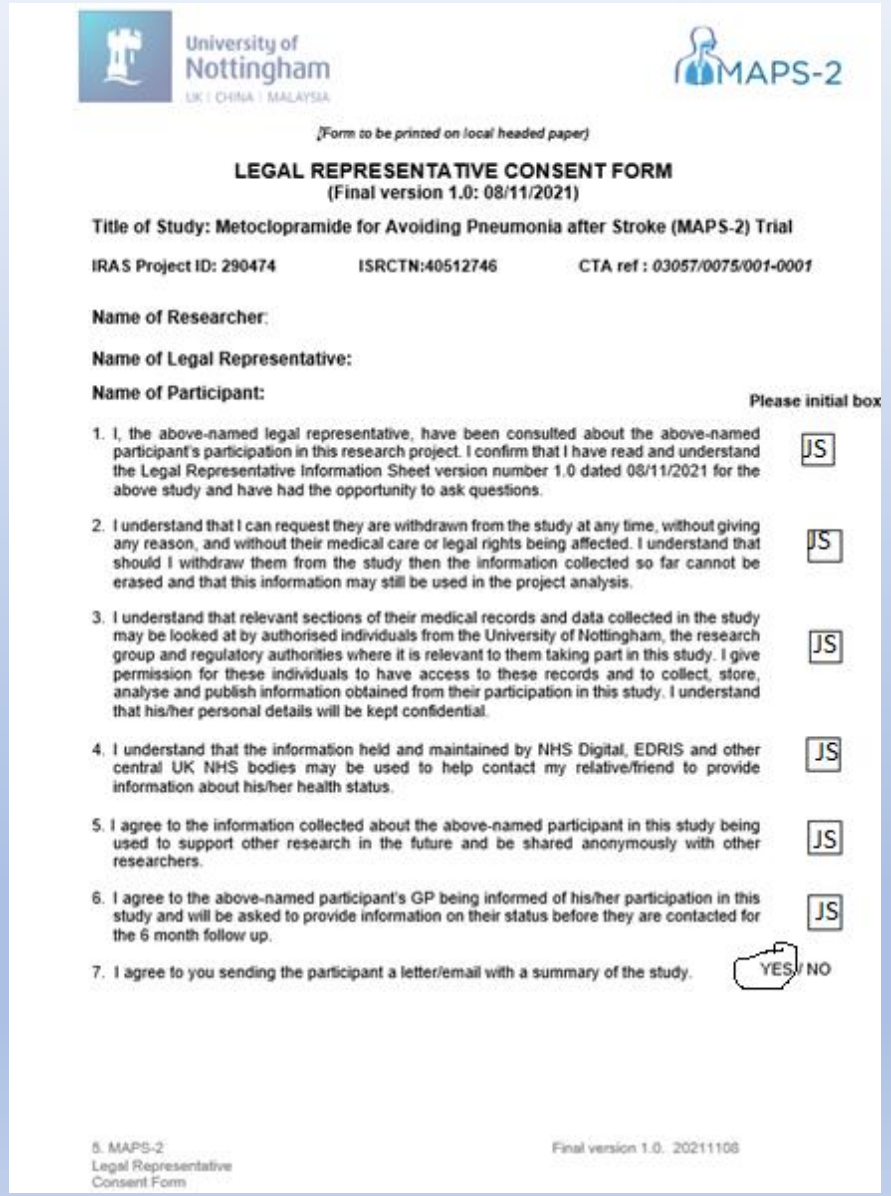
- Personal representatives must know, and can represent, the participant's wishes with regards to entering the trial. This should be someone who the patient would trust with important decisions about their welfare:

- For English/Welsh/N. Irish sites → cannot be a paid, professional carer for the patient.

- For Scottish sites → a welfare attorney/guardian, followed by the participant's nearest relative.

- These personal representatives should initial all boxes, sign and date the ***5. Legal Representative Consent Form***, after being provided with the ***4. Legal Representative Information Sheet***.

Legal Representative Consent Form



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MAPS-2

[Form to be printed on local headed paper]

LEGAL REPRESENTATIVE CONSENT FORM
(Final version 1.0: 08/11/2021)

Title of Study: Metoclopramide for Avoiding Pneumonia after Stroke (MAPS-2) Trial

IRAS Project ID: 290474 **ISRCTN:40512746** **CTA ref : *03057/0075/001-0001***

Name of Researcher:

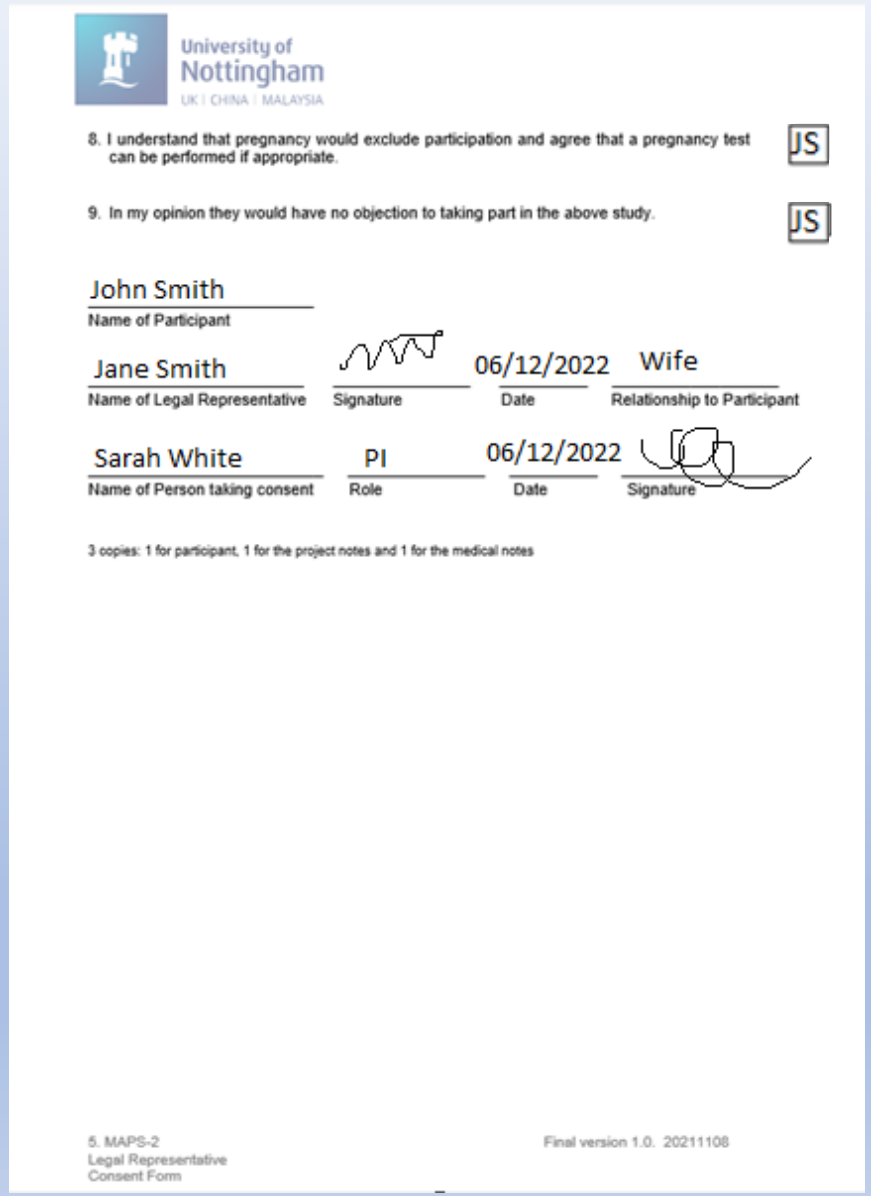
Name of Legal Representative:

Name of Participant:

Please initial box

1. I, the above-named legal representative, have been consulted about the above-named participant's participation in this research project. I confirm that I have read and understand the Legal Representative Information Sheet version number 1.0 dated 08/11/2021 for the above study and have had the opportunity to ask questions. JS
2. I understand that I can request they are withdrawn from the study at any time, without giving any reason, and without their medical care or legal rights being affected. I understand that should I withdraw them from the study then the information collected so far cannot be erased and that this information may still be used in the project analysis. JS
3. I understand that relevant sections of their medical records and data collected in the study may be looked at by authorised individuals from the University of Nottingham, the research group and regulatory authorities where it is relevant to them taking part in this study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from their participation in this study. I understand that his/her personal details will be kept confidential. JS
4. I understand that the information held and maintained by NHS Digital, EDRIS and other central UK NHS bodies may be used to help contact my relative/friend to provide information about his/her health status. JS
5. I agree to the information collected about the above-named participant in this study being used to support other research in the future and be shared anonymously with other researchers. JS
6. I agree to the above-named participant's GP being informed of his/her participation in this study and will be asked to provide information on their status before they are contacted for the 6 month follow up. JS
7. I agree to you sending the participant a letter/email with a summary of the study. YES / NO

5. MAPS-2 Legal Representative Consent Form — Final version 1.0. 20211108



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8. I understand that pregnancy would exclude participation and agree that a pregnancy test can be performed if appropriate. JS
9. In my opinion they would have no objection to taking part in the above study. JS

John Smith			
Name of Participant			
Jane Smith		06/12/2022	Wife
Name of Legal Representative	Signature	Date	Relationship to Participant
Sarah White	PI	06/12/2022	
Name of Person taking consent	Role	Date	Signature

3 copies: 1 for participant, 1 for the project notes and 1 for the medical notes

5. MAPS-2 Legal Representative Consent Form — Final version 1.0. 20211108

Adults Lacking Capacity (cont.)

- Personal representatives may also be provided with a shorter, pictorial version of the information sheet and consent form.
- It is recommended to use this form if faced with significant time pressures.
- Personal representatives are required to sign and date the ***6. Legal Representative Information and Consent Form***. The consenting investigator must also sign this form.
- Representatives who use this form must also be provided with a copy of the ***4. Legal Representative Information Sheet.***
- Representatives may sign the longer ***5. Legal Representative Consent Form*** after consent has already been obtained on the combined form.
- The participant's unique trial ID should be handwritten on the consent form.

Combined LRIS and Consent Form ('Short' LRIS)

Local header

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MAPS-2

/

(Form to be printed on local headed paper)

Metoclopramide for Avoiding Pneumonia after Stoke (MAPS-2) study
Legal Representative Information and Consent Form
(Final version 1.0: 08/11/2021)

	**What is this about?** • This study will test whether metoclopramide (an anti-sickness medicine) can prevent pneumonia and death in patients who have had a stroke
	**Whilst your friend / relative is in hospital:** • The doctor or nurse will ask them a few questions, and will test their swallowing, speech, eyesight, head, arms and legs to find out how the stroke has affected them. • They may then have a scan of their head and blood tests. • They will be given treatment for their stroke. • Research staff will discuss the study with you and can answer any questions you may have.
	**If you agree for them to take part in the study:** • If your relative is a woman of childbearing age and may be pregnant, with permission we would do a pregnancy test. • They will then be assigned at random to take either the trial treatment or a dummy treatment. They will not know which treatment they are receiving. • They will be given the treatment 3 times a day for 2 weeks or until they are discharged.
	**2 weeks and 6 months after their stroke:** • For the first 2 weeks research staff will record details of their condition, their test results and what medication they are taking. • A researcher will call them after 6 months to see how they are, whether they have had any problems and how well they have recovered.
	**Risks** • The side-effects are generally mild but include drowsiness, diarrhoea, low blood pressure and feeling of weakness, all of which can be treated.
	**During the study:** • If you have any questions, then please ask. • You may decide you do not want them to take part anymore. This will not affect any of their care now or in the future. • All the information we hold about them will be kept in the strictest confidence.

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Metoclopramide for Avoiding Pneumonia after Stoke (MAPS-2) study

IRAS Project ID: 290474 **ISRCTN4 0512746** **CTA ref : 03057/0075/001-0001**

Name of Researcher: Johnny Palmer

Name of Participant: John Smith

I confirm that I have been given a copy of the Legal Representative Information Sheet (Version *1.0* and I agree:

- My friend / relative to take part in the MAPS-2 study.
- My friend / relative will have a pregnancy test if deemed necessary because they are of a childbearing age.
- For my friend's / relative's medical records to be accessed.
- For my friend / relative to be followed up for 2 weeks and at 6 months
- For my friend's / relative's GP to be informed of their participation and to provide information on their status before the telephone follow up.
- For my friend's / relative's contact details to be collected and used for the purpose of the study.
- For my friend's / relative's information held by NHS digital and other UK NHS bodies may be used to help contact them or provide information about their health.

I understand that I am free to withdraw my friend / relative from the study at any point without giving a reason.

Legal Representative Consent

John Smith Name of Participant		
Jane Smith Name of Legal Representative	06/12/2022 Date	 Signature
Wife Relationship to Participant		
Johnny Palmer Name of Person taking consent	06/12/2022 Date	 Signature

3 copies: 1 for participant/relative, 1 for the project notes and 1 for the medical notes

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, the consenting investigator and an **independent witness** must sign the ***7. Legal Representative Telephone Consent Form***.

- The 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**.

Telephone Consent Example

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MAPS-2

(Form to be printed on local headed paper)

LEGAL REPRESENTATIVE TELEPHONE CONSENT FORM
(Final version 1.0: 08/11/2021)

Title of Study: Metoclopramide for Avoiding Pneumonia after Stroke (MAPS-2) Trial

IRAS Project ID: 290474 **ISRCTN:40512746** **CTA ref : 03057/0075/001-0001**

Name of Researcher:

Name of Legal Representative:

Name of Participant:

Please tick box once verbally agreed:

1. I, the above-named legal representative, have been consulted about the above-named participant's participation in this research project. I confirm that I have read and understand the Legal Representative Information Sheet version number 1.0 dated 08/11/2021 for the above study and have had the opportunity to ask questions. ☑
2. I understand that I can request they are withdrawn from the study at any time, without giving any reason, and without their medical care or legal rights being affected. I understand that should I withdraw them from the study then the information collected so far cannot be erased and that this information may still be used in the project analysis. ☑
3. I understand that relevant sections of their medical records and data collected in the study may be looked at by authorised individuals from the University of Nottingham, the research group and regulatory authorities where it is relevant to them taking part in this study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from their participation in this study. I understand that their personal details will be kept confidential. ☑
4. I understand that the information held and maintained by NHS Digital, EDRIS and other central UK NHS bodies may be used to help contact you to provide information about my relative's / friend's / the patient's I have been asked to provide independent physician consent for health status. ☑
5. I agree to the information collected about my relative / friend / patient I have been asked to provide independent physician consent for in this study being used to support other research in the future and be shared anonymously with other researchers. ☑
6. I agree to my relative's / friend's / the patient's I have been asked to provide independent physician consent for GP being informed of their participation in this study and will be asked to provide information on their status before they are contacted for the 6 month follow up. ☑
7. I agree to you sending my relative / friend / the patient I have been asked to provide independent physician consent for a letter/email with a summary of the study. (YES) NO
8. I understand that pregnancy would exclude participation and agree that a pregnancy test can be performed if appropriate. ☑
9. I agree to signing a consent form on behalf of my relative / friend / the patient I have been asked to provide independent physician consent for when I next attend the hospital. ☑

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10. In my opinion they would have no objection to taking part in the above study. ☑

John Smith Name of Participant		
Jane Smith Name of Legal Representative	Wife Relationship to Participant	
Joanna Hutchinson Name of Person taking consent	06/06/2022 Date	 Signature
Ben Jones Name of Independent Witness	06/06/2022 Date	 Signature
Ward Nurse Role of Independent Witness		

3 copies: 1 for participant, 1 for the project notes and 1 for the medical notes

7. MAPS-2 Final version 1.0. 20211108
Legal Representative Telephone Consent Form

Independent Physician Consent

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

- Must be registrar or above.

- 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 initial all boxes, sign and date the ***5. Legal Representative Consent Form*** after reviewing the ***4. Legal Representative Information Sheet.***

- The independent physician cannot be connected to the research and must not be on the delegation log.

Independent Physician Consent Example

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MAPS-2

(Form to be printed on local headed paper)

LEGAL REPRESENTATIVE CONSENT FORM
(Final version 1.0: 08/11/2021)

Title of Study: Metoclopramide for Avoiding Pneumonia after Stroke (MAPS-2) Trial

IRAS Project ID: 290474 **ISRCTN:40512746** **CTA ref : *03057/0075/001-0001***

Name of Researcher:

Name of Legal Representative:

Name of Participant:

Please initial box

1. I, the above-named legal representative, have been consulted about the above-named participant's participation in this research project. I confirm that I have read and understand the Legal Representative Information Sheet version number 1.0 dated 08/11/2021 for the above study and have had the opportunity to ask questions. **FJ**

2. I understand that I can request they are withdrawn from the study at any time, without giving any reason, and without their medical care or legal rights being affected. I understand that should I withdraw them from the study then the information collected so far cannot be erased and that this information may still be used in the project analysis. **FJ**

3. I understand that relevant sections of their medical records and data collected in the study may be looked at by authorised individuals from the University of Nottingham, the research group and regulatory authorities where it is relevant to them taking part in this study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from their participation in this study. I understand that his/her personal details will be kept confidential. **FJ**

4. I understand that the information held and maintained by NHS Digital, EDRIS and other central UK NHS bodies may be used to help contact my relative/friend to provide information about his/her health status. **FJ**

5. I agree to the information collected about the above-named participant in this study being used to support other research in the future and be shared anonymously with other researchers. **FJ**

6. I agree to the above-named participant's GP being informed of his/her participation in this study and will be asked to provide information on their status before they are contacted for the 6 month follow up. **FJ**

7. I agree to you sending the participant a letter/email with a summary of the study. (YES) NO

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8. I understand that pregnancy would exclude participation and agree that a pregnancy test can be performed if appropriate. **FJ**

9. In my opinion they would have no objection to taking part in the above study. **FJ**

John Smith			
Name of Participant			
Frank James		06/12/2022	A&E Consultant
Name of Legal Representative	Signature	Date	Relationship to Participant
Stephen Thomas	PI	06/12/2022	
Name of Person taking consent	Role	Date	Signature

3 copies: 1 for participant, 1 for the project notes and 1 for the medical notes

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:

- ***1. MAPS-2 Participant Information Sheet***
- ***8. MAPS-2 Participant Re-consent Form***

- 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.

- This whole process should be documented in the participant's medical notes.

- 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 legal representative raises an objection to this.

Participant Re-consent Example

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MAPS-2

(Form to be printed on local headed paper)

PARTICIPANT RE-CONSENT FORM
(Final version 1.0 08/11/2021)

Title of Study: Metoclopramide for Avoiding Pneumonia after Stroke (MAPS-2) Trial

IRAS Project ID: 290474 **ISRCTN: 40512746** **CTA ref.: 03057/0075/001-0001**

Name of Researcher: Hugh Baxter

Name of Participant: John Smith

Recently, your legal representative (relative, friend or an independent doctor where a relative or friend could not be contacted, acting on your behalf) consented you to take part in the MAPS-2 clinical trial. Your doctor or nurse has now deemed you to have regained the mental capacity to consent yourself into this clinical trial. If you wish to continue being in the MAPS-2 clinical trial, please read and sign the consent form below:

Please initial box

1. I, the above-named participant, confirm that I have read and understand the participant information sheet version number 1.0 dated 08/11/2021 for the above study and have had the opportunity to ask questions. JS
2. I understand that I can withdraw from the study at any time, without giving any reason, and without my medical care or legal rights being affected. I understand that should I withdraw from the study then the information collected so far cannot be erased and that this information may still be used in the project analysis. JS
3. I understand that relevant sections of my medical records and data collected in the study may be/have been looked at by authorised individuals from the University of Nottingham, the research group and regulatory authorities where it is relevant to me taking part in this study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential. JS
4. I understand that the information held and maintained by NHS Digital, EDRIS and other central UK NHS bodies may be used to help contact me or my named contact to provide information about my health status. JS
5. I agree to the information collected about me in this study will be used to support other research in the future and may be shared anonymously with other researchers. JS
6. I agree to my GP being informed of my participation in this study and will be asked to provide information on my status before I am contacted for the 6 month follow up. JS
7. I agree to you sending me a letter/email with a summary of the results. (Yes) No

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8. If I lose the capacity to make decisions for myself during the course of the study, I'd be happy to continue in the study unless my legal representative (relative, friend or independent doctor acting on my behalf) raises an objection to this. JS

9. I consent to take part in the above study. JS

John Smith	06/12/2022	
Name of Participant	Date	Signature
Hugh Baxter	06/12/2022	
Name of Person taking consent	Date	Signature
Name of Independent Witness (if necessary)	Date	Signature

Role of Independent Witness

3 copies: 1 for participant, 1 for the project notes and 1 for the medical notes

8. MAPS-2 Participant re-consent Form Final version 1.0 20211108

Databases

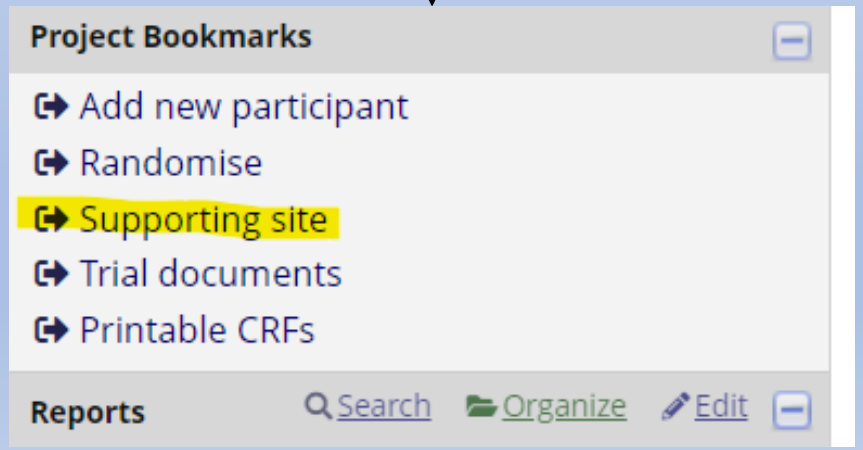
REDCap:

Basic data entry, e.g:

- Baseline;
- Daily clinical monitoring log;
- Day-14/discharge follow-up;
- Pneumonia diagnoses;
- Vital status;
- Microbiology / Antibiotics.

Supporting site:

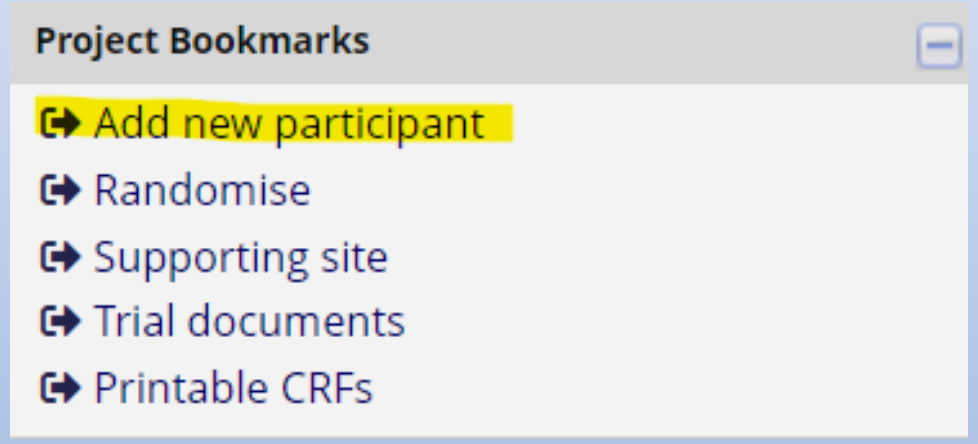
- Randomisation;
- Electronic delegation log;
- Uploading of documents via *secure vault*.

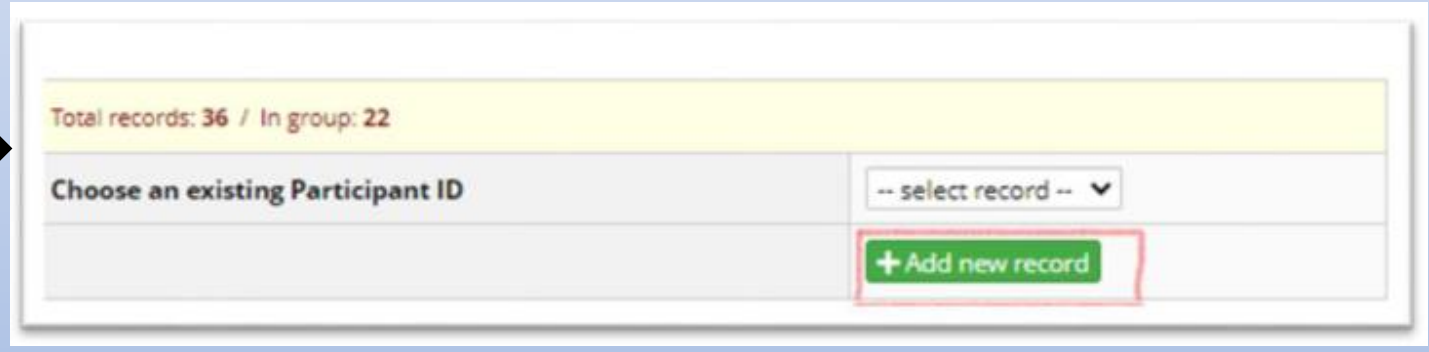


Randomisation

1. In REDCap, select ‘Add participant’ on left toolbar

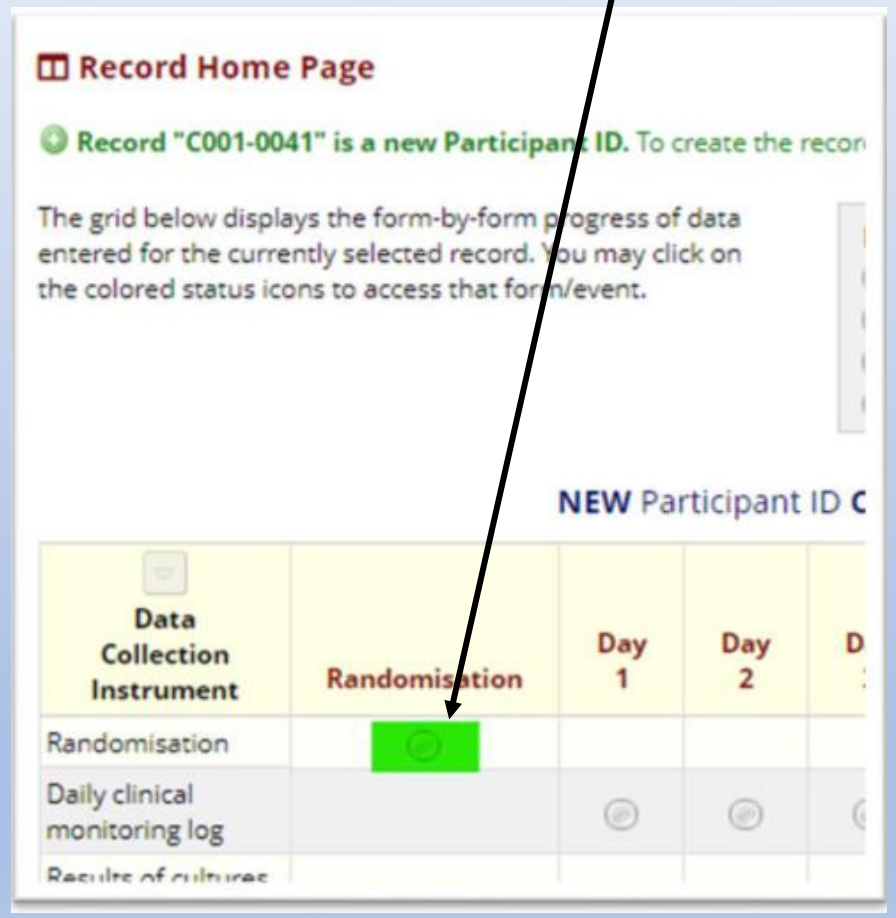
2. Add a new record



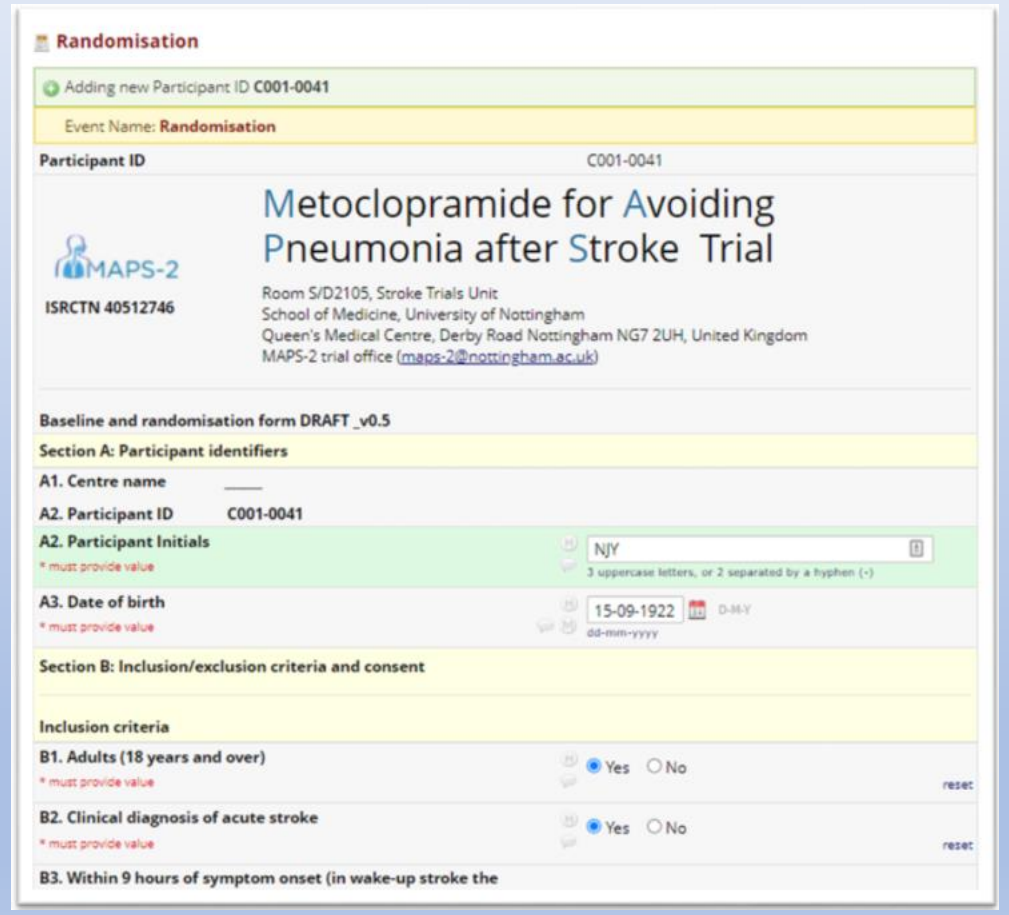


Randomisation

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

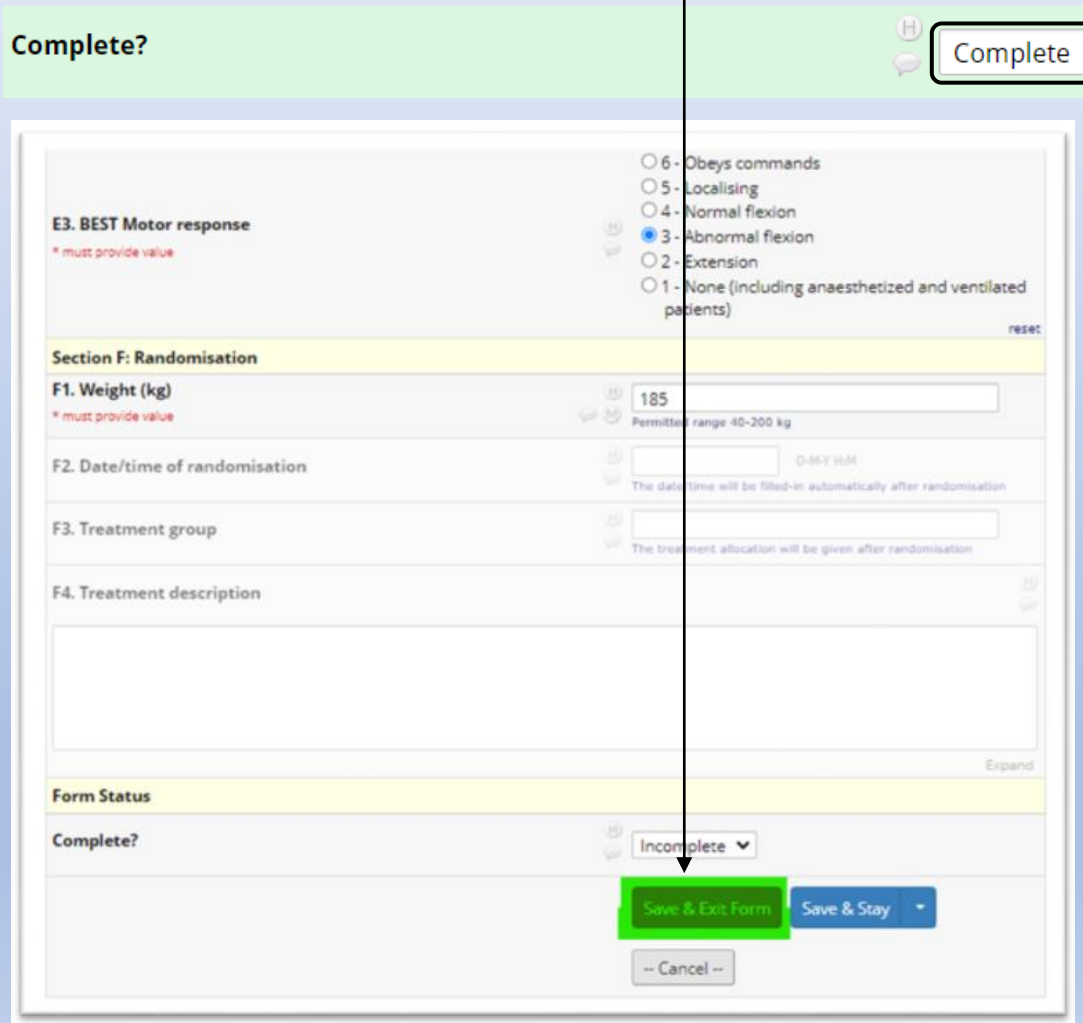


4. Complete the Randomisation CRF

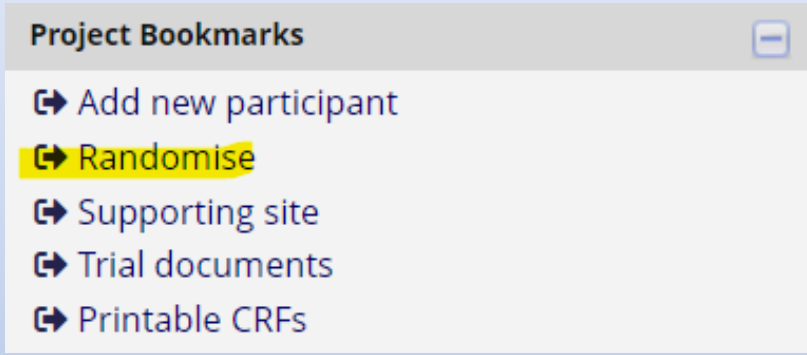


Randomisation

5. 'Complete' the form, click 'save and exit form'.

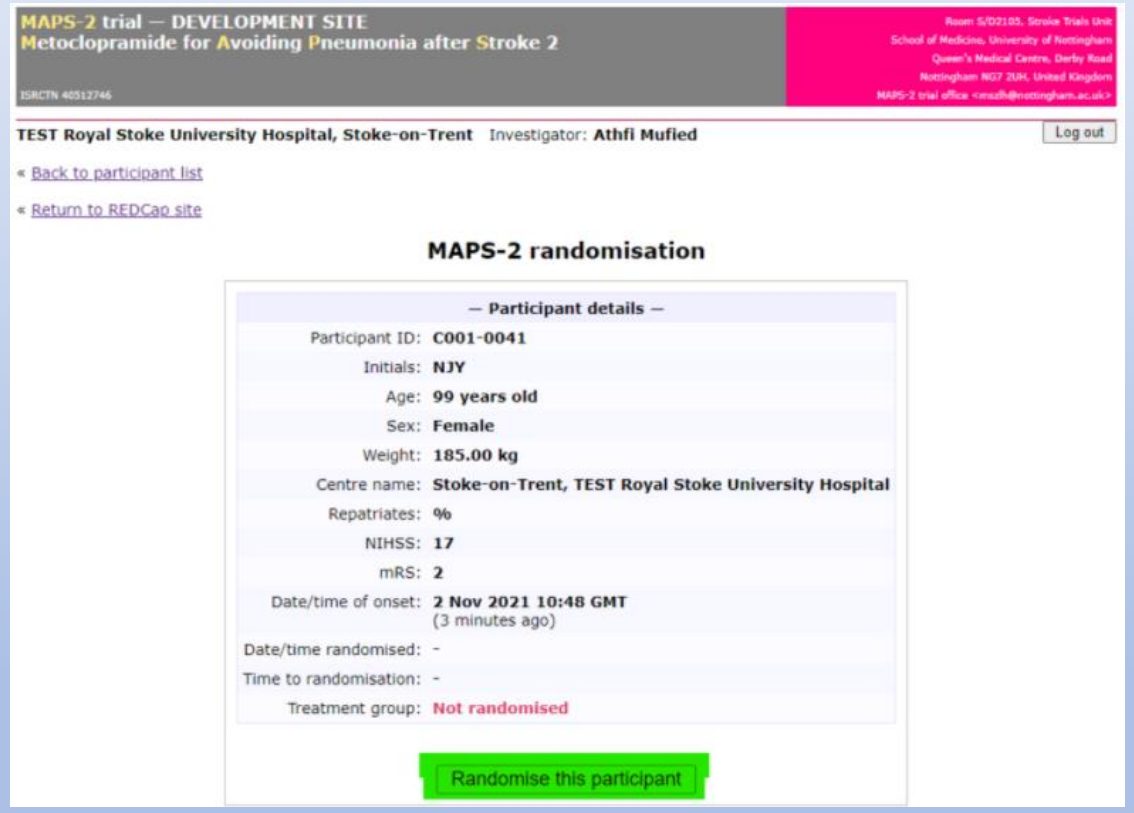


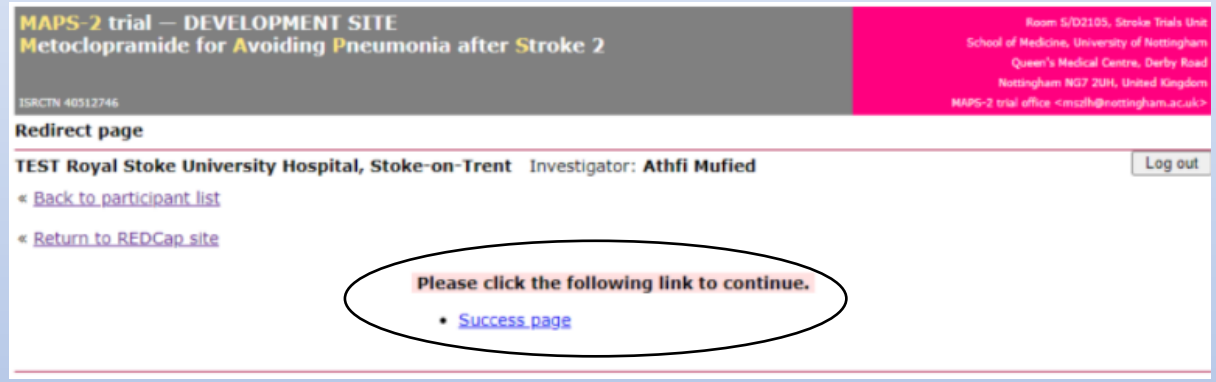
6. Click the 'Randomise' link on the left toolbar

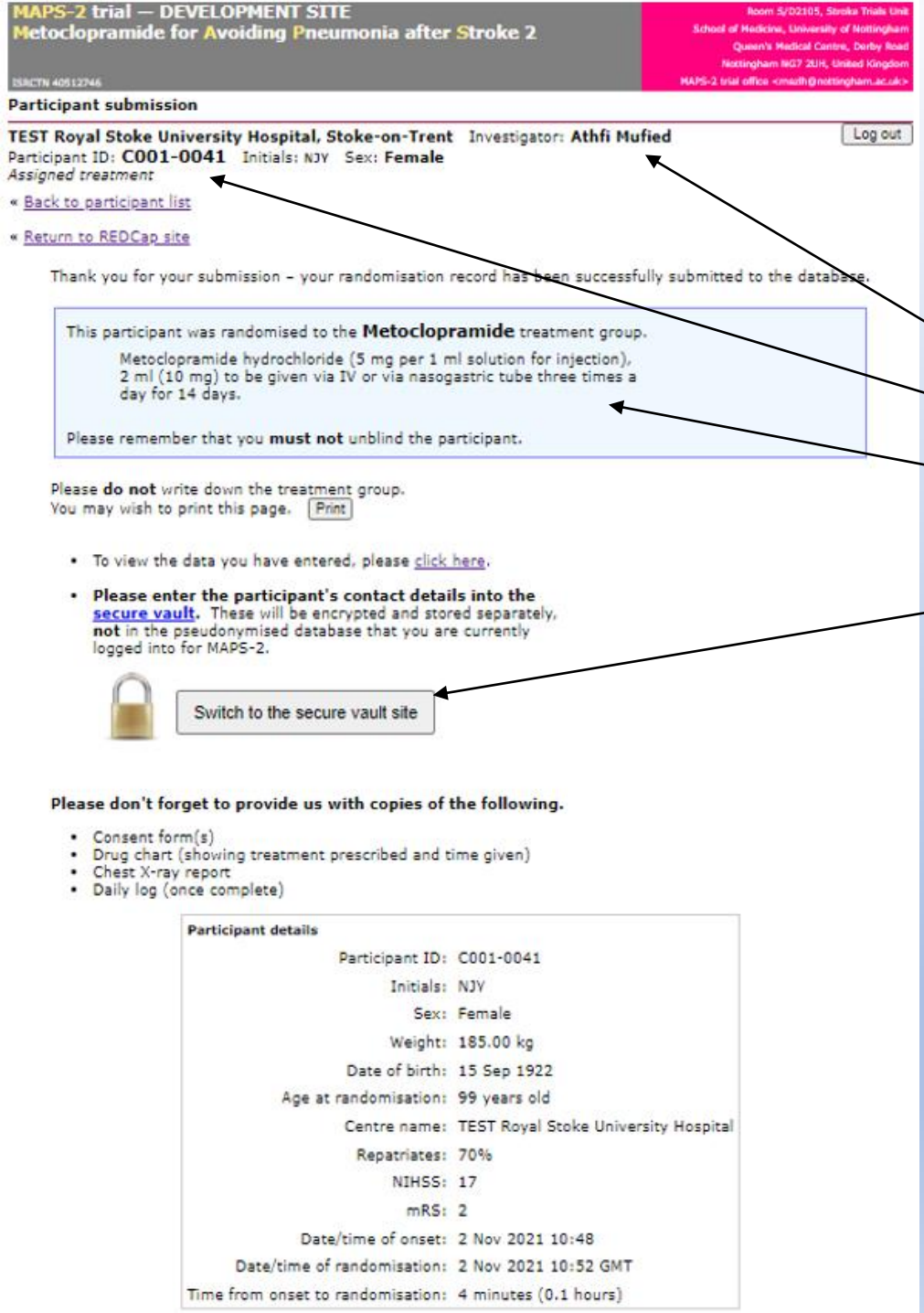


Randomisation

7. Check the information in the randomisation summary, and click the link to the the 'success page'.







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

The name of the randomising investigator

Participant's trial ID number

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.

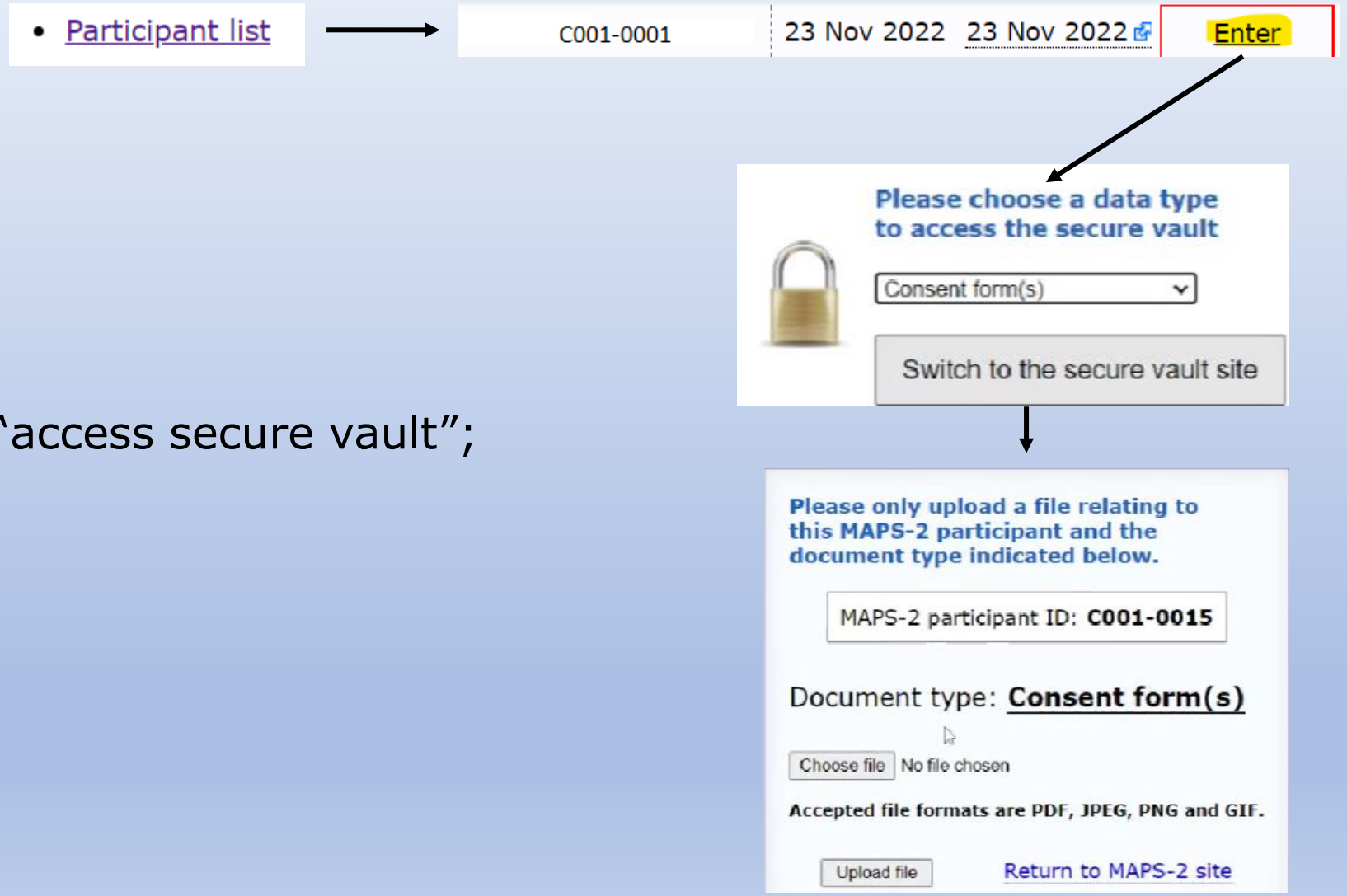
Identifiable data will be kept separately in the secure vault, whereas all other data will be kept in the REDCap database.

Manual Randomisation Instructions

1. In cases where sites are unable to randomise a patient and require a manual randomisation, contact the CI (or delegate)on the 24hr emergency contact number.
2. The CI will inform the site of the participant's allocated treatment.
3. If still unable to access REDCap, sites should use the randomisation paper CRF.
4. Nottingham STU will attempt to resolve the REDCap login issue. Sites should continue to use paper CRFs in the meantime.
5. When able to, the randomisation details should be entered into REDCap retrospectively by the site investigator as soon as possible **(remember to 'complete' the form, and do not randomise the participant again!).**
6. UoN will manually update the system with the participant's randomisation result.

Accessing the Secure Vault

1. Log into REDCap;
2. Select “supporting site”;
3. Select “participant list”;
4. Select relevant participant;
5. Choose data type and click “access secure vault”;
6. Choose file to upload;
7. Upload file!



Documents Upload

- The following documents are to required to be uploaded for each participant:

✓Consent form (within **one working day** of obtaining consent);

✓**[PSEUDONYMISED]** drug chart showing correctly allocated treatment for **all** days the participant received treatment → upload at end of treatment period;

✓**[PSEUDONYMISED]** completed daily clinical monitoring log CRFs → upload at end of treatment period;

✓**[PSEUDONYMISED]** any chest x-ray *reports* (not images).

Electronic Delegation Log

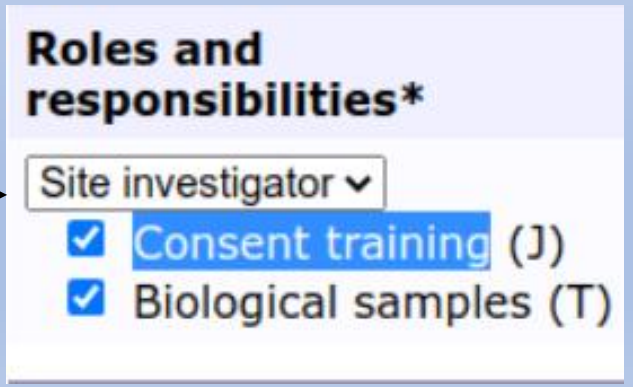
- Same delegation log system as the PhEAST, TICH-3, LACI-2 and DASH studies.
- REDCap accounts will link through to the bespoke system. Nottingham clinical trial managers will create and update the details of all site staff within the supporting site.
- Pharmacy staff are **not** required to be on the delegation log.
- Activation email will be sent to all users from the supporting site:

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



Electronic Delegation Log

- When accounts are activated, they will appear on their electronic delegation log as 'not authorised':

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

- The local 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!

New Trial Personnel

- 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 Events

Collected up until day-14 / discharge, and reported on day-14 / discharge CRF.

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 Events (not to report)

1) Medical / surgical procedures (e.g., 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. hospitalisations for cosmetic elective surgery).

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.

Adverse Events (not to report)

- Outlined in Appendix 3. in protocol → **do not** report these in the CRF.

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

Serious Adverse Events (SAE)

- Collected until day-14 (but hospital readmissions collected at six month follow-up).

- 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

- CI will conclude event as not related, possibly related, probably related or definitely related to treatment.

Serious Adverse Events (SAE)

- Sites should advise participants / carers to 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:

a) Sudden in its onset (e.g., anaphylaxis);

b) Unexpected in its severity and seriousness; and

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.

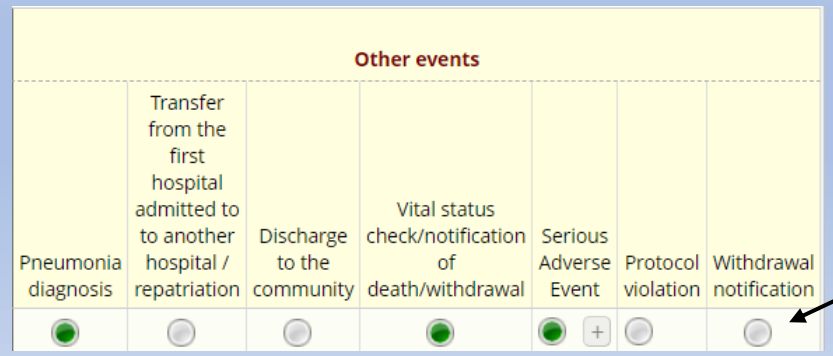
Participant Withdrawal

- Participants who experience an AE or SAE may be withdrawn temporarily or permanently from the trial at the discretion of the Investigator.

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

- Patients who withdraw overall consent will not be followed up at six-months and their time in the trial will be finished.

- Participants should be made aware that all data up until the point of withdrawal cannot be erased, **but** no further data will be collected from them.



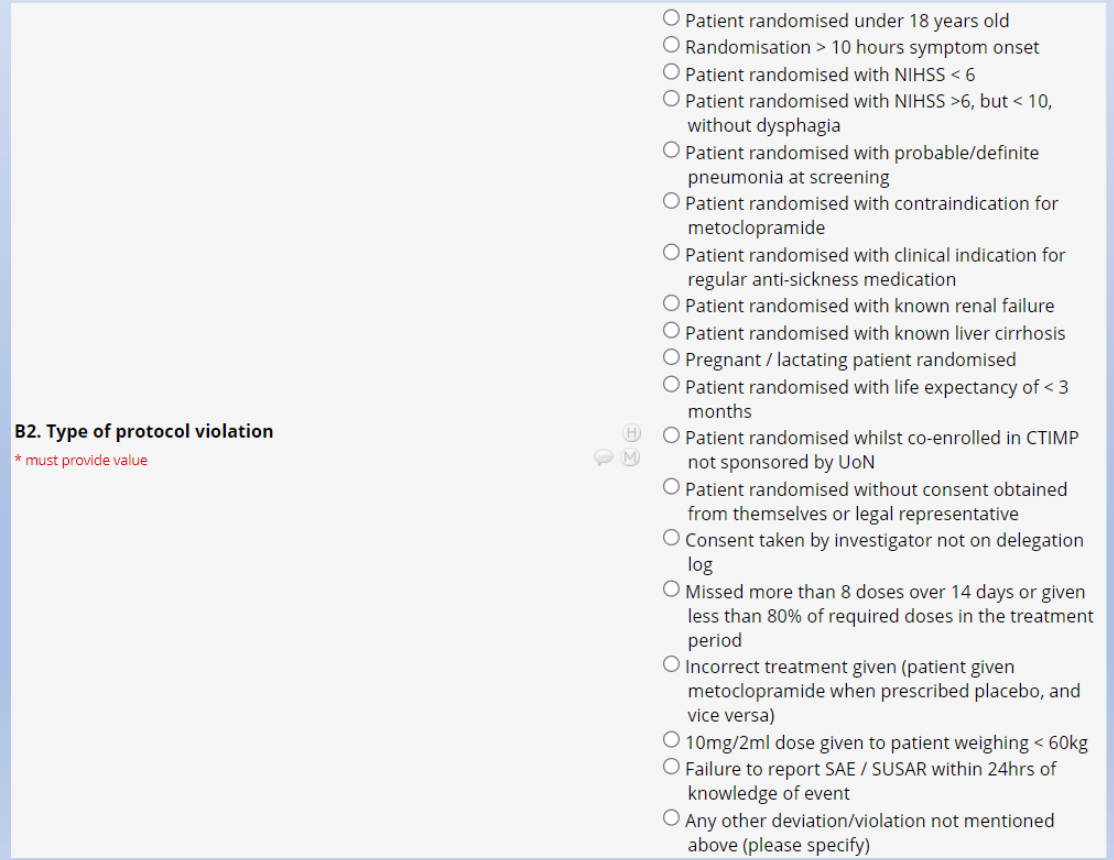
Complete for participants who withdraw

Protocol Violations

- Any protocol violation should be reported to MAPS-2@nottingham.ac.uk and be accompanied by a signed file note.

- Violations should also be entered into the REDCap database:

Other events						
Pneumonia diagnosis	Transfer from the first hospital admitted to to another hospital / repatriation	Discharge to the community	Vital status check/notification of death/withdrawal	Serious Adverse Event	Protocol violation	Withdrawal notification
●	○	○	●	● +	○	○



B2. Type of protocol violation

* must provide value

- Patient randomised under 18 years old
- Randomisation > 10 hours symptom onset
- Patient randomised with NIHSS < 6
- Patient randomised with NIHSS >6, but < 10, without dysphagia
- Patient randomised with probable/definite pneumonia at screening
- Patient randomised with contraindication for metoclopramide
- Patient randomised with clinical indication for regular anti-sickness medication
- Patient randomised with known renal failure
- Patient randomised with known liver cirrhosis
- Pregnant / lactating patient randomised
- Patient randomised with life expectancy of < 3 months
- Patient randomised whilst co-enrolled in CTIMP not sponsored by UoN
- Patient randomised without consent obtained from themselves or legal representative
- Consent taken by investigator not on delegation log
- Missed more than 8 doses over 14 days or given less than 80% of required doses in the treatment period
- Incorrect treatment given (patient given metoclopramide when prescribed placebo, and vice versa)
- 10mg/2ml dose given to patient weighing < 60kg
- Failure to report SAE / SUSAR within 24hrs of knowledge of event
- Any other deviation/violation not mentioned above (please specify)

Investigator Site File (ISF)

- May be physical or electronic (e.g. shared drive or other system):

✓Contacts sheet

✓Trial development documentation

✓MAPS-2 protocol (final & superseded)

✓Regulatory approvals

✓Training log, CVs & GCPs of trial personnel

✓Amendments

✓Signed file notes

✓Approved and localised patient-facing documents (consent forms, PIS, GP letter)

✓Signed clinical trial agreement (CTA)

✓Signed consent forms

✓Signed SAE forms

✓Site monitoring plan

- We are not sending physical binders to sites.

Trial Monitoring

- On-site monitoring visits will **not routinely** be performed → remote only.
- However… if issues are highlighted from remote monitoring, an on-site monitoring visit may be required.
- All sites will be remotely monitored continuously throughout the duration of the trial, including:

✓ Confirmation of informed consent (via *secure vault*);

✓ Monitoring missing data and verifying existing data (via CRFs uploaded to *secure vault* and secure video conference screen sharing, if required);

✓ ISF monitoring;

✓ Patient file monitoring.

Monitoring the ISF

- An Investigator Site File checklist will be sent to sites **in advance** of a monitoring visit. This will include, but not limited to:

1. Training
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

Monitoring the Patient Files

- A patient file checklist will be sent to sites **in advance** of a monitoring visit. This will include, 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

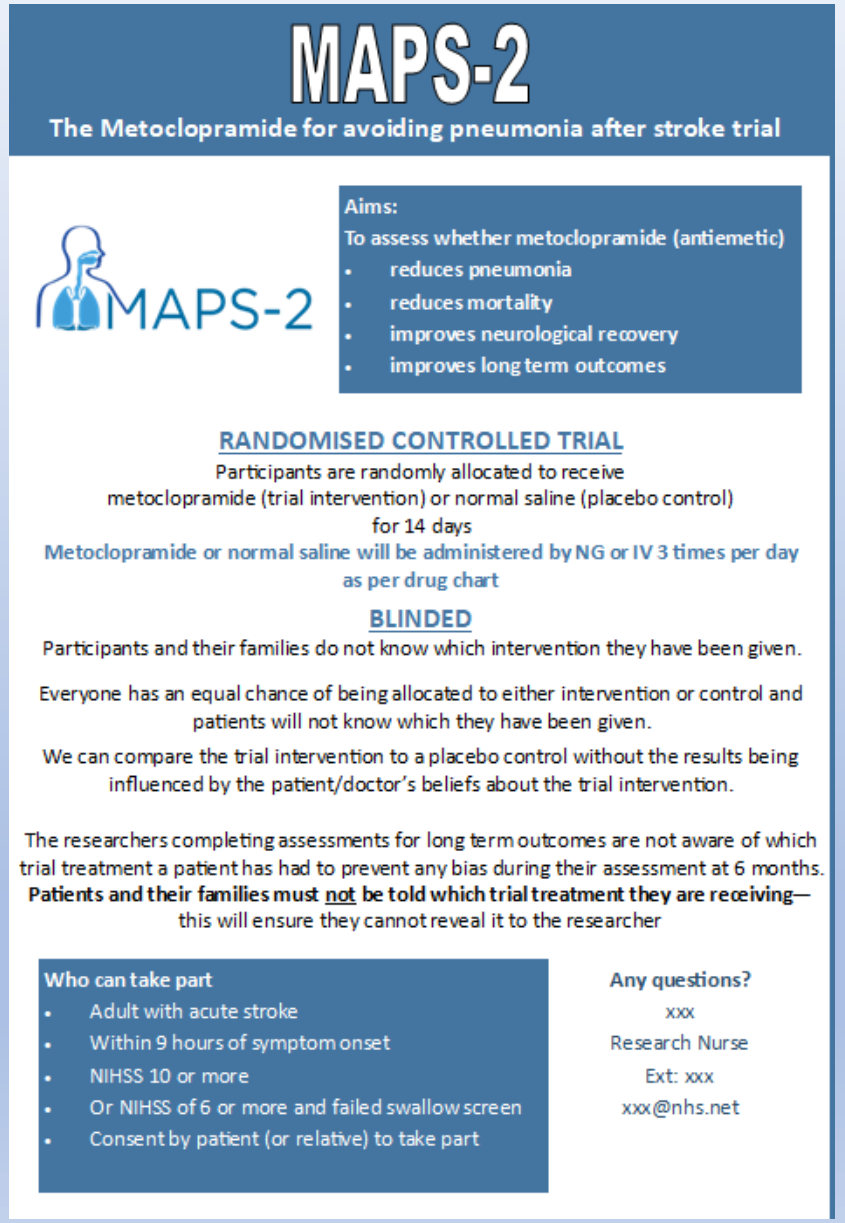
- Ethical approval letters missing from ISF or difficult to locate.
- Incorrect ICF/PIS versions being provided to patients.
- SAEs not signed off by local PI.
- Screening log not kept up to date / not signed off.
- File notes missing which identify where documents are stored outside of the ISF (e.g., CVs and GCP certificates).
- Consent forms should be initialled, not ticked.
- Drug charts should show the participants' **full course** of treatment.
- Daily logs should be uploaded for **all days** during the treatment period.

Co-enrolment

- Participants cannot co-enroll into trials **not** sponsored by the University of Nottingham, e.g.:

✓	✗
TICH-3	ATTEST 2
PhEAST	
RECAST 3	OPTIMAS OPTIMAL TIMING OF ANTICOAGULATION AFTER STROKE

Awareness Poster



- Poster is available to raise awareness of trial amongst hospital staff.
- Should **not** be displayed in areas accessible by patients.
- Should only be displayed in areas restricted to hospital staff (e.g. staff rooms).
- Downloadable from MAPS-2 documents websites.

Green Light Checklist

- ✓Signed training log for all staff.
- ✓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?

Thank you for listening.

Clinical/emergency queries: 07740 372 852

Email: MAPS-2@nottingham.ac.uk

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