Amendment Tool

v1.5 25 Mar 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*:	AM030
Sponsor amendment date* (enter as DD/MM/YY):	01 December 2021
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)*:	I am submitting substantial amendment AM030 for the REMAP-CAP study. This involves: The addition of a new intervention, TRV027 into the ACE2 RAS domain The reopening of the immunoglobulin domain with new interventions The addition of the Monoclonal Antibody Domain I have also made the below changes to the MHRA CTA. TRV027 casirivimab / imdevimab (Ronapreve) I have also updated all the participant information sheets

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
	◉	○	○	○
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 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 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:	◉	○	○	○
Which nations had participating NHS/HSC organisations prior to this amendment?	☑	☑	☑	☑
Which nations will have participating NHS/HSC organisations after this amendment?	☑	☑	☑	☑

Section 2: Summary of change(s)

What do you want to update?:	○ Chief Investigator ○ Sponsor ○ Administrative ◉ Project information

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, tick 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)*:	IMP being added to the study for the first time			
Further information (free text - note that this field will adapt to the amount of text entered):	We are adding TRV027 to the ACE2 RAS domain, this will be part of the ACEi in combination with TRV-027, an angiotensin (1,7) analogue (ACEi + TRV-027) arm within the domain. TRV027 is a similar peptide to angiotensin1-7 but selectively recruits β-arrestin to AT1. This translates into unique downstream signalling. This recruitment of β-arrestin stimulates the activation of endothelial cell nitic oxide synthase and prostacyclin production which may contribute to its in vivo vasodilatory properties. TRV027 IMP stock comes with clinical trial labelling (provided as part of this substantial amendment).			
Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:	☑	☑	☑	☑
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: ☑

Change 2				
Area of change (select)*:	CTIMP IMP			
Specific change (select - only available when area of change is selected first)*:	IMP being added to the study for the first time			
Further information (free text - note that this field will adapt to the amount of text entered):	Monoclonal Antibody Therapy (additional samples) Casirivimab and Imdevimab are neutralising monoclonal antibodies that have been shown to bind to SARS-CoV2 virus , blocking its entry into the body's cells, reducing the virus' effects. The interventions available are: 1.2g casirivimab / 1.2g imdevimab (low dose) 4g casirivimab / 4g imdevimab (high dose) This study is taking into account evidence derived from other clinical trials, and a UK wide policy that recommends the use of low dose casirivimab /imdevimab for use in patients hospitalised due to COVID-19 and have blood tests that show, they do not have antibodies against SARS-CoV-2. We are comparing the effects of low dose compared to a higher dose. Additional samples will be collected as part of this domain. These samples will be transported to a central laboratory for testing. All samples collected under this study will be used within this study or in other ethically approved studies. The 1st sample will be taken with 24hours of the treatment being completed, one sample between days 3 and 7 and one sample between days 7 and 14. We will take a final sample between says 14 and 28 if the participant is still in hospital. Each blood sample will take up to 6mls (2 teaspoons or less).			
Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:	☑	☑	☑	☑
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: ☑

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):	The reopening of the immunoglobulin domain with new interventions Immunoglobulin; Convalescent Plasma Therapy (additional samples) COVID-19 immunoglobulin therapy is a blood-based treatment, giving patients antibodies to help fight infection. Antibodies are found in plasma, which is the liquid part of blood. It contains a mixture of proteins including antibodies, clotting factors, and natural anticoagulants. Convalescent plasma is plasma collected from volunteers who have recovered from COVID-19, which contains antibodies to help fight COVID-19. The interventions available are: No Immunoglobulin Therapy (no placebo) High Titre Convalescent Plasma This study is taking into account evidence derived from the results from the 1st stage of this domain in REMAP-CAP, as well as other clinical trials. There are a significant number of patients with an impaired immune system who would be eligible to be included within this trial and may benefit from this intervention. This population of patients are potentially also less likely to respond to COVID-19 vaccinations and are therefore more at risk of COVID-19 disease. Additional samples will be collected as part of this domain. These samples will be transported to a central laboratory for testing. All samples collected under this study will be used within this study or in other ethically approved studies. We will take blood and respiratory samples from participants on entering the study and then a single respiratory sample each week until hospital discharge. The blood sample will take up to 15mls (3 teaspoons or less). Patients would only be randomised to these treatments if participants have acute illness due to confirmed COVID-19 and are immunosuppressed at the time of eligibility.

Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:	☑	☑	☑	☑
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: ☑

Change 4				
Area of change (select)*:	Study Documents			
Specific change (select - only available when area of change is selected first)*:	Other significant change to study documents (e.g. information sheets, consent forms, questionnaires, letters) that will have additional resource implications for participating organisations - Please specify in the free text below			
Further information (free text - note that this field will adapt to the amount of text entered):	Participant information sheets have been updated with all the additional interventions and domains.			
Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:	☑	☑	☑	☑
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

Applicant identification:	◉ Sponsor ○ 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
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		N		Y				Y				Y	A
Change 3:	Y	Y				Y		(Y)		(Y)				(Y)				(Y)	A
Change 4:	Y	N				Y		(Y)		Y				Y				Y	A
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																		

This amendment relates to:	
Part 1:	Yes
Part 2:	Yes
Notification for authorisation to the competent authority (MHRA - Medicines):	Yes
Notification for an opinion to the ethics committee (REC):	Yes