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RECAST 3

REMOTE ISCHAEMIC CONDITIONING AFTER STROKE TRIAL 3

RECAST-3: A multicentre randomised controlled trial

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Protocol Version 4.0 (Investigator Training Slides Final V2.2 11/06/2024)

Overview

- Background
- Study design
- Inclusion and exclusion criteria
- Consent process
- Randomisation
- Intervention: Remote Ischaemic Conditioning Device
- RECAST-3 database
- Study flow
- NIHR Associate PI Scheme
- Safety
- Monitoring
- Contacts

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BACKGROUND (1)

Stroke:

- Second leading cause of death worldwide
- Devastating to both patients and carers.
- In the UK, there are 100,000 strokes per year (85% of these ischaemic) which costs society ~£9billion/year[1]
- Reducing stroke severity and recurrence will improve functional dependency and the considerable social and financial burden to patients, carers and society.
- Recent research has failed to demonstrate efficacy of novel drug treatments[2], therefore, new approaches to reduce the burden of stroke on society are required.

Ischaemic Reperfusion Injury (IRI):

- IRI can occur after an ischaemic stroke
- Clinically manifests as early recurrent stroke, symptomatic intracranial haemorrhage, swelling of the original infarct and neurological deterioration, which are common causes of worsening outcomes[3-5]

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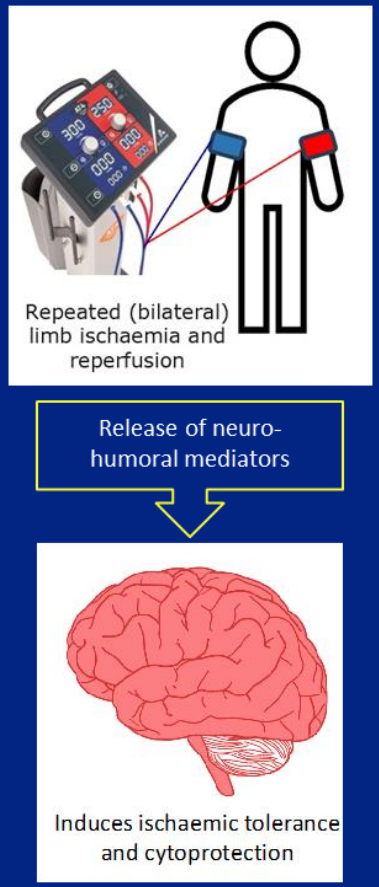
BACKGROUND (2)

Remote Ischaemic Conditioning (RIC):

- Remote ischaemic per-conditioning (RIC) in experimental ischaemic stroke is neuroprotective and may reduce ischaemic reperfusion injury.
- It is simply achieved by repeated transient occlusion of the blood supply to a limb using a blood pressure cuff.
- RIC uses repeated cycles of transient limb ischaemia and reperfusion and helps protect the brain from ischaemic reperfusion injury (IRI) through the release of neuroprotective neuro-humoral chemical messengers from the limb, resulting in immediate (first 2-3 hours) and late (24-72 hours) windows of protection from ongoing and delayed cerebral IRI. [6,7]
- RIC is an attractive strategy since it bears minimal cost, should be safe and would be simple to administer by medics and allied health professionals



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BACKGROUND (3)

- **Pre-clinical evidence:** [8]
  - → Meta-analysis: 54 publications, >1500 animals
  - → RIC reduces infarct size by 35% & improves neurological score.
- **RECAST-1:** [9]
  - → RIC after acute stroke is well tolerated and appears safe and feasible.
  - → RIC may improve neurological outcome and reduce vascular event rates.
- **RECAST-2:** [10]
  - → Verified feasibility of RIC within 6 hours of acute ischaemic stroke.
  - → RIC appears safe and well tolerated **including in those thrombolysed**
  - → Trend to reduction in recurrent cerebral events by day 90 in favour of RIC.
  - → Biochemical signals of efficacy were evidenced by increased plasma biomarkers of brain injury (S100ß) in the placebo group not seen in the RIC group.

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BACKGROUND (4)

Recent RIC findings

- **RICAMIS[1] (n=1776)** Positive trial
  - → Bilateral RIC within 48 hours of ischaemic stroke
  - → No sham (comparator – standard care), excluded rtPA and MT
  - → Treatment with RIC (10-14 days) increased the likelihood of excellent neurological function at day 90 (mRS score of 0-1).

- **RESIST[2] (n=1500)** Neutral trial
  - → Single limb RIC within 4 hours, pre-hospital setting (737 ischaemic, 165 ICH, remainder TIA or mimic)
  - → 80% received 7 days of twice daily treatment (20% 1 day of treatment)
  - → No differences between RIC and sham groups in the primary outcome (shift in mRS)

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STUDY DESIGN & PURPOSE

PURPOSE: To perform a multicentre randomised controlled trial assessing remote ischaemic conditioning (RIC) in patients with acute ischaemic stroke

- Prospective, randomised, sham-controlled, blinded-endpoint, parallel-group multicentre trial of RIC versus control.
- 1,300 patients with acute (within 24 hours) ischaemic stroke
- Randomised 1:1 across 60 UK based NHS Trusts
- Around 21 patients per site across 29 months of recruitment

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HYPOTHESIS

Hypothesis:

- Remote ischaemic perconditioning (RIC) is safe and improves functional outcome in patients presenting with acute stroke

Primary research question

- Does RIC improve functional outcome (ordinal shift in mRS) at day 90 in patients with acute ischaemic stroke?

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SECONDARY RESEARCH QUESTIONS

- Does RIC **reduce early and recurrent cerebrovascular events** by day 90 in patients with acute ischaemic stroke?
- Does RIC impact on other clinical outcomes at 3 months: major adverse cardiac and cerebral events (**MACCE**); acute kidney injury (**AKI**); cognition; mood; frailty; and quality of life?
- Is RIC **safe** when applied in patients with acute stroke?

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INCLUSION CRITERIA

- Acute ischaemic stroke (within 24 hours of onset)
- Spontaneous intracerebral haemorrhage ruled out on baseline clinical neuroimaging; Haemorrhagic transformation of infarction (HTI) HI1, HI2, PH1 is permitted
- NIHSS score 5 - 25
- Age 18 or over

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EXCLUSION CRITERIA

- Pre-morbid dependency (mRS greater than 3)
- Systolic blood pressure less than 80mmHg
- Spontaneous intracranial haemorrhage
- Haemorrhagic transformation of infarction PH2 – (haematoma occupying 30% or more of the infarcted tissue)
- Pre-existing diagnosis of dementia
- Coma (GCS less than 8)
- Malignancy, and significant co-morbidity (life expectancy <6 months)
- Capillary blood glucose <3.0mmol/L
- Seizure on presentation unless brain imaging identifies evidence of significant brain ischaemia
- Significant tissue injury of upper limbs, which in the opinion of the investigator, will be exacerbated by RIC
- Taking part in another interventional trial (unless co-enrolment agreed between CIs and Sponsors)
- Known pregnancy
- Expected repatriation of the participant to another hospital not participating in RECAST-3 where RIC or sham cannot continue.

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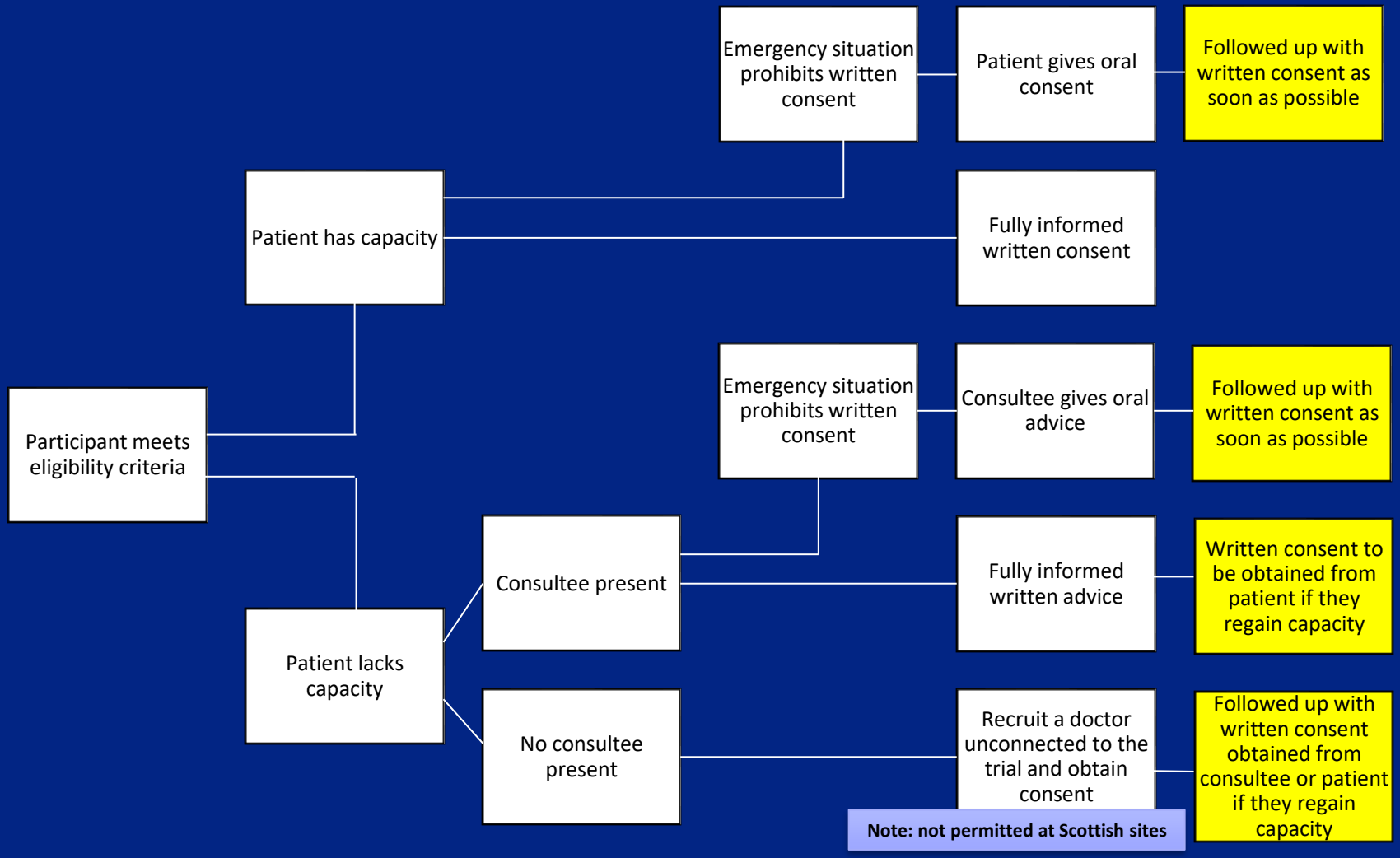
CONSENT FLOW CHART



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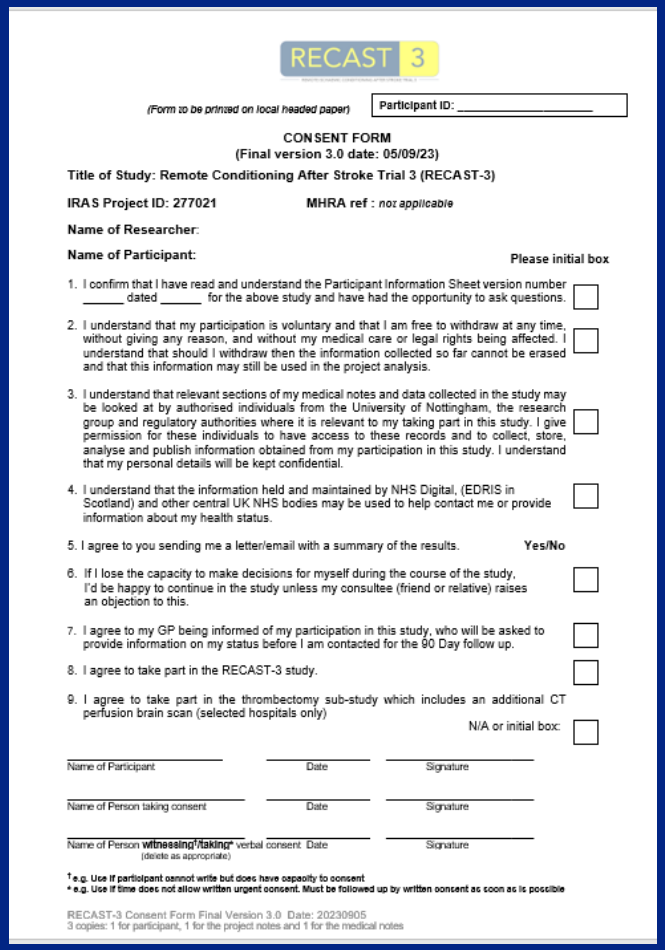
CONSENT FORMS



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(Form to be printed on local headed paper) Participant ID: _____

CONSENT FORM
(Final version 3.0 date: 05/09/23)

Title of Study: Remote Conditioning After Stroke Trial 3 (RECAST-3)

IRAS Project ID: 277021 **MHRA ref :** *not applicable*

Name of Researcher:

Name of Participant: **Please initial box**

1. I confirm that I have read and understand the Participant Information Sheet version number _____ dated _____ for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected. I understand that should I withdraw 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 my medical notes 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 my 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. ☐
4. I understand that the information held and maintained by NHS Digital, (EDRIS in Scotland) and other central UK NHS bodies may be used to help contact me or provide information about my health status. ☐
5. I agree to you sending me a letter/email with a summary of the results. **Yes/No**
6. 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 consultee (friend or relative) raises an objection to this. ☐
7. I agree to my GP being informed of my participation in this study, who will be asked to provide information on my status before I am contacted for the 90 Day follow up. ☐
8. I agree to take part in the RECAST-3 study. ☐
9. I agree to take part in the thrombectomy sub-study which includes an additional CT perfusion brain scan (selected hospitals only) N/A or initial box: ☐

Name of Participant _____ Date _____ Signature _____

Name of Person taking consent _____ Date _____ Signature _____

Name of Person witnessing†/taking* verbal consent (delete as appropriate) _____ Date _____ Signature _____

† e.g. Use if participant cannot write but does have capacity to consent
* e.g. Use if time does not allow written urgent consent. Must be followed up by written consent as soon as is possible

RECAST-3 Consent Form Final Version 3.0 Date: 20230905
3 copies: 1 for participant, 1 for the project notes and 1 for the medical notes

- Local header required
- Record the PIS version and date in section 1
- Ensure that each box is initialed rather than ticked
- Ensure that all fields are complete
- Record the consent process in the medical records
- **3 copies of the consent form – 1 for patient, 1 for medical notes and original to be kept in the site file**

- Please ensure to have some localised copies prepared in advance but ensure that all copies can be retrieved in the event of an amendment

Participant Consent Form

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REMOTE ISCHAEMIC CONDITIONING AFTER STROKE TRIAL 3

INFORMATION SHEETS

Participant Information Sheet

Local Letterhead to be added

Participant Information Sheet
(Final version 3.0: date: 05/09/23)

IRAS Project ID: 277021

Title of Study: Remote Conditioning After Stroke Trial-3 (RECAST-3)

Name of Chief Investigator: Professor Tim England
Local Researcher(s):

Introduction
As part of routine clinical care, research staff check if patients are eligible for research studies. You are eligible to take part in the RECAST-3 study which aims to assess whether Remote Ischaemic Conditioning improves disability at 90 days following your stroke.

We would like to invite you to take part in our research study. Before you decide, we would like you to understand why the research is being done and what it would involve for you. One of our team will go through the information sheet with you and answer any questions you have. Talk to others about the study if you wish. Ask us if there is anything that is not clear.

What is the purpose of the study?
There are very few effective treatments for stroke and we are looking for new ways to treat and help prevent strokes from getting worse or new ones happening. 'Remote Ischaemic Conditioning' (RIC) may be one way of doing this. Evidence from experiments and other conditions suggests that interrupting the blood supply to the arms (for example, by inflating blood pressure cuffs) for brief episodes may help protect the brain from further damage. It is not clear exactly how this may work but it has been suggested that RIC may lead to the body releasing substances into the blood stream (such as 'anti-oxidants') that help protect the brain from injury caused by a stroke.

We would like to see if this intervention is effective in people immediately after they have had a stroke. We want to involve people like you in this multi-centre trial and investigate reasons how RIC might work.

Why have I been invited?
You are being invited to take part because you have had a stroke and we feel that you fit the requirements for this research project. We are inviting 1300 participants like you to take part.

Do I have to take part?
It is up to you to decide whether or not to take part. If you do decide to take part, you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part, you are still free to withdraw at any time and without giving a reason. This would not affect your legal rights.
You cannot take part in the trial if any of the following apply to you:

- Age less than 18
- Dementia
- Participation in another study that involves taking a trial drug, unless co-enrolment in the two trials has been approved

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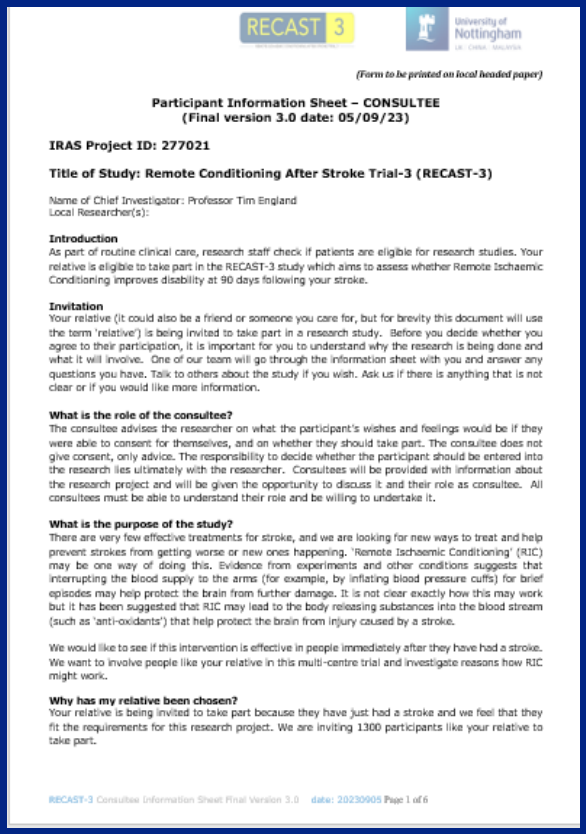
RECAST-3 Participant Information Sheet Final Version 3.0 date: 20230905

Consultee Information Sheet



(Form to be printed on local headed paper)

Participant Information Sheet – CONSULTEE
(Final version 3.0 date: 05/09/23)

IRAS Project ID: 277021

Title of Study: Remote Conditioning After Stroke Trial-3 (RECAST-3)

Name of Chief Investigator: Professor Tim England
Local Researcher(s):

Introduction
As part of routine clinical care, research staff check if patients are eligible for research studies. Your relative is eligible to take part in the RECAST-3 study which aims to assess whether Remote Ischaemic Conditioning improves disability at 90 days following your stroke.

Invitation
Your relative (it could also be a friend or someone you care for, but for brevity this document will use the term 'relative') is being invited to take part in a research study. Before you decide whether you agree to their participation, it is important for you to understand why the research is being done and what it will involve. One of our team will go through the information sheet with you and answer any questions you have. Talk to others about the study if you wish. Ask us if there is anything that is not clear or if you would like more information.

What is the role of the consultee?
The consultee advises the researcher on what the participant's wishes and feelings would be if they were able to consent for themselves, and on whether they should take part. The consultee does not give consent, only advice. The responsibility to decide whether the participant should be entered into the research lies ultimately with the researcher. Consultees will be provided with information about the research project and will be given the opportunity to discuss it and their role as consultee. All consultees must be able to understand their role and be willing to undertake it.

What is the purpose of the study?
There are very few effective treatments for stroke, and we are looking for new ways to treat and help prevent strokes from getting worse or new ones happening. 'Remote Ischaemic Conditioning' (RIC) may be one way of doing this. Evidence from experiments and other conditions suggests that interrupting the blood supply to the arms (for example, by inflating blood pressure cuffs) for brief episodes may help protect the brain from further damage. It is not clear exactly how this may work but it has been suggested that RIC may lead to the body releasing substances into the blood stream (such as 'anti-oxidants') that help protect the brain from injury caused by a stroke.

We would like to see if this intervention is effective in people immediately after they have had a stroke. We want to involve people like your relative in this multi-centre trial and investigate reasons how RIC might work.

Why has my relative been chosen?
Your relative is being invited to take part because they have just had a stroke and we feel that they fit the requirements for this research project. We are inviting 1300 participants like your relative to take part.

RECAST-3 Consultee Information Sheet Final Version 3.0 date: 20230905 Page 1 of 6

Patient Re-Consent

Local Letterhead to be added

Participant Information Sheet (re-consent)
(Final version 3.0 date: 05/09/23)

IRAS Project ID. 277021

Title of Study: Remote Conditioning After Stroke Trial-3 (RECAST-3)

Name of Chief Investigator: Professor Tim England
Local Researcher(s):

Introduction
As part of routine clinical care, research staff check if patients are eligible for research studies. You were eligible to take part in the RECAST-3 study which aims to assess whether Remote Ischaemic Conditioning improves disability at 90 days following your stroke.

You have been taking part in a research study assessing new treatments for stroke. Your relative or consultee advised us that in their opinion you would have wanted to take part when you were unwell, soon after your stroke started. Before you decide if you want to continue, it is important for you to understand why the research is being done and what it involves. Please take time to read the following information carefully. Talk to others about the study if you wish. Ask us if there is anything that is not clear to you, or if you would like more information. Take time to decide whether or not you wish to continue to take part.

What is the purpose of the study?
There are very few effective treatments for stroke, and we are looking for new ways to treat and help prevent strokes from getting worse or new ones happening. 'Remote Ischaemic Conditioning' (RIC) may be one way of doing this. Evidence from experiments and other conditions suggests that interrupting the blood supply to the arms (for example, by inflating blood pressure cuffs) for brief episodes may help protect the brain from further damage. It is not clear exactly how this may work but it has been suggested that RIC may lead to the body releasing substances into the blood stream (such as 'anti-oxidants') that help protect the brain.

We would like to see if this intervention is effective in people immediately after they have had a stroke. We want to involve people like you in this multi-centre trial and investigate reasons how RIC might work.

Why have I been invited?
You have been chosen because you have had a stroke, and we feel that you fit the requirements for this research project. It is up to you to decide whether or not to continue to take part. If you do decide to continue to take part, you will be given this information sheet to keep and be asked to sign a consent form. We are inviting 1300 participants like you to take part.

You cannot take part in the trial if any of the following apply to you:

- Age less than 18
- Dementia
- Participation in another study that involves taking a trial drug, unless co-enrolment in the two trials has been approved

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RECAST-3 Participant Information Sheet Re-Consent Final Version 3.0 date: 20230905

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TELEPHONE CONSENT RECORD

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(Form to be printed on local headed paper)

Participant ID: _____

TELEPHONE CONSENT RECORD
(Final version 2.0: date 05/09/23)

Title of Study: Remote Conditioning After Stroke Trial 3 (RECAST-3)

IRAS Project ID: 277021 (England, Wales & NI), 282606 (Scotland)

Principle Investigator: _____

Site Name: _____ Site Number: _____

Patient name: _____

DOB: __/__/____

Date and time of phone call/verbal consent: __/__/____ (Date) __:__ (Time)

Consent obtained from:
- ☐ Personal Consultee (England, Wales & NI)
- ☐ Personal Legal Representative (Scotland)

Name of consultee / representative: _____

Contact number: _____

Was verbal consent obtained for the patient to participate in RECAST-3? ☐ Yes ☐ No

Name of person obtaining verbal consent: _____

Signature: _____

Name/role of person witnessing phone call (if applicable): _____

Signature: _____ ☐ Not Applicable

PLEASE COMPLETE IF VERBAL CONSENT IS OBTAINED:

Has the relevant information sheet and consent form been sent to the Consultee / Representative? ☐ By post ☐ By Email

Email address / Postal address: _____

_____

_____

Version no. of Information Sheet: V____ Date: __/__/____

Version no. of Consent Form: V____ Date: __/__/____

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PLEASE COMPLETE ONCE THE SIGNED CONSENT FORM IS RETURNED:

Has the consent form been returned and signed by the above-named Consultee / Representative? ☐ Yes ☐ No

Date received: __/__/____

Has the consent form been counter-signed by the person who obtained the verbal consent? ☐ Yes ☐ No

Date counter-signed: __/__/____

Date copy of the fully signed consent form was sent back to the Consultee / Representative: __/__/____

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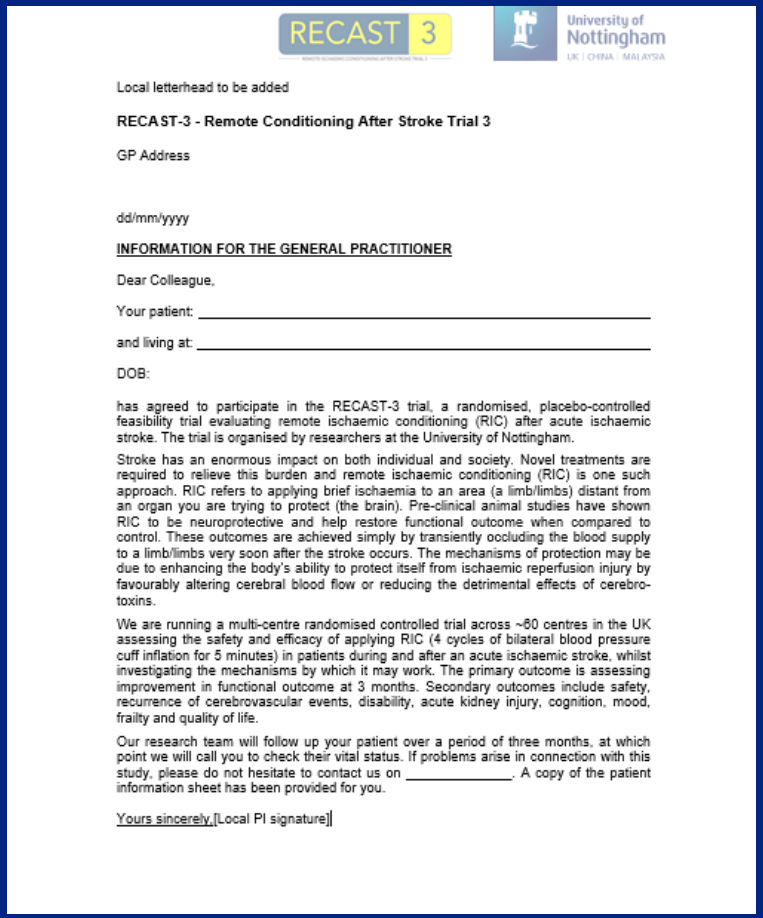
GP LETTER



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Local letterhead to be added

RECAST-3 - Remote Conditioning After Stroke Trial 3

GP Address

dd/mm/yyyy

INFORMATION FOR THE GENERAL PRACTITIONER

Dear Colleague,

Your patient: _____

and living at: _____

DOB:

has agreed to participate in the RECAST-3 trial, a randomised, placebo-controlled feasibility trial evaluating remote ischaemic conditioning (RIC) after acute ischaemic stroke. The trial is organised by researchers at the University of Nottingham.

Stroke has an enormous impact on both individual and society. Novel treatments are required to relieve this burden and remote ischaemic conditioning (RIC) is one such approach. RIC refers to applying brief ischaemia to an area (a limb/limbs) distant from an organ you are trying to protect (the brain). Pre-clinical animal studies have shown RIC to be neuroprotective and help restore functional outcome when compared to control. These outcomes are achieved simply by transiently occluding the blood supply to a limb/limbs very soon after the stroke occurs. The mechanisms of protection may be due to enhancing the body's ability to protect itself from ischaemic reperfusion injury by favourably altering cerebral blood flow or reducing the detrimental effects of cerebro-toxins.

We are running a multi-centre randomised controlled trial across ~60 centres in the UK assessing the safety and efficacy of applying RIC (4 cycles of bilateral blood pressure cuff inflation for 5 minutes) in patients during and after an acute ischaemic stroke, whilst investigating the mechanisms by which it may work. The primary outcome is assessing improvement in functional outcome at 3 months. Secondary outcomes include safety, recurrence of cerebrovascular events, disability, acute kidney injury, cognition, mood, frailty and quality of life.

Our research team will follow up your patient over a period of three months, at which point we will call you to check their vital status. If problems arise in connection with this study, please do not hesitate to contact us on _____. A copy of the patient information sheet has been provided for you.

Yours sincerely,[Local PI signature]

- Always send a letter to the participant's general practitioner
- Local header required
- Send with a copy of the participant information sheet
- File a copy in the ISF and in the patient's medical notes
- Anonyomised/unanomymised documentation should be kept separate
- Please keep GP letter, consent form(s) and patient details together in the ISF

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RECAST-3 DELEGATION LOG/DATABASE

https://stroke.nottingham.ac.uk/recast-3/live/recast-3_login.php

- Sign off by the PI via the electronic delegation log will allow access to the trial database
- Request access by emailing recast-3@nottingham.ac.uk along with:

→ Signed CV and GCP (both within last 2 years)

→ Signed training log (either live training or self-directed)

- Account details and PIN will then be sent via email
- Staff member will need to accept invitation to participate, which will send a notification to PI
- PI will need to log in and sign off each staff member, which adds the staff member to the online delegation log and database access is granted.
- **Investigators may only work on the trial once signed off on the delegation log**

Log ID	Investigator name/ID	Certificate/ date assessed or trained	Number of correct answers/score	Roles and responsibilities*	Delegation log status
13	[redacted]	P6Y3N6 3 Jun 2021	- -	Site investigator BFHIJKLNOPQRSTY	9 Aug 2021 12:10 **Authorised** [redacted]
14	[redacted]	Y3K6X6 3 Jun 2021	- -	Site investigator BFHIJKLNOPQRSTY	9 Aug 2021 12:10 **Authorised** [redacted]

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DEMO DATABASE

- The demonstration database is available to be used by site investigators to get an understanding of the database functions and CRF completion, meaning that any potential queries can be resolved prior to opening.
- Log in using the credentials below, which can be found via the RECAST-3 website (http://recast-3.ac.uk/).

Demonstration database

For practice, please go to
http://recast-3.ac.uk/demo/
and use the following credentials.

User	demoinv1
Password	nottingham
PIN	8888

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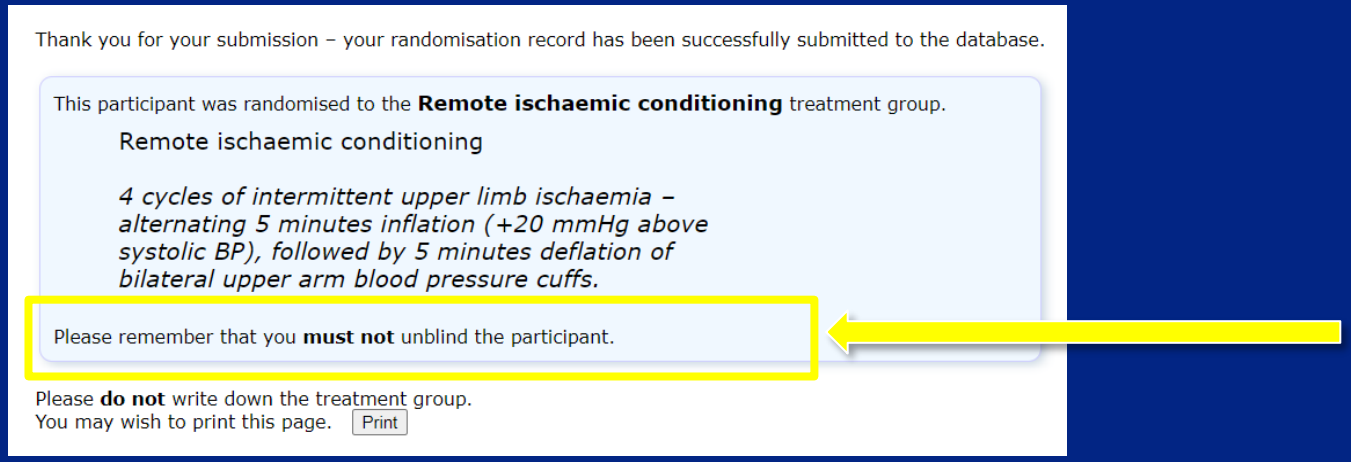
ONLINE RANDOMISATION PROCESS

- DAY 1: Patients will be randomised (1:1 to receive either RIC or sham)
- Randomisation will be performed locally using the trial's secure internet site
- Log into the RECAST-3 online database (https://stroke.nottingham.ac.uk/recast-3/live/recast-3_login.php)
- Click to randomise new patient
- Confirm the patient's eligibility and complete the randomisation form
- Once the form has been submitted, the database will display the allocated treatment



- An email will be sent to site staff as confirmation

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Please see WPD 007 Manual Randomisation for further detail

EMERGENCY RANDOMISATION PROCEDURES

1. **Randomisation performed by the coordinating centre**
   The site investigator is unable to reach the RECAST-3 database from their location, but the RECAST-3 database itself is working. → **The coordinating centre will randomise patient on behalf of the site**

2. **Manual randomisation**
   The RECAST-3 database is unavailable, which means that no one (including the team at the co-ordinating centre) can perform any online data entry at all. Manual randomisation means that a person chooses whether the active RIC or sham device is used, without the use of computerised randomisation. → **The coordinating centre will perform manual randomisation and input the data when once database is working**

As soon as the site discovers that they are unable to use the RECAST-3 database to randomise their eligible patient, they should contact the coordinating centre (0115 823 1770).

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INTERVENTION

- **Active**: RIC group
  - 4 cycles of intermittent upper limb ischaemia - alternating 5 minutes inflation (20mmHg above the systolic BP) followed by 5 minutes deflation of bilateral upper arm blood pressure cuffs.
- **Control**: Sham RIC
  - Blood pressure cuff inflated to 50 mmHg for 4 cycles of inflation and deflation
- **Duration**
  - First 'dose' (4 cycles) within ≤24 hours of onset.
  - Second dose 4 hours after the first dose.
  - Twice a day (once in the morning, once in the afternoon) for 14 days
  - Total 28 doses over 14 days

Heart rate and blood pressure readings should be recorded immediately before each dose

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INTERVENTION

- **Additional Notes:**
  - Since the AneticAid device pressures increase in 5 mmHg increments, RIC treatment cuffs should be inflated to at least 20 mmHg above systolic BP, to the nearest 5 mmHg. For example, if systolic BP is 140 mmHg, the target is 160 mmHg; if systolic BP is 141-145mmHg, the target is 165mmHg.
  - Some centres will be unable to administer RIC over a weekend due to absence of trained staff. In these cases we accept RIC/sham may be omitted over the weekend so long as they have already received a minimum of 48 hours of RIC/sham (i.e. 4 x 4 cycles).
  - A minimum of 4 hours is required between twice daily dosing. If randomisation occurs late on day 1, not allowing a second dose on day 1, then dose 2 occurs on day 2.
  - If a participant omits dosing due to a weekend, the total number of RIC doses should remain 28. For example, if 4 days (8 doses) are omitted over 2 weekends, then total treatment time may be over 18 days.
  - If a participant is due to be discharged or transferred to another facility that cannot deliver the trial treatment (i.e. not a RECAST-3 participating site) prior to the full treatment course being completed, RIC/sham is discontinued.
  - If a dose is omitted due to treatment intolerance, there is no need to extend the treatment period but further doses at the usual timepoints will be offered.

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INTERVENTION

- **Additional notes:**
  - As long as patients meet all eligibility criteria, they can be recruited to the trial and the intervention should be delivered for as long as possible, up to a maximum of 14 days (28 doses).
  - Sites that routinely discharge patients to a rehabilitation centre within the 14 days post stroke can join the trial and should aim to deliver the intervention to participants for as long as possible (up to a maximum of 14 days/28 doses) before they are moved.
  - Patients that have an NIHSS score towards the lower end of the 5-25 inclusion range should still be approached to take part in the trial if all other eligibility criteria are met. Again, the intervention should be delivered for as long as possible up to 14 days/28 doses maximum.
  - For the following exclusion criteria: 'expected repatriation of the participant to another hospital not participating in RECAST-3 where RIC or sham cannot continue', this will be applicable when it is known that a patient will be repatriated early on, for example in comprehensive centres that receive out of region patients who are due to be moved within ~72 hours.
  - A patient admitted to a hospital outside of their locality (for example when they are on holiday) can still be recruited unless it is known that they are planned for repatriation to their local hospital within ~72 hours.

RECAST 3

REMOTE ISCHAEMIC CONDITIONING AFTER STROKE TRIAL 3

Please see the Product Training document for further detail

RIC & SHAM DEVICE

- Anetic Aid Ltd. will supply one AT4 Electronic Tourniquet to each participating site.
- The same device will be used to deliver both RIC and sham protocols.
- When not in use, the devices should be held in a secure location, connected to the mains.
- Devices should be cleaned after each use.
- Those treating the participant will be unblinded, but efforts should be made to ensure as little staff as possible are unblinded to ensure the patient, family and the day 90 outcome assessor remain blinded.

1. Control Panel
2. Cuff Supply Hose Storage Connectors
3. Cuff Supply Hose Connectors
4. Cuff Supply Hose
5. Pulling Handle
6. Cuff Hooks
7. Storage Facility
8. Additional Storage Facility Locating Pins
9. IEC Socket

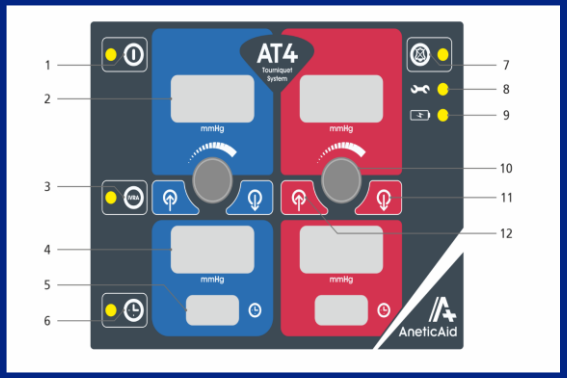
RECAST 3

REMOTE ISCHAEMIC CONDITIONING AFTER STROKE TRIAL 3

Please see the Product Training document for further detail

OPERATING THE DEVICE

1. Equipment check: The battery indicator should be green (if not it must be connected to mains supply). Connect the red and blue cuff hoses to the front panel. Ensure you have a standalone timer ready.
2. Participant check: Inspect the participant's arms and skin condition and make a note of any skin changes or damage. Check the participant's blood pressure (twice). Record values on the **Treatment log**
3. Switch the AT4 on: Press the ON button. The LED will be lit green.
4. Cuff attachment: Apply appropriately sized cuffs to the participant's upper arms. At the end of the cuff supply hoses (attached in step 1), depress the metal connector clip before fully inserting the tourniquet cuff connector.
5. Pressure selection: Rotate the control on both channels clockwise to increase and anticlockwise to decrease (RIC +20 mmHg above systolic BP, sham 50 mmHg)
6. Cuff inflation: Depress the inflate buttons on both channels in turn. The applied pressure will be displayed. Cuffs remain inflated for 5 minutes.
7. Cuff deflation: Depress the deflate buttons on both channels in turn (single push = slow deflation, second push = fast deflation). The screen will flash during deflation. Cuffs remain deflated for 5 minutes prior to reinflation (until the 4th cycle has been completed).
8. Treatment log: Record all cycle details
9. Switch the AT4 off: When the intervention is finished, press the OFF button.

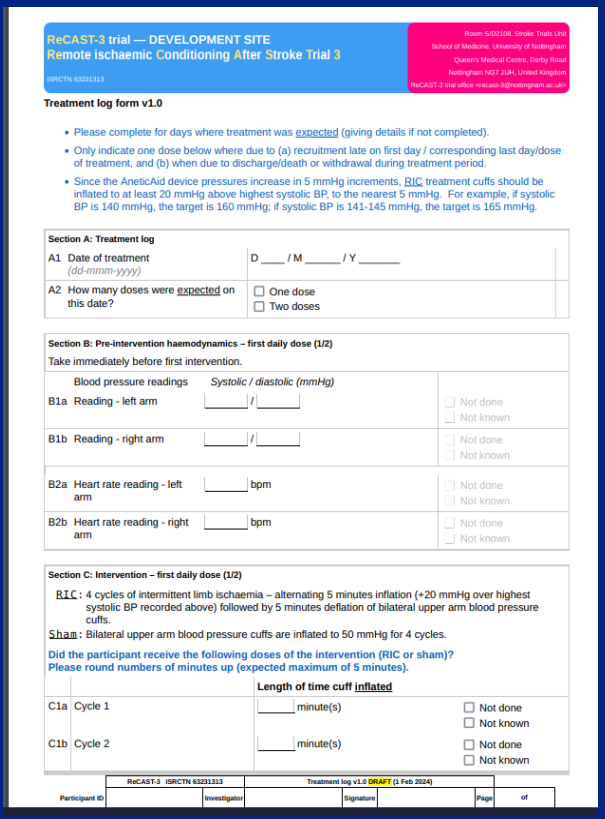


1. ON/OFF
2. Set Pressure display
3. IVRA (Intravenous Regional Anaesthesia) **Not applicable for RECAST-3**
4. Applied Pressure Display
5. Elapsed Time H:MM
6. Reminder control **Not applicable for RECAST-3**
7. Audible alarm, pause and indicator
8. Maintenance indicator
9. Battery level indicator
10. Pressure controller
11. Deflate button
12. Inflate button

RECAST 3

REMOTE ISCHAEMIC CONDITIONING AFTER STROKE TRIAL 3

TREATMENT LOG



ReCAST-3 trial — DEVELOPMENT SITE
Remote ischaemic Conditioning After Stroke Trial 3

ISRCTN 63231313

Room SJD2108, Stroke Trials Unit
School of Medicine, University of Nottingham
Queen's Medical Centre, Derby Road
Nottingham NG7 2UH, United Kingdom
ReCAST-3 trial office <recast-3@nottingham.ac.uk>

Treatment log form v1.0

- Please complete for days where treatment was expected (giving details if not completed).
- Only indicate one dose below where due to (a) recruitment late on first day / corresponding last day/dose of treatment, and (b) when due to discharge/death or withdrawal during treatment period.
- Since the AneticAid device pressures increase in 5 mmHg increments, RIC treatment cuffs should be inflated to at least 20 mmHg above highest systolic BP, to the nearest 5 mmHg. For example, if systolic BP is 140 mmHg, the target is 160 mmHg; if systolic BP is 141-145 mmHg, the target is 165 mmHg.

Section A: Treatment log

A1	Date of treatment *(dd-mmm-yyyy)*	D ___ / M _____ / Y _____
A2	How many doses were expected on this date?	☐ One dose ☐ Two doses

Section B: Pre-intervention haemodynamics – first daily dose (1/2)

Take immediately before first intervention.

	Blood pressure readings	*Systolic / diastolic (mmHg)*	
B1a	Reading - left arm	_____ / _____	☐ Not done ☐ Not known
B1b	Reading - right arm	_____ / _____	☐ Not done ☐ Not known
B2a	Heart rate reading - left arm	_____ bpm	☐ Not done ☐ Not known
B2b	Heart rate reading - right arm	_____ bpm	☐ Not done ☐ Not known

Section C: Intervention – first daily dose (1/2)

RIC: 4 cycles of intermittent limb ischaemia – alternating 5 minutes inflation (+20 mmHg over highest systolic BP recorded above) followed by 5 minutes deflation of bilateral upper arm blood pressure cuffs.

Sham: Bilateral upper arm blood pressure cuffs are inflated to 50 mmHg for 4 cycles.

Did the participant receive the following doses of the intervention (RIC or sham)?
Please round numbers of minutes up (expected maximum of 5 minutes).

		Length of time cuff inflated	
C1a	Cycle 1	_____ minute(s)	☐ Not done ☐ Not known
C1b	Cycle 2	_____ minute(s)	☐ Not done ☐ Not known
C1c	Cycle 3	_____ minute(s)	☐ Not done ☐ Not known
C1d	Cycle 4	_____ minute(s)	☐ Not done ☐ Not known
C2	Which arm was used to deliver the intervention?	☐ Left ☐ Right ☐ Both	☐ Not applicable ☐ Not known
C3	How was the intervention given?	☐ Automated trial device ☐ Manual BP cuff ☐ Both	☐ Not applicable ☐ Not known
C4a	Date/time intervention started *(dd-mmm-yyyy hh:mm 24hr)*	D ___ / M _____ / Y _____ H _____ : M _____	☐ Not applicable ☐ Not known
C4b	Date/time intervention ended *(dd-mmm-yyyy hh:mm 24hr)* *This is when the last cuff deflation has ended*	D ___ / M _____ / Y _____ H _____ : M _____	☐ Not applicable ☐ Not known

Do not unblind the participant

C5a	If cycles not completed, please indicate reason	☐ Participant did not tolerate cuff pressure ☐ Participant refused the intervention ☐ Adverse event from the intervention (complete SAE form) ☐ Participant medically unwell (please check if SAE) ☐ Recruited late on first day ☐ Final dose already recorded ☐ Participant discharged or died ☐ Other	☐ Not applicable ☐ Not known
C5b	If cycles not completed, please give details		☐ Not applicable
C6a	Please indicate any other deviation from the intended intervention – e.g. interruptions, delayed start	☐ Interrupted - participant factors, e.g. sick, needed toilet ☐ Device failure ☐ Device not available and treatment delivered manually ☐ Other	☐ Not applicable
C6b	If such a deviation occurred, please give details		☐ Not applicable

At least 4 hours should elapse from the end of the first dose until the second dose begins.

ReCAST-3 ISRCTN 63231313		Treatment log v1.0 DRAFT (1 Feb 2024)				
Participant ID		Investigator		Signature		Page of

- Please complete a separate Treatment log for each day when the treatment was expected
- Keep original in the site file
- File a copy in the patient's medical notes
- Enter the data onto the Training log eCRF
- On the RECAST-3 database

RECAST 3

REMOTE ISCHAEMIC CONDITIONING AFTER STROKE TRIAL 3

WARD STAFF TRAINING

- Training for ward staff who have the capacity to assist with the trial
- Training will consist of a shortened GCP slide set and device training, which must be completed before the intervention is delivered to any trial patients
- This would allow ward staff to **deliver the intervention** when research staff are not available i.e. over the weekend/out of hours, meaning patients could be recruited later in the afternoon or on a Friday, who might otherwise be missed
- Staff will need to complete the training and sign the ward staff training log
- Staff will need to be added to a paper delegation log, assigned codes **B, O** and **Q** and signed off by the PI

RECAST 3

REMOTE ISCHAEMIC CONDITIONING AFTER STROKE TRIAL 3

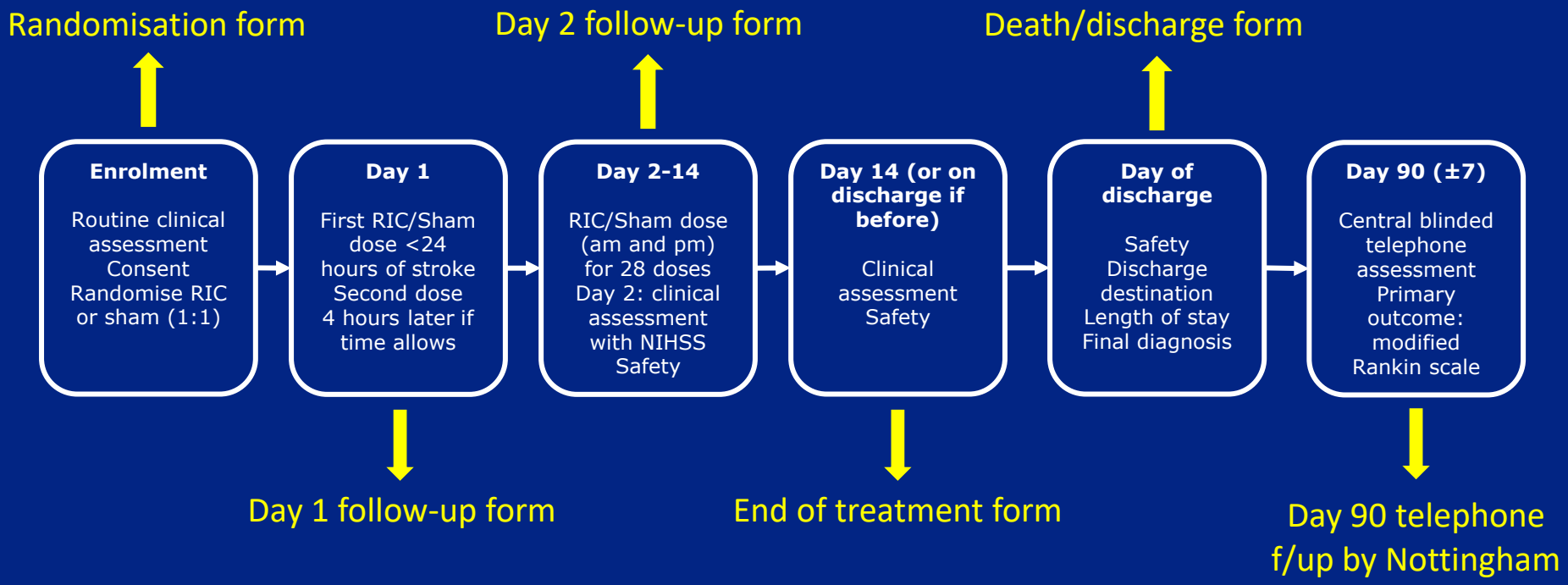
WARD STAFF TRAINING

Ward staff will be permitted to deliver the intervention only, they should not consent or randomise patients

RECAST 3

REMOTE ISCHAEMIC CONDITIONING AFTER STROKE TRIAL 3

STUDY FLOW



SCANS:

- Baseline CT scan prior to enrolment

RECAST 3

REMOTE ISCHAEMIC CONDITIONING AFTER STROKE TRIAL 3

REPATRIATION

- Please record all site-to-site transfers between RECAST-3 centres up to day 90 by completing the site-to-site transfer CRF.
- This must be to an existing RECAST-3 site. Please contact us to query whether the hospital the patient is moving to is a RECAST-3 site.
- If the patient is being transferred to a non-RECAST-3 site, the discharge form should be completed with details of where the patient has been transferred to.
- Please let us know if a patient is transferring to a non-RECAST-3 site before completing all 28 doses and before all data entry is complete.

RECAST 3

REMOTE ISCHAEMIC CONDITIONING AFTER STROKE TRIAL 3

PARTICIPANT FOLLOW-UP DAY 90

- The coordinating centre follow-up coordinator will conduct the day 90 telephone follow-up
- Please ensure that the following information is uploaded to the secure vault:
  - Participant trial number
  - Name
  - Home address
  - Telephone number
  - NHS number
  - GP name and surgery address
  - NOK contact details
- If you have become aware that the patient's contact details have changed, please inform the trial coordinating centre
- **Note:** if the participant cannot be contacted or located, the site research staff will be requested to check the hospital system for changes in address or details

RECAST 3

REMOTE ISCHAEMIC CONDITIONING AFTER STROKE TRIAL 3

NIHR ASSOCIATE PI SCHEME

NIHR | National Institute for Health Research

- The scheme is open to any healthcare professional willing to make a significant contribution to the conduct and delivery of a study at a local level over a period of at least six months
- The local PI acts as a mentor to the Associate PI, helping them to understand what it means to be a local PI on an NIHR portfolio study
- During their time on the Associate PI Scheme, the Associate PI must complete a checklist of study activities and a learning pathway on NIHR Learn. This checklist needs to be signed off by the Local PI and the National Study Coordinator at the end of an Associate PI's time on the scheme
- The NIHR Associate PI Scheme team will then issue a certificate confirming Associate PI Status which can be added to their training portfolio
- Find out more here: https://www.nihr.ac.uk/health-and-care-professionals/career-development/associate-principal-investigator-scheme.htm

RECAST 3

REMOTE ISCHAEMIC CONDITIONING AFTER STROKE TRIAL 3

SAFETY REPORTING (1)

An adverse event (AE) is any unfavourable and unintended sign, symptom, syndrome or illness that develops or worsens during the period of observation in the study. Including:

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

An **Adverse Device Effect (ADE)** is any untoward and unintended response to a medical device and includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment, the installation, the operation, or any malfunction of the investigational medical device

Includes any event that is a result of a user error or intentional abnormal use of the investigational medical device

RECAST 3

REMOTE ISCHAEMIC CONDITIONING AFTER STROKE TRIAL 3

SAFETY REPORTING (2)

Serious Adverse Event (SAE) is any adverse event occurring following study mandated procedures, having received the intervention that results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalisation or prolongation of existing hospitalisation
- A disability / incapacity
- A congenital anomaly in the offspring of a participant
- Important medical events that may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes above.

Serious Adverse Device Effect (SADE) is an adverse device effect that resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune. Note that this definition captures “near misses” as well as actual incidents. Further categorised into either of the below:

→ **Unanticipated, serious adverse device effect (USADE)** is a serious adverse device effect which by its nature, severity or outcome has not been identified in the current version of the risk analysis report

→ **Anticipated, serious adverse device effect (ASADE)** has been identified in the current version of the risk analysis report

RECAST 3

REMOTE ISCHAEMIC CONDITIONING AFTER STROKE TRIAL 3

SAFETY REPORTING (3)

- **All SAEs/SADEs/USADEs/ASADEs during the RIC/Sham period (up to 20 days post randomisation) will be collected**
- SAEs after the RIC/Sham treatment period will not be collected; thereafter, only fatal SAEs and outcomes will be recorded and blindly adjudicated.
- Discuss with clinicians and PI
- All SAEs/SADEs/USADEs/ASADEs are reported electronically on the website
- Participants will be asked to contact the study site immediately in the event of any SAEs/SADEs/USADEs/ASADEs
- Sites must report SAEs/SADEs/USADEs/ASADEs to the coordinating centre within 24 hours upon knowledge of the event
- Must be signed off by the PI
- The Chief Investigator shall determine seriousness and relationship in conjunction with any treating medical practitioners.
- Sites should record and monitor all SAEs/SADEs until resolution, stabilisation or until the AE has been found to **not** be caused by study treatment

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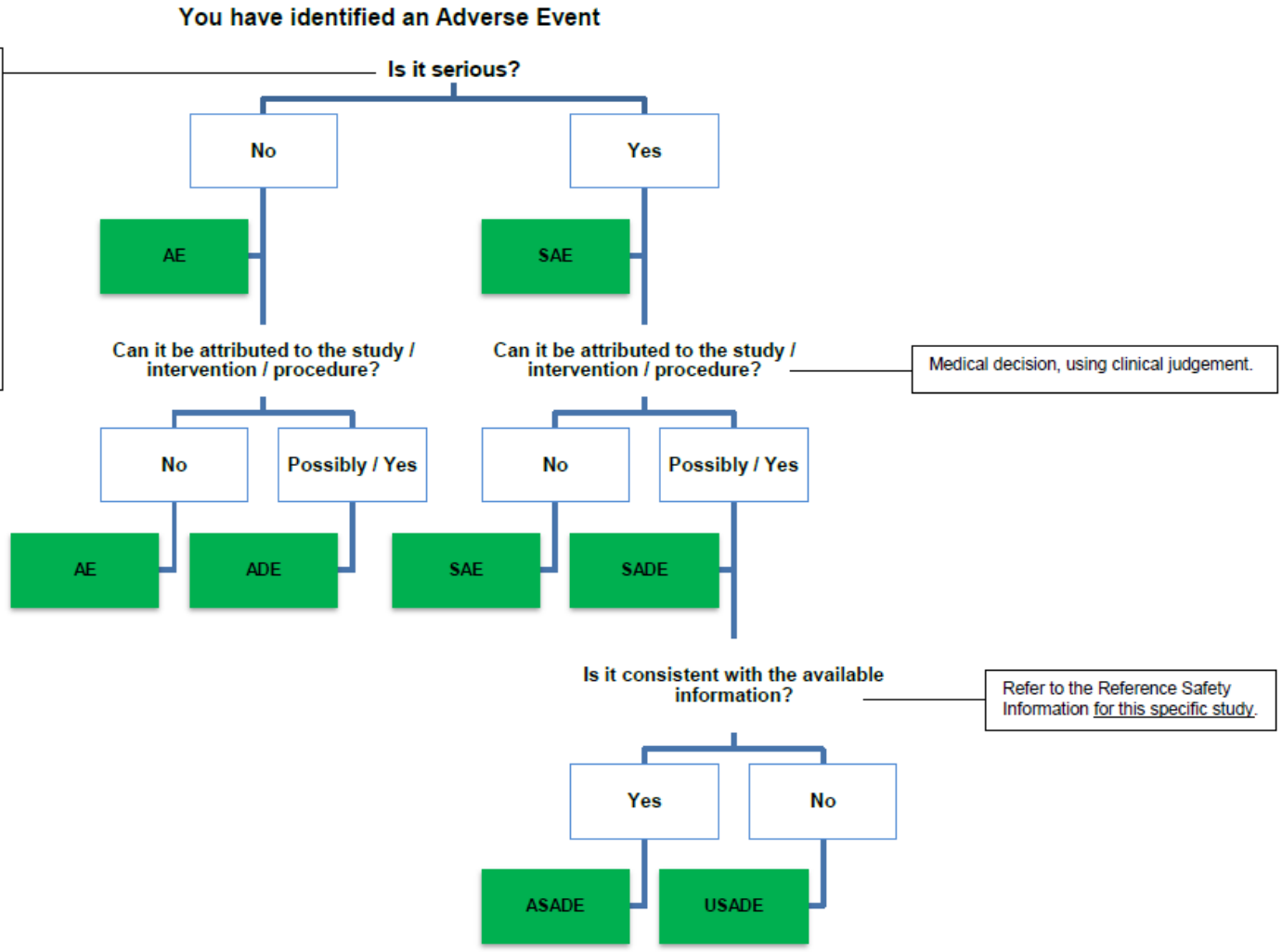
Decision Tree for Adverse Event Reporting – MEDICAL DEVICES

A **Serious** Adverse Event (SAE) is any adverse event that:

- results in death
- is a life-threatening situation
- requires hospitalisation or prolongation of hospitalisation
- results in persistent or significant disability or incapacity
- consists of a congenital abnormality or birth defect

Check the definition of **Serious** in each Protocol



Medical Device Acronyms

AE	Adverse Event
ADE	Adverse Device Effect
SAE	Serious Adverse Event
ASADE	Anticipated Serious Adverse Device Effect
ASADE	Unanticipated Serious Adverse Device Effect

RECAST 3

REMOTE ISCHAEMIC CONDITIONING AFTER STROKE TRIAL 3

SAFETY OUTCOMES

- **The following events are considered as safety or secondary end points:**

- **Major adverse cardiac and cerebral events (MACCE):**

→ Recurrent ischaemic stroke
→ Symptomatic Intracranial haemorrhage
→ Symptomatic swelling of the original infarct
→ Extension of ischaemic stroke
→ Neurological deterioration (increase in NIHSS score by 4 points or more)
→ Systemic embolism
→ Neurovascular limb compromise
→ Myocardial infarction
→ Acute Kidney Injury

Report safety outcomes **(up to Day 90)** by completing the SAE eCRF. For definitions, refer to the RECAST-3 protocol (Appendix B: Outcome event definitions)

RECAST 3

REMOTE ISCHAEMIC CONDITIONING AFTER STROKE TRIAL 3

PROTOCOL VIOLATIONS

- **Major** deviation from the trial protocol where a participant is enrolled in spite of **not fulfilling all the inclusion and exclusion criteria**, or where deviations from the protocol could affect the **trial delivery** or **interpretation** significantly.

Examples:

- Failure to obtain appropriate consent prior to randomisation
- Randomising/treating a patient who does not meet inclusion criteria
- Patient not receiving the randomised treatment
- Failure to complete SAEs where appropriate

- Complete the protocol violation CRF on the RECAST-3 database.
- The CI will review the protocol violation and will advise on the appropriate measures to address the violation.
- Violations are reviewed annually by the DMC (unblinded) and TSC (blinded)
- If in doubt contact the trial office

RECAST 3

REMOTE ISCHAEMIC CONDITIONING AFTER STROKE TRIAL 3

PROTOCOL DEVIATIONS

- **Minor** deviation from the protocol that affects the conduct of the trial in a minor way.
- This includes any deviation from the trial protocol that is not listed as a protocol violation.

Examples:
Follow-up assessments are performed (as opposed to submitted) outside the specified time as shown below:
•2-day follow-up: >1day past the due date
•Discharge/death in hospital: >7days past the due date

- Submitted in the same way as protocol violations but will be downgraded by the CI on review

RECAST 3

REMOTE ISCHAEMIC CONDITIONING AFTER STROKE TRIAL 3

Please see WPD 009 Site Monitoring for further detail

MONITORING

- The trial manager will carry out the site monitoring visit remotely. A face-to-face visit may be triggered if there are ongoing concerns about a site despite remedies being suggested to resolve issues.
- The expectation is that sites will complete the monitoring documents, which will be signed off by the PI and returned to the trial's office. These documents include an ISF checklist and patient file checklists
- Sites will be notified of a sub-set of patients that have been randomly selected from the trial database to be monitored
- The completed monitoring documents will be reviewed by the trial coordinator and followed up with a report and action list

RECAST 3

REMOTE ISCHAEMIC CONDITIONING AFTER STROKE TRIAL 3

Please see WPD 004 Uploading Images, WPD 005 Secure Vault Uploads WPD and WPD 009 Site Monitoring for further detail

ONGOING MONITORING

As part of the ongoing monitoring process, sites will be required to upload documentation to the secure vault for each recruited patient. Please upload as soon as possible after enrolment.

- Consent form
- Participant contact details (for the day 90 follow-up)
- Any clinical neuroimaging reports for all clinical brain scans done during 90-day follow-up period **(anonymised)**
- Participant-specific file notes if applicable **(anonymised)**
- Scan data for the baseline CT should be uploaded via the database (encrypted DICOM data). If scans cannot be uploaded, please post to us on a CD **(anonymised).**

NB:- It is not necessary to 'prescribe' the intervention on the drug chart. Delivery of each treatment 'dose' must be recorded (i) in the medical notes and (ii) on the Treatment Log CRF (entered onto the database).

Please note:

Any documentation with patient details should **not** be sent to the generic RECAST-3 email address

To anonymise please block out the patient's name and any other identifiable information and add their participant ID to the document. Consent forms should not be anonymised but the participant ID should be added.

RECAST 3

REMOTE ISCHAEMIC CONDITIONING AFTER STROKE TRIAL 3

Please see WPD 009 Site Monitoring and WPD 001 Screening and Enrolment Log for further detail

ONGOING MONITORING

To be sent to recast-3@nottingham.ac.uk on a monthly basis (anonymised):

- Screening logs

Please include all patients presenting within 24 hours of their stroke, including:

Eligible patients who are recruited

Eligible patients who did not want to take part

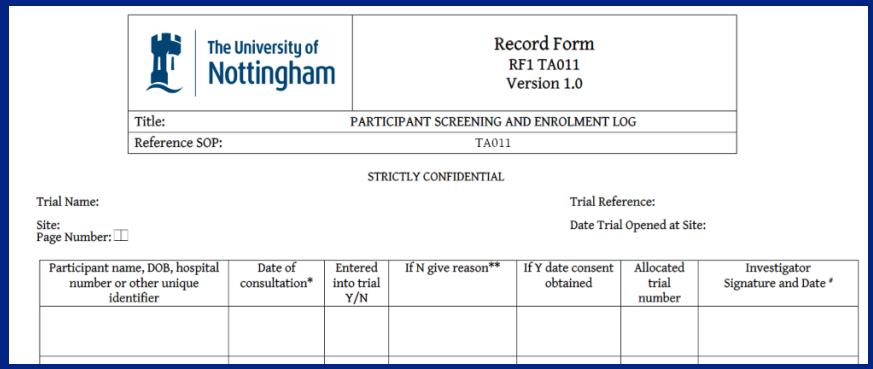
- Totals for ineligible patients (i.e., they do not meet the inclusion criteria, or they fulfil one of more of the exclusion criteria)

The cumulative totals must be recorded and sent across to the coordinating centre monthly

For example, 10 patients were ineligible in March 2024 because they had an NIHSS score of 4 or below.

Please note:

Patient details should **not** be sent to the generic RECAST-3 email address – the log should be anonymised prior to sending.



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 #

RECAST 3

REMOTE ISCHAEMIC CONDITIONING AFTER STROKE TRIAL 3

Please refer to 'Co-enrolment log for Sites' on the RECAST-3 documents page for an up-to-date list

CO-ENROLMENT

- Enrolment into observational studies does not require sponsor approval.
- Co-enrolment between certain interventional trials is permitted:

MAPS-2

ENOS-2

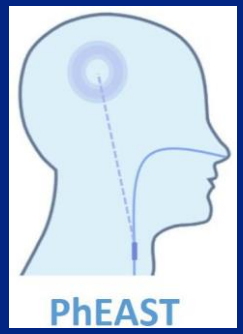
PhEAST (PhEAST to recruit after day 14)

- This has been agreed between Chief Investigators as the trials have the same Sponsor.
- For any other interventional trial, co-enrolment would need to be discussed on a trial by trial basis and a decision taken by sponsors of both trials, with permission from the relevant safety committees. Contracts will also need to be in place.
- Please always consider the burden on the patient
- Record on the discharge or death in hospital CRF

MAPS-2

E N S–2

Efficacy of Nitric Oxide in Stroke-2



RECAST 3

REMOTE ISCHAEMIC CONDITIONING AFTER STROKE TRIAL 3

SITE FILE

- Please see the RECAST-3 documents page where you can download the contents of the investigator site file (https://stroke.nottingham.ac.uk/recast-3/docs/public.php)
- The coordinating centre will not send hardcopy site files in the post for reasons of sustainability and version control
- Must be stored in a secure location and only accessible by the research team

Includes:

- Coordinating centre contact sheet
- Trial staff details – CVs, GCP certificates, training logs
- Current protocol
- Localised information sheets, consent forms and GP letter
- Screening logs
- Regulatory approvals (inc. NCA, OID, local R&D approvals, sponsor greenlight)
- Working Practice documents
- Monitoring documents
- Safety – file SAE forms here after sign off by PI
- All 'wet-ink' signed informed consent forms
- File notes/correspondence

RECAST 3

REMOTE ISCHAEMIC CONDITIONING AFTER STROKE TRIAL 3

WHAT NEXT?

Before we issue green light and you can start recruiting…

- ✓ Signed training log after today's session
- ✓ CVs and GCPs for trial staff
- ✓ Signed contract
- ✓ Confirmation of C&C from R&D
- ✓ Staff to be authorised by PI on online delegation log
- ✓ Confirmation that the device has been received and is ready for use

Please can we remind you to add recast-3@nottingham.ac.uk to your contacts list – not doing so may mean you miss important automated emails from our database (including randomisation and SAE alerts).

RECAST 3

REMOTE ISCHAEMIC CONDITIONING AFTER STROKE TRIAL 3

WHAT NEXT?

Please ensure to read through the following sponsor SOPs which can be found on our trial documents page and in your ISF: (https://stroke.nottingham.ac.uk/recast-3/docs/public.php)

- SOP TA008 Trial Initiation
- SOP TA010 TMF TSF
- SOP TA016 Serious GCP Breach Reporting

RECAST 3

REMOTE ISCHAEMIC CONDITIONING AFTER STROKE TRIAL 3

RECAST-3 CONTACTS

Email: recast-3@nottingham.ac.uk

Website: https://stroke.nottingham.ac.uk/recast-3/

Twitter: @recast3trial

Telephone: 0115 823 1770

Professor Tim England

Chief Investigator

Di Havard

Senior Trial Manager

0115 823 1775

Dr Jen Craig

Trial Manager

0115 823 1770

Joanne Del Buono

Follow Up Coordinator

0115 823 1770

RANDOMISATION QUERIES: 0115 823 1770

OUT OF HOURS EMERGENCY CONTACT DETAILS: Please log in to the RECAST-3 database to access

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RECAST 3
REMOTE ISCHAEMIC CONDITIONING AFTER STROKE TRIAL 3

Remote Ischaemic Conditioning After Stroke (RECAST-3)

Questions?

Please complete and return a copy of the Investigator Training Log (RF1 TA008) for all those who have attended today's training!

RECAST 3

REMOTE ISCHAEMIC CONDITIONING AFTER STROKE TRIAL 3

Audit trail of updates to training slides:

V1.0 (20240202)

- First version

V2.0 (20240216)

- Slide 41: updated to indicate that it is not necessary to 'prescribe' the intervention on the drug chart

V2.1 (20249416)

- Slide 27: removed reference to ward staff needing to complete a GCP assessment
- Slide 33: reference to reporting AEs and ADEs on the database removed
- Slide 41: comment indicating that RIC or sham should not be specified in the medical notes has been removed.
- Slide 47: Joanne Del Buono photo and contact details added.

V2.2 (20240611)

- Slide 35: Clarified that all SAEs and SADEs to be reported for 20 days post randomisation
- Slide 42: Clarified which patients need to be listed on the screening logs – only those eligible that were approached and recruited or declined.