Amendment Tool

v1.6 06 December 2021

For office use

QC: Yes

Section 1: Project information

Short project title*:	REMAP-CAP
IRAS project ID* (or REC reference if no IRAS project ID is available):	237150
Sponsor amendment reference number*:	AM034
Sponsor amendment date* (enter as DD/MM/YY):	02 March 2022
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)*:	Addition of releasing site information to section D9 of the MHRA CTA for licensed ascorbic acid This involves changes to the MHRA CTA for the Ascorbic Acid stock for use within REMAP-CAP Stock: 50ml vials of concentrate for solution for injection/infusion contains: 7,5g ascorbic acid (commercial stock rather than unlicenced clinical trial stock) Addition of UK Releasing site: Alliance Healthcare; Unit 1, High View Road Ind Units, South Normanton, Derbyshire; DE55 2DT Marketing Authorisation holder: Pascoe pharmazeutische Präparate GmbH UK MA number: PL 14369/0009 and Submission of associated SmPc

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	
EudraCT number*:	2015-002340-14			
Was this clinical trial of an investigational medicinal product (CTIMP) processed under the CTIMP combined review service (formerly known as the Combined Ways of Working (CWoW) pilot)?:	Yes		**No**	
Did the study receive Pharmacy Assurance?:	**Yes**		No	
Was the study a clinical investigation or other study of a medical device OR does the amendment make it one?:	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 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)

What do you want to update?:	**Project information**
	New site/PI only

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)*:	CTIMP IMP
Specific change (select - only available when area of change is selected first)*:	Other - Please specify in the free text below
Further information (free text - note that this field will adapt to the amount of text entered):	This involves changes to the MHRA CTA for the Ascorbic Acid stock for use within REMAP-CAP Stock: 50ml vials of concentrate for solution for injection/infusion contains: 7,5g ascorbic acid (commercial stock rather than unlicenced clinical trial stock) Addition of UK Releasing site: Alliance Healthcare; Unit 1, High View Road Ind Units, South Normanton, Derbyshire; DE55 2DT Marketing Authorisation holder: Pascoe pharmazeutische Präparate GmbH UK MA number: PL 14369/0009 Submission of associated SmPc

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)*:	Stop or Restart	
Specific change (select - only available when area of change is selected first)*:	Temporary halt of CTIMP	
Date of temporary halt (enter as DD/MM/YY):	24 February 2022	
Recruitment has been stopped:	Yes	**No**
Treatment has been stopped:	**Yes**	No
Number of participants still receiving treatment in the UK at the time of the temporary halt:	3	

In the further information free text below, briefly describe:

- Justification for a temporary halt of the trial
- The proposed management of participants receiving treatment at the time of the halt
- The consequences of the temporary halt for the evaluation of the results and for the overall risk benefit assessment of the investigational medicinal product
- Details of any other trials in the UK that will also be affected by the temporary halt

Further information (free text - note that this field will adapt to the amount of text entered):	On the 24th of February, 2022, we received correspondence from the REMAP-CAP Data Safety and Monitoring Board (DSMB) regarding the ACE2 Renin Angiotensin System (RAS) Domain. The DSMB has raised concerns about the safety of ACE2 RAS domain interventions in severe state (critically ill) patients based on the most recent 2-monthly interim review of safety data. After reviewing the recommendations from the DSMB, REMAP-CAP has stopped enrolment of critically ill patients into this domain, which is currently in phase 2. We recommended that critically ill patients currently receiving an angiotensin converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) – including in combination with DMX-200 – as part of the study protocol should have their study drug discontinued. Although the DSMB did not raise safety concerns for patients in the moderate state (noncritically ill), we believe that it is best to temporarily pause enrolment of noncritically ill patients into this domain to allow review of additional data prior to potentially resuming enrolment. Note that a fourth intervention in the domain, TRV-027, had not yet commenced recruitment.

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

	Sponsor
Applicant identification:	Legal representative of the sponsor Person or organisation authorised by the sponsor
Organisation:	University Medical Centre Utrecht
Name [first name and surname]:*	Clementina Okundaye
Address:	Heidelberglaan 100, 3584 CX, Utrecht, The Netherlands
Telephone number:	0031 (0) 88 755 5196
Fax number:	NA
Purchase Order (PO) number for MHRA invoicing:	R5418.70
Email address:*	eu.remapcap@umcutrecht.nl

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		N		Y				Y				Y	A
Change 2:	Y	Y				(Y)		(Y)		(Y)				(Y)				(Y)	B
Overall reviews for the amendment:																			
Full review:	Y	Y				Y		N		Y				Y				Y	
Notification only:	N	N				N		Y		N				N				N	
Overall amendment type:	Substantial for review																		
Overall Category:	A																		

For MHRA office use:
This amendment notifies a temporary halt of the trial