# Amendment Tool

v1.5 25 Mar 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 16 |
| Sponsor amendment date* (enter as DD/MM/YY): | 12 July 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)*: | 1. Main protocol inclusion criteria updated - participants must have a positive test for SARS-CoV-2 infection. 2. Main protocol inclusion criteria updated - removal of the requirement for comorbidity and shortness of breath. 3. Patient facing documents updated with the changes described. 4. Reduction of inclusion age from 50 years and over to 18 years and over, for the favipiravir trial arm. 5. Ivermectin RSI section of IB updated (v3.0). 6. Favipiravir IB non-substantial changes (v13.0). 7. Formal notification that the colchicine arm of the trial has closed to recruitment. 8. New text message template to send to participants to return unused trial medication to the trial team |

| | | | | |
|---|---|---|---|---|
| Project type (select): | ◉ Specific study<br>○ Research tissue bank<br>○ 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<br>○ 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*: | 2020-001209-22 | | | |
| 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? | ☑ | ☑ | ☑ | ☑ |
| Which nations had participating non-NHS/HSC organisations prior to this amendment? | ☑ | ☐ | ☐ | ☐ |
| Which nations will have participating non-NHS/HSC organisations after this amendment? | ☑ | ☐ | ☐ | ☐ |

**Section 2: Summary of change(s)**

| | |
|---|---|
| What do you want to update?: | ◉ Project information<br>○ 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, tick 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 - Minor change unlikely to affect safety or scientific value of study |
| Further information (free text - note that this field will adapt to the amount of text entered): | Inclusion criteria updated in the main protocol: Participants must have a positive test for SARS-CoV-2 infection.<br>Originally, the trial also included people based on the clinical syndrome alone using the NHS Definition, without the necessity of a positive test, because testing has not always been widely available. Now that the testing is widely available, and infections with a similar presentation to COVID-19 are becoming increasingly prevalent, we consider it important that only those with a positive test are included from now on. |

| 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 | |
| Where are the participating non-NHS/HSC organisations located that will be affected by this change?*: | ☑ | ☐ | ☐ | ☐ |

Add another change: ☑

| Change 2 | |
|---|---|
| Area of change (select)*: | Study Design |
| Specific change (select - only available when area of change is selected first)*: | Inclusion/exclusion criteria - Minor change unlikely to affect safety or scientific value of study |
| Further information (free text - note that this field will adapt to the amount of text entered): | Inclusion criteria updated in the main protocol: removal of the requirement for comorbidity and shortness of breath as eligibility criteria.<br>The original focus of the trial was on people at higher risk of hospitalisation/death, and comorbidity and moderately severe illness put people at increased risk for this outcome. We are observing that the COVID-19 disease profile, given vaccination rollout and other factors, has changed considerably. Far fewer people with traditional risk factors for hospitalisation are having a poor outcome, and an increasing proportion of younger people without these risk factors are getting ill, and it is important to know whether treatments benefit these individuals or not. |

| 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 | |
| Where are the participating non-NHS/HSC organisations located that will be affected by this change?*: | ☑ | ☐ | ☐ | ☐ |

Add another change: ☑

| Change 3 | |
|---|---|
| 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 (free text - note that this field will adapt to the amount of text entered): | Patient facing documents updated with the changes described. Safety reporting arrangements for Ivermectin have been clarified in the Protocol, in line with the updated Investigator's Brochure. Primary outcome wording updated for clarity (primary outcome itself has not changed), i.e. Hospitalisation and/or death due to possible SARS-CoV-2 infection. Day 2 call updated to day 3. |

| 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 | |

| | | | | |
|---|---|---|---|---|
| Where are the participating non-NHS/HSC organisations located that will be affected by this change?*: | ☑ | ☐ | ☐ | ☐ |

Add another change: ☑

| Change 4 | |
|---|---|
| Area of change (select)*: | Study Design |
| Specific change (select - only available when area of change is selected first)*: | Inclusion/exclusion criteria - Minor change unlikely to affect safety or scientific value of study |
| Further information (free text - note that this field will adapt to the amount of text entered): | Reduction of the inclusion age from 50 years and over to 18 years and over for the favipiravir arm. The trial already has approval to recruit people aged 18 and above for certain treatment arms, but we would now like to make this criteria applicable to favipiravir, due to the growing need for treatments for the lower age group, as well as for older adults. We have implemented the following to mitigate the risk of pregnancy in the lower age group:<br>1. Pregnancy (known or suspected) and breast-feeding are exclusions for the arms of the trial.<br>2. During the day 1 call, the clinician confirms the pregnancy exclusion criteria with the participant.<br>3. The trial team will monitor daily diaries/participant phone calls for reports of pregnancy since entering the trial, on a daily basis. The clinician will inform the participant to stop taking the medication immediately if they become pregnant during the trial.<br>4. Pregnancy in the unlicensed treatment arms will be reported as an Adverse Event and follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be collected. |

| 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 | |
| Where are the participating non-NHS/HSC organisations located that will be affected by this change?*: | ☑ | ☐ | ☐ | ☐ |

Add another change: ☑

| Change 5 | |
|---|---|
| Area of change (select)*: | Study Documents |
| Specific change (select - only available when area of change is selected first)*: | IB - Changes to the reference safety information (RSI) |
| Further information (free text - note that this field will adapt to the amount of text entered): | RSI section of the Ivermectin Investigator's Brochure (v3.0, 04/05/2021) has been updated with the following statement as requested by the MHRA (see SA15 approval letter): 'For the purpose of safety reporting in the clinical trials only serious adverse reactions already listed as serious in the above table will be considered expected; Any other serious ADR will be considered unexpected'. The new RSI section will be used for assessment of safety events in the Ivermectin arm for the rest of this reporting period. The SA15 MHRA approval letter is submitted for information. |

| 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 | |
| Where are the participating non-NHS/HSC organisations located that will be affected by this change?*: | ☑ | ☐ | ☐ | ☐ |

Add another change: ☑

| Change 6 | |
|---|---|
| Area of change (select)*: | Study Documents |
| Specific change (select - only available when area of change is selected first)*: | IB, SmPC - Non-substantial changes (e.g. that do not affect risk/benefit assessment) |
| Further information (free text - note that this field will adapt to the amount of text entered): | Favipiravir IB v13-EU clean and tracked changes versions submitted. The RSI has not been updated. |

| 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 | |
| Where are the participating non-NHS/HSC organisations located that will be affected by this change?*: | ☑ | ☐ | ☐ | ☐ |

Add another change: ☑

| Change 7 | | | | |
|---|---|---|---|---|
| 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): | Formal notification that the colchicine arm of the trial has closed to recruitment. | | | |
| 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 | |
| Where are the participating non-NHS/HSC organisations located that will be affected by this change?*: | ☑ | ☐ | ☐ | ☐ |

Add another change: ☑

| Change 8 | | | | |
|---|---|---|---|---|
| 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 (free text - note that this field will adapt to the amount of text entered): | New text message template to send to participants to remind them to return unused trial medication to the trial team via courier | | | |
| 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 | |
| Where are the participating non-NHS/HSC organisations located that will be affected by this change?*: | ☑ | ☐ | ☐ | ☐ |

Add another change: ☑

| Change 9 | | | | |
|---|---|---|---|---|
| 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 (free text - note that this field will adapt to the amount of text entered): | In line with the amended inclusion criteria to include only people with a positive result, the secondary outcome 'To determine if effects are specific to those with a positive test for SARS-CoV-2' has been removed. | | | |
| 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 | |
| Where are the participating non-NHS/HSC organisations located that will be affected by this change?*: | ☑ | ☐ | ☐ | ☐ |

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<br>○ Legal representative of the sponsor<br>○ Person or organisation authorised by the sponsor |

| | |
|---|---|
| *Organisation:* | University of Oxford |
| *Name [first name and surname]*:* | Elaine Chick |
| *Address:* | CTRG, Boundary Brook House, Oxford |
| *Telephone number:* | 00000 000000 |
| *Fax number:* | 00000 000000 |
| *Purchase Order (PO) number for MHRA invoicing:* | TBC |
| *Email address*:* | principle@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: | N | N | | | | (Y) | | | | (Y) | | | | (Y) | | | | (Y) | A |
| Change 2: | N | N | | | | (Y) | | | | (Y) | | | | (Y) | | | | (Y) | A |
| Change 3: | N | N | | | | (Y) | | | | (Y) | | | | (Y) | | | | (Y) | C |
| Change 4: | N | N | | | | (Y) | | | | (Y) | | | | (Y) | | | | (Y) | A |
| Change 5: | N | Y | | | | (Y) | | | | (Y) | | | | (Y) | | | | (Y) | C |
| Change 6: | N | N | | | | (Y) | | | | (Y) | | | | (Y) | | | | (Y) | C |
| Change 7: | Y | Y | | | | Y | | | | Y | | | | Y | | | | Y | A |
| Change 8: | N | N | | | | (Y) | | | | (Y) | | | | (Y) | | | | (Y) | C |
| Change 9: | 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 | | | | | | | | | | | | | | | | | | |