Amendment Tool

v1.6 06 December 2021

For office use

QC: Yes

Section 1: Project information

Short project title*:	PRINCIPLE
IRAS project ID* (or REC reference if no IRAS project ID is available):	281958
Sponsor amendment reference number*:	Substantial Amendment 22
Sponsor amendment date* (enter as DD/MM/YY):	01 July 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)*:	1. We are updating the exclusion criteria regarding other COVID-19 therapeutics and CTIMPs to prevent interactions between potentially competing interventions and treatments particularly paxlovid and the PANORAMIC trial. 2. We are clarifying the timepoints and number of attempts that participants will be contacted for long-term follow-up as 3, 6 and 12 months after randomisation (and up to 15 months). Participants will be re-consented verbally during these long-term follow up calls to ensure they agree to be contacted at these timepoints. We have added in the requirement to call all participants before randomisation to confirm eligibility and ongoing symptoms. Clarification that participants who take the mandatory pregnancy test who receive a negative result can start IMP and confirm the result with the trial team when contacted. Removal of text confirmation of IMP receipt from participants and long term follow-up. Removal of reference to Day 2 diary follow-up call in PIS. Clarification in protocol of participant voucher allocation. We have removed from the protocol the need to re-consent those who are already enrolled onto the trial to participate in long-term follow-up. 3. Confirming the AE reporting window used in the trial has been and continues to be 28 days for patients allocated to unlicenced IMP in the UK in order to follow-up on lesser known interventions. 4. Update to name of sponsor (RGEA) and UKHSA (previously PHE) in pictorial PIS. 5. Removal of former trial team staff and addition of other trial team members listed in the Protocol. 6. Closure of two treatment arms (Favipiravir and Ivermectin) following recommendations from the TSC, due to trial data meeting pre-specified criteria

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*:	2020-001209-22			
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**
Which nations had participating non-NHS/HSC organisations prior to this amendment?	**Yes**	No	No	No
Which nations will have participating non-NHS/HSC organisations after this amendment?	**Yes**	No	No	No

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)*:	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):	Changing an exclusion criteria to allow participants to join PRINCIPLE if they have not participated in another CTIMP already during the current qualifying episode of COVID. Patients already participating in another COVID-19 CTIMPs are excluded from PRINCIPLE.			
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	
Where are the participating non-NHS/HSC organisations located that will be affected by this change?*:	**Yes**	No	No	No
			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 - minor 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)*	Protocol, PIS and ICF updated to confirm that participants will be contacted after the 3, 6 and 12 month time-point after randomisation (up to 15 months) for long-term follow-up by the trial team to collect information about any ongoing symptoms, hospitalisations and well-being via questionnaires. Participants will be re-consented verbally during these long-term follow up calls to ensure they agree to be contacted at these timepoints. They will be advised they can withdraw from the long-term follow calls at any time without giving a reason, and without their medical care or legal rights being affected. Patients will be contacted up to six times for each of these long term follow up points. Protocol and PIS updated to confirm that all participants must be called by the trial team or site staff before they are randomised in order to confirm eligibility and ongoing symptoms. Clarification made to PIS that participants who take the mandatory pregnancy test who receive a negative result can start IMP and confirm the result with the trial team when contacted. Removal of text confirmation of IMP receipt from participants and long term follow-up. Removal of reference to Day 2 diary follow-up call in PIS. Clarification in protocol of participant voucher allocation following 28 day follow-up. We have removed from the protocol the need to re-consent those who are already enrolled onto the trial to participate in long-term follow-up.			
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	
Where are the participating non-NHS/HSC organisations located that will be affected by this change?*:	**Yes**	No	No	No

Remove all changes below

Change 3				
Area of change (select)*:	CTIMP safety			
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):	Clarifying that the AE reporting window used in the trial has been and continues to be 28 days from randomisation for participants allocated to treatments not licensed as a COVID-19 therapeutic in the UK, whilst they are taking the drug, to allow thorough safety monitoring of these less familiar treatments			
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	
Where are the participating non-NHS/HSC organisations located that will be affected by this change?*:	**Yes**	No	No	No
			Remove all changes below	

Change 4				
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			
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)*	Update to name of sponsor (RGEA) and UKHSA (previously PHE) in pictorial PIS.			
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	
Where are the participating non-NHS/HSC organisations located that will be affected by this change?*:	**Yes**	No	No	No
			Remove all changes below	

Change 5				
Area of change (select)*:	Researchers			
Specific change (select - only available when area of change is selected first)*:	Changes to the research team (other than CIs or PIs)			
Further information (free text - note that this field will adapt to the amount of text entered):	Removal of former trial team staff and addition of other trial team members listed in the Protocol.			
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	
Where are the participating non-NHS/HSC organisations located that will be affected by this change?*:	**Yes**	No	No	No
			Remove all changes below	

Change 6	
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):	Closure of two treatment arms (Favipiravir and Ivermectin) following recommendations from the TSC, due to trial data meeting pre-specified criteria

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	
Where are the participating non-NHS/HSC organisations located that will be affected by this change?*:	**Yes**	No	No	No
			Remove all changes below	

Change 7				
Area of change (select)*:	Study Design			
Specific change (select - only available when area of change is selected first)*:	Other minor change to study design that can be implemented within existing resource in place 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)*	Correction to timeline for publication of trial results on EudraCT database and public registries (within 12 months of end of trial date instead of end of trial declaration).			
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	
Where are the participating non-NHS/HSC organisations located that will be affected by this change?*:	**Yes**	No	No	No
			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 of Oxford
Name [first name and surname]:*	Joseph Butchinsky
Address:	Boundary Brook House, Oxford
Telephone number:	0
Fax number:	0
Purchase Order (PO) number for MHRA invoicing:	TBC
Email address:*	jared.robinson@phc.ox.ac.uk; ctrg@admin.ox.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)				(Y)	A
Change 2:	N	N				(Y)				(Y)				(Y)				(Y)	C
Change 3:	Y	Y				Y				Y				Y				Y	A
Change 4:	N	N				(Y)				(Y)				(Y)				(Y)	C
Change 5:	N	N				N				N				N				N	N/A
Change 6:	Y	Y				Y				Y				Y				Y	A
Change 7:	N	N				(Y)				(Y)				(Y)				(Y)	C
Overall reviews for the amendment:																			
Full review:	Y	Y				Y				Y				Y				Y	
Notification only:	N	N				N				N				N				N	
Overall amendment type:	Substantial for review																		
Overall Category:	A																		