Amendment Tool

v1.6 06 December 2021

For office use

QC: No

Section 1: Project information

Short project title*:	RECAST-3
IRAS project ID* (or REC reference if no IRAS project ID is available):	282606
Sponsor amendment reference number*:	SA/06/23
Sponsor amendment date* (enter as DD/MM/YY):	12 October 2023
Briefly summarise in lay language the main changes proposed in this amendment. Explain the purpose of the changes and their significance for the study. If the amendment significantly alters the research design or methodology, or could otherwise affect the scientific value of the study, supporting scientific information should be given (or enclosed separately). Indicate whether or not additional scientific critique has been obtained (note: this field will adapt to the amount of text entered)*:	(1) Key contact for the Sponsor amended from Ms Angela Shone to Mr Ali Alshukry. (2) Device details changed from LifeCuff Technologies Inc to Medical Device Management Ltd. (3) Substantial protocol changes: References to previous device manufacturer removed and intervention delivery, device description, storage, installation, packaging and labelling details updated accordingly. Changes to intervention including RIC/sham intervention now bilateral, delivered over 14 days (28 'doses') and amended RIC and sham inflation pressures (+20mmHg above systolic BP and 50mmHg, respectively). Day 4 follow up and safety endpoint moved to end of treatment. Day 2 CT scan no longer required unless clinically indicated (associated mechanistic outcome measures removed). Sub-study follow up MRI amended to day 2-14. SAE reporting updated (timeframe amended and no longer reported to MHRA). (4) Inclusion criteria: change to acute, ≤24 hours post onset. NIHSS score changed to 5-25. New exclusion criteria: systolic BP<80mmHg, significant tissue injury of the upper limbs, expected repatriation to a non-RECAST-3 site. Additional details added regarding dementia and transformation of infarction PH2 exclusion criteria. Minimisation factors and sub-group analysis updated (removal of COVID-19 status and time since stroke cut values amended). (5) Non-substantial protocol changes: Minor formatting/grammar edits. Removal of space for MHRA reference. Contact details updated (CI/co-investigator/trial manager/coordinating centre). Dose compliance updated to be recorded by investigators. Malignancy and significant injury of upper limbs added to baseline protocol violations. Vanguard phase, stop-go decision, and recruitment targets updated. Clarification that it is recommended that a decision on consent is made as soon as possible due to potential time-dependent effects informed and consent will be provided before the participant participates in the study (written consent and verbal consent permitted). Exclusion criteria in synopsis updated to be consistent with section 6.5.1.2. (6) Study documents: Minor formatting/grammar edits. Key contact details amended. Space for participating sites to add the participant ID to the consent forms added. Updates to information sheets to reflect protocol changes. New documents: Day 90 GP and practice manager letters. Day 90 postal questionnaire minor update to item B1. (7) Ongoing and recent stroke studies section updated as trials have reached completion. (8) Updated mNCA template and SoECAT

Project type (select):	**Specific study**			
	Research tissue bank			
	Research database			
Has the study been reviewed by a UKECA-recognised Research Ethics Committee (REC) prior to this amendment?:	**Yes**		No	
What type of UKECA-recognised Research Ethics Committee (REC) review is applicable? (select):	**NHS/HSC REC**			
	Ministry of Defence (MoDREC)			
Is all or part of this amendment being resubmitted to the Research Ethics Committee (REC) as a **modified amendment** (i.e. a substantial amendment previously given an unfavourable opinion)?	Yes		**No**	
Where is the NHS/HSC Research Ethics Committee (REC) that reviewed the study based?:	England	Wales	Scotland	Northern Ireland
	Yes	No	No	No
Was the study a clinical trial of an investigational medicinal product (CTIMP) OR does the amendment make it one?:	Yes		**No**	
Was the study a clinical investigation or other study of a medical device OR does the amendment make it one?:	**Yes**		No	
Does this clinical investigation or other study of a medical device require a Notice of No Objection from MHRA Devices?:	Yes		**No**	
Did the study involve the administration of radioactive substances, therefore requiring ARSAC review, OR does the amendment introduce this?:	Yes		**No**	
Did the study involve the use of research exposures to ionising radiation (not involving the administration of radioactive substances) OR does the amendment introduce this?:	**Yes**		No	

Did the study have Radiation Assurance OR is Radiation Assurance being sought for the first time because of this amendment?:	Yes	**No**
Did the study involve adults lacking capacity OR does the amendment introduce this?:	**Yes**	No
Did the study involve access to confidential patient information outside the direct care team without consent OR does the amendment introduce this?:	Yes	**No**
Did the study involve prisoners or young offenders who are in custody or supervised by the probation service OR does the amendment introduce this?:	Yes	**No**
Did the study involve children OR does the amendment introduce this?:	Yes	**No**
Did the study involve NHS/HSC organisations prior to this amendment?:	**Yes**	No
Did the study involve non-NHS/HSC organisations OR does the amendment introduce them?:	Yes	**No**

	England	Wales	Scotland	Northern Ireland
Lead nation for the study:	**Yes**	No	No	No
Which nations had participating NHS/HSC organisations prior to this amendment?	**Yes**	**Yes**	**Yes**	**Yes**
Which nations will have participating NHS/HSC organisations after this amendment?	**Yes**	**Yes**	**Yes**	**Yes**

Section 2: Summary of change(s)

Please note: Each change being made as part of the amendment must be entered separately. For example, if an amendment to a clinical trial of an investigational medicinal product (CTIMP) involves an update to the Investigator's Brochure (IB), affecting the Reference Safety Information (RSI) and so the information documents to be given to participants, these should be entered into the Amendment Tool as three separate changes. A list of all possible changes is available on the "Glossary of Amendment Options" tab. To add another change, click the "Add another change" box.

Change 1	
Area of change (select)*:	Administrative details for the project
Specific change (select - only available when area of change is selected first)*:	Contact details - Sponsor or representative
Further information (free text - note that this field will adapt to the amount of text entered):	Mr Ali Alshukry Head of Research Integrity, Risk & Compliance & Interim Head of Research Governance Research and Innovation E Floor, Yang Fujia, Jubilee Campus The University of Nottingham, Wollaton Road Nottingham, NG8 1BB T: +44 (0) 115 74 85224 Mob: +44 (0) 7866 137607 sponsor@nottingham.ac.uk Please see the accompanying letter of authorisation: Sponsor contact delegation letter

Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:	**Yes**	**Yes**	**Yes**	**Yes**
Will all participating NHS/HSC organisations be affected by this change, or only some? (**please note** that this answer may affect the categorisation for the change):	**All**		Some	
			Remove all changes below	

Change 2	
Area of change (select)*:	Participant Procedures
Specific change (select - only available when area of change is selected first)*:	Participant procedures - significant change that can be implemented within existing resource at participating organisations - Please specify in the free text below
Further information In particular, please describe why this change can be implemented within the existing resource in place at the participating organisations (free text - note that this field will adapt to the amount of text entered)*	Device manufacturer details changed from LifeCuff Technologies Inc to: Model: AT4 Electronic Tourniquet System (CE mark 631139) Manufacturer: Medical Device Management Ltd Distributed by: Anetic Aid Ltd The tourniquet has been classified as a 'Class IIa' medical device in accordance with the European Medical Device Directive 93/42EEC as amended by 2007/47. The following documentation associated with the new device has been submitted: - 995104 - Iss 01 - Product Training Guidance - AT4 Electronic Tourniquet - RECAST-3

	The label to be used to indicate the device is for research only has also been submitted.

Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:	**Yes**	**Yes**	**Yes**	**Yes**
Will all participating NHS/HSC organisations be affected by this change, or only some? (**please note** that this answer may affect the categorisation for the change):	**All**		Some	
			Remove all changes below	

Change 3	
Area of change (select)*:	Study Documents
Specific change (select - only available when area of change is selected first)*:	Protocol - Substantial changes (e.g. affecting safety or the scientific value of the trial)
Further information (free text - note that this field will adapt to the amount of text entered):	References to previous device manufacturer removed (LifeCuff) and intervention delivery, device description, storage, installation, packaging and labelling details updated in line with the updated device manufacturer. RIC inflation in active arm amended to +20mmHg above systolic blood pressure (previously +25 mmHg) and inflation in sham arm amended to 50mmHg (previously 20mmHg). RIC/sham intervention amended to bilateral (previuosly unilateral) and delivered twice daily over 14 days, total 28 'doses' (previously twice daily over 2 days, total 4 'doses'). Day 2 CT scan no longer required unless clinically indicated (associated mechanistic outcome measures removed). Sub-study follow-up MRI scan date amended to day 2-14. Day 4 follow up and safety endpoint moved to end of treatment. All SAEs to be reported during the treatment period, only fatal SAEs and outcomes will be collected thereafter. Due to changing to a CE marked device, SAEs/SADEs no longer need to be reported to MHRA.

Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:	**Yes**	**Yes**	**Yes**	**Yes**
Will all participating NHS/HSC organisations be affected by this change, or only some? (**please note** that this answer may affect the categorisation for the change):	**All**		Some	
			Remove all changes below	

Change 4	
Area of change (select)*:	Study Design
Specific change (select - only available when area of change is selected first)*:	Inclusion/exclusion criteria - Significant change (e.g. to age range) likely to affect safety or scientific value of study
Further information (free text - note that this field will adapt to the amount of text entered):	Addition of new exclusion criteria: Systolic blood pressure <80mmHg Significant tissue injury of the limb, which in the opinion of the investigator, will be exacerbated by remote ischaemic conditioning Expected repatriation to a non-RECAST-3 site not participating in RECAST-3 where RIC or sham cannot continue. Exclusion criteria clarification: Amended to make it clear that a pre-existing diagnosis of dementia is an exclusion criterion. Clarified that transformation of infarction PH2 is an exclusion if known before randomisation (not excluded or withdrawn if occurs after randomisation). Amended inclusion criteria: Change from hyperacute ischaemic stroke (≤6 hours post onset) to acute ischaemic stroke (≤24 hours post onset) NIHSS score at randomisation updated to a score of 5-25 (previously ≥4) Added inclusion criteria for the MT sub-study

	Randomisation and blinding: minimisation details updated (removal of COVID-19 status, time since stroke cut amended to 12 hours). Sub-group analysis updated accordingly (removal of COVID-19 status, updated time cuts to 0-6 hours/6-12 hours/12-24 hours)

Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:	**Yes**	**Yes**	**Yes**	**Yes**
Will all participating NHS/HSC organisations be affected by this change, or only some? (**please note** that this answer may affect the categorisation for the change):	**All**		Some	

Remove all changes below

Change 5	
Area of change (select)*:	Study Documents
Specific change (select - only available when area of change is selected first)*:	Protocol - Non-substantial changes (e.g. not affecting safety or the scientific value of the trial)
Further information (free text - note that this field will adapt to the amount of text entered):	Minor formatting/grammataical edits Removal of space for MHRA reference. Exclusion criteria in synopsis section updated to be consistent with exclusion criteria in main body of protocol (section 6.5.1.2). Contact details in the protocol updated (CI, co-investigator, trial manager, trial coordinating centre). Dose compliance updated to be recorded by investigators. Vanguard phase, stop-go decision, and recruitment targets updated. Clarification that it is recommended that a decision on consent is made as soon as possible due to potential time-dependent effects. Clarification that informed consent will be provided before the participant participates in the study (written consent and verbal consent permitted). Malignancy and significant injury of the upper limbs added to baseline characteristic protocol violations

Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:	**Yes**	**Yes**	**Yes**	**Yes**
Will all participating NHS/HSC organisations be affected by this change, or only some? (**please note** that this answer may affect the categorisation for the change):	**All**		Some	

Remove all changes below

Change 6	
Area of change (select)*:	Study Documents
Specific change (select - only available when area of change is selected first)*:	Other minor change to study documents (e.g. information sheets, consent forms, questionnaires, letters) that can be implemented within existing resource in place at participating organisations - Please specify in the free text below
	Information sheets: - Minor formatting/grammar edits - Contact details updated (CI title/address, trial office address/email address/twitter handle) - Reference to Remote Ischaemic Conditioning (RIC) used throughout for consistency - Clarified that co-enrolment with another trial acceptable if approved (inclusion criteria) - Clarified that the sub-study CT perfusion scan may be done as part of routine care - Updates throughout to reflect the following protocol changes: Change to bilateral cuffs, 6 hour gap between treatments on day 1, 'treatment' for 28 doses over 14 days or until discharge - Removal of reference to discomfort caused by blood samples (no research samples taken)

Further information In particular, please describe why this change can be implemented within the existing resource in place at the participating organisations (free text - note that this field will adapt to the amount of text entered)*	Consent forms: Space for participating sites to add the participant ID to the consent forms added. Indicated that MHRA reference not applicable. Minor formatting GP letter: Amended to indicate local letter head needs to be added. Clarified that the trial is acute not hyperacute. Updated to reflect change to bilateral intervention Submission of two letters that are to be used by the coordinating centre to request follow-up information from GP practices. The practice manager letter will be used as a covering letter with the accompanying GP letter attached. The letter will request that the GP provides the mRS value of a patient who has been unable to be contacted to perform their follow-up. This will reduce the data loss of those lost to follow-up. RECAST-3 Day 90 GP Postal Letter (V1.0, 20230905) and RECAST-3 Practice Manager Letter (V1.0, 20230905). ReCAST-3_Day_90_follow-up_20230202_v1.1_postal: Removal of 'care home' option on question B1 of the day 90 postal questionnaire to ensure clarity – participants should pick between nursing home and residential home.

Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:	No	**Yes**	**Yes**	**Yes**
Will all participating NHS/HSC organisations be affected by this change, or only some? (**please note** that this answer may affect the categorisation for the change):	**All**		Some	
			Remove all changes below	

Change 7	
Area of change (select)*:	Study Design
Specific change (select - only available when area of change is selected first)*:	Background information - Change that affects scientific value of study
Further information (free text - note that this field will adapt to the amount of text entered):	Ongoing and recent stroke studies section updated as trials have reached completion.

Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:	**Yes**	**Yes**	**Yes**	**Yes**
Will all participating NHS/HSC organisations be affected by this change, or only some? (**please note** that this answer may affect the categorisation for the change):	**All**		Some	
			Remove all changes below	

Change 8	
Area of change (select)*:	Study Management
Specific change (select - only available when area of change is selected first)*:	Contract/agreement arrangements
Further information (free text - note that this field will adapt to the amount of text entered):	mNCA updated to the most recent template. Document submitted: unmodified mNCA_July_2022. SoECaT updated and submitted: RECAST-3 SoECaT - Signed 11 Oct 2023

Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:	**Yes**	**Yes**	**Yes**	**Yes**
Will all participating NHS/HSC organisations be affected by this change, or only some? (**please note** that this answer may affect the categorisation for the change):	**All**		Some	

Add another change

Section 3: Declaration(s) and lock for submission

Declaration by the Sponsor or authorised delegate

- I confirm that the Sponsor takes responsibility for the completed amendment tool
- I confirm that I have been formally authorised by the Sponsor to complete the amendment tool on their behalf

Name [first name and surname]:*	Alison Thorpe
Email address:*	sponsor@nottingham.ac.uk

Lock for submission

Please note: This button will only become available when all mandatory (*) fields have been completed. When the button is available, clicking it will generate a locked PDF copy of the completed amendment tool which must be included in the amendment submission. Please ensure that the amendment tool is completed correctly before locking it for submission.

Lock for submission

After locking the tool, proceed to submit the amendment online. The "Submission Guidance" tab provides further information about the next steps for the amendment.

Section 4: Review bodies for the amendment

Please note: This section is for **information only**. Details in this section will complete automatically based on the options selected in Sections 1 and 2.

	Review bodies																
	UK wide:						England and Wales:				Scotland:				Northern Ireland:				
	REC	Competent Authority MHRA - Medicines	Competent Authority MHRA - Devices	ARSAC	Radiation Assurance	UKSW Governance	REC (MCA)	CAG	HMPPS	HRA and HCRW Approval	REC (AWIA)	PBPP	SPS (RAEC)	National coordinating function	HSC REC	HSC Data Guardians	Prisons	National coordinating function	Category:
Change 1:	(Y)					Y				(Y)				(Y)				(Y)	C
Change 2:	Y					Y				Y				Y				Y	C
Change 3:	Y					Y				(Y)				(Y)				(Y)	A
Change 4:	Y					(Y)				(Y)				(Y)				(Y)	A
Change 5:	N					(Y)				(Y)				(Y)				(Y)	A
Change 6:	N					(Y)				(Y)				(Y)				(Y)	C
Change 7:	Y					(Y)				(Y)				(Y)				(Y)	A
Change 8:	N					Y				Y				Y				Y	A
Overall reviews for the amendment:																			
Full review:	Y					Y				Y				Y				Y	
Notification only:	N					N				N				N				N	
Overall amendment type:	Substantial																		
Overall Category:	A																		

For national coordinating function office use:	
Update HARP:	This amendment may involve an update to contact details, project end date, or other project details. Ensure that HARP is updated with the current details. If this is the only change, no further study-wide review is required.