# Fw: PID14903: PRINCIPLE | Amendment PID14903-A017: 14/02/2021 - SA12 | IRAS ID: 281958

Hannah Swayze <hannah.swayze@phc.ox.ac.uk>

Fri 2/19/2021 16:24

**To:** Hannah Swayze <hannah.swayze@phc.ox.ac.uk>

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**From:** Heather House
**Sent:** 19 February 2021 16:13
**To:** Emma Ogburn <emma.ogburn@phc.ox.ac.uk>
**Cc:** oxfordjro@mail.studyline.uk.com; Christopher Butler <christopher.butler@phc.ox.ac.uk>
**Subject:** PID14903: PRINCIPLE | Amendment PID14903-A017: 14/02/2021 - SA12 | IRAS ID: 281958


**Clinical Trials & Research Governance (CTRG)**
University of Oxford
Joint Research Office
1st floor, Boundary Brook House
Churchill Drive, Headington
Oxford OX3 7GB

**Heather House**

Email: Heather.House@admin.ox.ac.uk


| | |
|---|---|
| **PID14903** | **Platform Randomised trial of INterventions against COVID-19 In older peoPLE** |

**Our reference:** PID14903-A017-SP001-AC001 **REC Ref:** 20/SC/0158
**Title:** 14/02/2021 - SA12

Dear Emma

I can confirm that the above referenced substantial amendment has been reviewed in CTRG and we are happy for it to be submitted to the relevant organisations for approval. This email can be forwarded as confirmation of sponsor approval for the amendment as required.

Please find attached the PDF version of the signed and locked amendment tool. Please submit this signed amendment tool, together with the tracked and clean copies of all amended documents, to the REC via the online amendment submission portal (for further guidance please refer to the HRA training video: how to complete online submission of amendments). Please make your MHRA submission through the Common European Submission Platform (CESP).

When you have received the submission confirmation, please email this, with the final documents you submitted, to the CTRG generic email address (ctrg@admin.ox.ac.uk). Please send a copy of the approval letter(s) to the CTRG generic email address (ctrg@admin.ox.ac.uk) once you have received it/them.

Please do not implement your amendment until all approval(s) are in place.

Do let me know if you have any questions, or need any further information.

Kind regards,

Heather House.

## IRAS PROJECT ID 281958, REC Reference 20/SC/0158 Confirmation of favourable opinion for substantial amendment

berkshire.rec@hra.nhs.uk <noreply@harp.org.uk>

Mon 2/22/2021 09:39

**To:** Christopher Butler <christopher.butler@phc.ox.ac.uk>; CTRG Sponsorship Correspondence <ctrg@admin.ox.ac.uk>
**Cc:** gram.nrspcc@nhs.scot <gram.nrspcc@nhs.scot>; research-permissions@wales.nhs.uk <research-permissions@wales.nhs.uk>; Hannah Swayze <hannah.swayze@phc.ox.ac.uk>

1 attachments (129 KB)

IRAS 281958 SL32_Favourable_opinion_of_a_substantial_amendment .pdf;

Dear Professor Butler

| | |
|---|---|
| **IRAS project ID:** | 281958 |
| **REC reference:** | 20/SC/0158 |
| **Short Study title:** | PRINCIPLE [COVID-19] [UPH] |
| **Date complete amendment submission received:** | 19 February 2021 |
| **Amendment No./ Sponsor Ref:** | SA 12 |
| **Amendment Date:** | 14 February 2021 |
| **Amendment Type:** | **Substantial** |
| **Outcome of HRA Assessment** | **HRA and HCRW Approval for the amendment is pending** – HRA and HCRW Approval for the amendment will be separately confirmed by email. |

I am pleased to confirm that this amendment has been reviewed by the Research Ethics Committee and has received a Favourable Opinion. Please find attached a copy of the Favourable Opinion letter.

**HRA and HCRW Approval Status**

As detailed above, **HRA and HCRW Approval for this amendment is pending**. HRA and HCRW Approval for the amendment will be separately confirmed by email. You should not implement this amendment at participating NHS organisations in England and/or Wales until HRA and HCRW Approval is issued.

If you require further information, please contact me.

Kind regards

**Alison Doherty**
**Approvals Administrator**
Bristol REC Centre | Whitefriars | BS1 2NT
**T.** 020 7104 8049
**E.** berkshire.rec@hra.nhs.uk
**W.** www.hra.nhs.uk

Medicines & Healthcare products Regulatory Agency

MHRA

**MHRA**
10 South Colonnade
Canary Wharf
London
E14 4PU
United Kingdom

**gov.uk/mhra**

Prof C Butler
UNIVERSITY OF OXFORD
NUFFIELD DEPARTMENT OF PRIMARY CARE HEALTH SCIENCES,
RADCLIFFE OBSERVATORY QUARTER, WOODSTOCK ROAD
OXFORD
OX2 6GG
UNITED KINGDOM

22/02/2021

Dear Prof C Butler,

**THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) REGULATIONS 2004 S.I. 2004/1031**

| | |
|---|---|
| Our Reference: | CTA 21584/0426/001-0010 |
| Eudract Number: | 2020-001209-22 |
| Product: | Plaquenil-Hydroxychloroquine, Azithromycin, Doxycycline, Pulmicort Turbohaler 400, Colchicine |
| Protocol number: | PRINCIPLE |
| Substantial Amendment Code Number: | SA 12, 14 February 2021 |

**NOTICE OF ACCEPTANCE OF AMENDMENT**

I am writing to inform you that the Licensing Authority accepts the proposed amendment to your clinical trial authorisation (CTA), received on 19/02/2021.

MEDICAL - Remarks: Clinical Remarks:
The following comments are for future consideration / information only and do not affect the approval status of your study. No response is required.
1. The change to the age range is acceptable, but it is noted the study title still refers to older people only. This may need to be considered in the future to align the title and the trial objectives.
TOXICOLOGY
PHARMACEUTICAL

This amendment may therefore be made.

If applicable, you should ensure your trial details have been updated on the database where you have registered your trial.

You are reminded that where it is appropriate, the Ethics Committee should also be notified of amendments.

Yours sincerely,

**Clinical Trials Unit**
**MHRA**

Medicines and Healthcare Products Regulatory Agency

# IRAS Project ID 281958. HRA and HCRW Approval for the Amendment

berkshire.rec@hra.nhs.uk <noreply@harp.org.uk>

Tue 2/23/2021 08:38

**To:** Christopher Butler <christopher.butler@phc.ox.ac.uk>; CTRG Sponsorship Correspondence <ctrg@admin.ox.ac.uk>
**Cc:** Hannah Swayze <hannah.swayze@phc.ox.ac.uk>

Dear Christopher Butler,

| | |
|---|---|
| **IRAS Project ID:** | 281958 |
| **Short Study Title:** | PRINCIPLE [COVID-19] [UPH] |
| **Amendment No./Sponsor Ref:** | SA12 |
| **Amendment Date:** | 14 February 2021 |
| **Amendment Type:** | Substantial CTIMP - for review |

I am pleased to confirm **HRA and HCRW Approval** for the above referenced amendment.

You should implement this amendment at NHS organisations in England and Wales, in line with the guidance in the amendment tool.

**User Feedback**

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/.

Please contact [amendments@hra.nhs.uk]amendments@hra.nhs.uk for any queries relating to the assessment of this amendment.

Kind regards

**Kevin Ahmed**
**Approvals Manager**
**Health Research Authority**
Ground Floor | Skipton House | 80 London Road | London | SE1 6LH
**E.**amendments@hra.nhs.uk
**W.** www.hra.nhs.uk

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***Substantial Amendment Notification Form (Cf. Section 3.7.b of the Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial [1] )***

**NOTIFICATION OF A SUBSTANTIAL AMENDMENT TO A CLINICAL TRIAL ON A MEDICINAL PRODUCT FOR HUMAN USE TO THE COMPETENT AUTHORITIES AND FOR OPINION OF THE ETHICS COMMITTEES IN THE EUROPEAN UNION**

*For official use:*

| | |
|---|---|
| Date of receiving the request: | Grounds for non acceptance/negative opinion: ☐<br>Date: |
| Date of start of procedure: | Authorisation/positive opinion: ☐<br>Date: |
| Competent authority registration number of the trial:<br><br>Ethics committee registration number of the trial: | Withdrawal of amendment application: ☐<br>Date: |

*To be filled in by the applicant:*

This form is to be used both for a request to the Competent Authority for authorisation of a **substantial** amendment and to an Ethics Committee for its opinion on a **substantial** amendment. Please indicate the relevant purpose in Section A.

## A TYPE OF NOTIFICATION

| | |
|---|---|
| **A.1 Member State in which the substantial amendment is being submitted:** | **United Kingdom** |
| **A.2 Notification for authorisation to the competent authority:** | ☑ |
| **A.3 Notification for authorisation to the ethics committee:** | ☑ |

(1) OJ, C82, 30.3.2010, p. 1; hereinafter referred to as 'detailed guidance CT-1'.

## B TRIAL IDENTIFICATION *(When the amendment concerns more than one trial, repeat this form as necessary.)*

| | |
|---|---|
| **B.1 Does the substantial amendment concern several trials involving the same IMP?[2]** | yes ☐ no ☑ |
| B.1.1 If yes repeat this section as necessary. | |

(2) Cf. Section 3.7. of the detailed guidance CT-1.

| | |
|---|---|
| **B.2 Eudract number:** | 2020-001209-22 |
| **B.3 Full title of the trial:** | |
| Platform Randomised trial of INterventions against COVID-19 In older peoPLE | |
| **B.4 Sponsor's protocol code number, version, and date:** | |
| PRINCIPLE, v7.0, 16.01.2021 | |

## C IDENTIFICATION OF THE SPONSOR RESPONSIBLE FOR THE REQUEST

| **C.1** | **Sponsor** | |
|---|---|---|
| C.1.1 | Organisation: | University of Oxford |
| C.1.2 | Name of person to contact: | CTRG |
| C.1.3 | Address: | Joint Research Office 1st floor, Boundary Brook House, Churchill Drive, Headi |
| C.1.4 | Telephone number: | |
| C.1.5 | Fax number: | |
| C.1.6 | e-mail: | ctrg@admin.ox.ac.uk |

| C.2 | Legal representative[3] of the sponsor in the European Union for the purpose of this trial (if different from the sponsor) |
|---|---|
| C.2.1 | Organisation: |
| C.2.2 | Name of person to contact: |
| C.2.3 | Address: |
| C.2.4 | Telephone number: |
| C.2.5 | Fax number: |
| C.2.6 | e-mail: |

(3) As stated in Article 19 of Directive 2001/20/EC.

## D APPLICANT IDENTIFICATION (please tick the appropriate box)

| D.1 | Request for the competent authority | | |
|---|---|---|---|
| D.1.1 | Sponsor | | ☐ |
| D.1.2 | Legal representative of the sponsor | | ☐ |
| D.1.3 | Person or organisation authorised by the sponsor to make the application | | ☑ |
| D.1.4 | Complete below: | | |
| D.1.4.1 | Organisation: | University of Oxford | |
| D.1.4.2 | Name of person to contact: | Christopher Butler | |
| D.1.4.3 | Address: | Department of Primary Care Health Sciences, Radcliffe Observatory Quarter, Woodstock Road, Oxford, OX2 6GG | |
| D.1.4.4 | Telephone number: | 01865 289670 | |
| D.1.4.5 | Fax number: | | |
| D.1.4.6 | e-mail: | christopher.butler@phc.ox.ac.uk | |

| D.2 | Request for the Ethics Committee | | |
|---|---|---|---|
| D.2.1 | Sponsor | | ☐ |
| D.2.2 | Legal representative of the sponsor | | ☐ |
| D.2.3 | Person or organisation authorised by the sponsor to make the application | | ☑ |
| D.2.4 | Investigator in charge of the application if applicable[4]: | | |
| | • Co-ordinating investigator (for multicentre trial) | | ☐ |
| | • Principal investigator (for single centre trial) | | ☐ |
| D.2.5 | Complete below: | | |
| D.2.5.1 | Organisation: | University of Oxford | |
| D.2.5.2 | Name of person to contact: | Christopher Butler | |
| D.2.5.3 | Address: | Department of Primary Care Health Sciences, Radcliffe ObservatoryQuarter, Wo | |
| D.2.5.4 | Telephone number: | 01865 289670 | |
| D.2.5.5 | Fax number: | | |
| D.2.5.6 | e-mail: | christopher.butler@phc.ox.ac.uk | |

(4) According to national legislation.

## E SUBSTANTIAL AMENDMENT IDENTIFICATION

| E.1 | Sponsor's substantial amendment code number, version, date for the clinical trial concerned: |
|---|---|
| | SA 12, 14 February 2021 |

| E.2 | Type of substantial amendment | |
|---|---|---|
| E.2.1 | **Amendment to information in the CT application form** | yes ☐ no ☑ |

| | | |
|---|---|---|
| E.2.2 | **Amendment to the protocol** | yes ☑ no ☐ |
| E.2.3 | **Amendment to other documents appended to the initial application form** | yes ☐ no ☑ |
| E.2.3.1 | If yes specify: | |
| E.2.4 | **Amendment to other documents or information** | yes ☑ no ☐ |
| E.2.4.1 | If yes specify:<br><br>CTIMP IMP<br>Other change<br><br>Discontinuation of doxycycline arm - confirmation | |
| E.2.5 | **This amendment concerns mainly urgent safety measures already implemented**[5] | yes ☐ no ☑ |
| E.2.6 | **This amendment is to notify a temporary halt of the trial**[6] | yes ☐ no ☑ |
| E.2.7 | **This amendment is to request a restart of the trial**[7] | yes ☐ no ☑ |

(5) Cf. Section 3.9. of the detailed guidance CT-1.

(6) Cf. Section 3.10. of the detailed guidance CT-1.

(7) Cf. Section 3.10. of the detailed guidance CT-1.

| **E.3** | **Reasons for the substantial amendment** | |
|---|---|---|
| E.3.1 | **Changes in safety or integrity of trial subjects** | yes ☐ no ☑ |
| E.3.2 | **Changes in interpretation of scientific documents/value of trial** | yes ☐ no ☑ |
| E.3.3 | **Changes in quality of IMP(s)** | yes ☐ no ☑ |
| E.3.4 | **Changes in conduct or management of trial** | yes ☑ no ☐ |
| E.3.5 | **Change or addition of principal investigator(s), co-ordinating investigator** | yes ☐ no ☑ |
| E.3.6 | **Change/addition of site(s)** | yes ☐ no ☑ |
| E.3.7 | **Other change** | yes ☑ no ☐ |
| E.3.7.1 | **If yes specify:**<br><br>CTIMP IMP<br>Other change<br><br>Discontinuation of doxycycline arm - confirmation | |
| E.3.8 | **Other case** | yes ☐ no ☑ |
| E.3.8.1 | **If yes specify:**<br><br>Change to CTIMP IMP - see E.2.4.1 for details | |

| **E.4** | **Information on temporary halt of trial**[8] | |
|---|---|---|
| E.4.1 | **Date of temporary halt** | |
| E.4.2 | **Recruitment has been stopped** | yes ☐ no ☑ |
| E.4.3 | **Treatment has been stopped** | yes ☐ no ☑ |

| | |
|---|---|
| E.4.4 | Number of patients still receiving treatment at time of the temporary halt in the MS concerned by the amendment |
| E.4.5 | **Briefly describe (free text):**<br>• Justification for a temporary halt of the trial<br>• The proposed management of patients receiving treatment at time of the halt *(free text).*<br>• The consequences of the temporary halt for the evaluation of the results and for overall risk benefit assessment of the investigational medicinal product *(free text).* |

(8) Cf. Section 3.10. of the detailed guidance CT-1.

**F DESCRIPTION OF EACH SUBSTANTIAL AMENDMENT[9]** *(free text)* **:**

| Previous and new wording in track change modus | New wording | Comments/explanations/reasons for substantial amendment |
|---|---|---|
| | | |

(9) Cf. Section 3.7.c. of the detailed guidance CT-1. The sponsor may submit this documentation on a separate sheet.

**G CHANGE OF CLINICAL TRIAL SITE(S)/INVESTIGATOR(S) IN THE MEMBER STATE CONCERNED BY THIS AMENDMENT**

| G.1 | Type of change |
|---|---|
| G.1.1 | **Addition of a new site** |
| G.1.1.1 | **Principal investigator** (provide details below) |
| G.1.1.1.1 | Given name |
| G.1.1.1.2 | Middle name (if applicable) |
| G.1.1.1.3 | Family name |
| G.1.1.1.4 | Qualifications (MD……..) |
| G.1.1.1.5 | Professional address |
| G.1.2 | **Removal of an existing site** |
| G.1.2.1 | **Principal investigator** (provide details below) |
| G.1.2.1.1 | Given name |
| G.1.2.1.2 | Middle name (if applicable) |
| G.1.2.1.3 | Family name |
| G.1.2.1.4 | Qualifications (MD……..) |
| G.1.2.1.5 | Professional address |
| G.1.3 | **Change of co-ordinating investigator** (provide details below of the new coordinating investigator) |
| G.1.3.1 | Given name |
| G.1.3.2 | Middle name |
| G.1.3.3 | Family name |
| G.1.3.4 | Qualifications (MD……..) |
| G.1.3.5 | Professional address |
| G.1.3.6 | Indicate the name of the previous co-ordinating investigator: |
| G.1.4 | **Change of principal investigator at an existing site** (provide details below of the new principal investigator) |
| G.1.4.1 | Given name |
| G.1.4.2 | Middle name |
| G.1.4.3 | Family name |
| G.1.4.4 | Qualifications (MD……..) |
| G.1.4.5 | Professional address |
| G.1.4.6 | Indicate the name of the previous co-ordinating investigator: |

## H CHANGE OF INSTRUCTIONS TO CA FOR FEEDBACK TO SPONSOR

| | | |
|---|---|---|
| **H.1** | **Change of e-mail contact for feedback on application*** | |
| **H.2** | Change to request to receive an .xml copy of CTA data | yes ☐ no ☑ |
| H.2.1 | Do you want a .xml file copy of the CTA form saved on EudraCT? | yes ☐ no ☑ |
| H.2.1.1 | If yes provide the e-mail address(es) to which it should be sent (up to 5 addresses): | |
| H.2.2 | Do you want to receive this via password protected link(s)[10]? | yes ☐ no ☑ |
| If you answer no to question H.2.2 the .xml file will be transmitted by less secure e-mail link(s) | | |
| H.2.3 | Do you want to stop messages to an email for which they were previously requested? | yes ☐ no ☑ |
| H.2.3.1 | If yes provide the e-mail address(es) to which feedback should no longer be sent: | |
| **(*This will only come into effect from the time at which the request is processed in EudraCT).** | | |

(10) This requires a EudraLink account. (See https://eudract.ema.europa.eu/ for details)

## I LIST OF THE DOCUMENTS APPENDED TO THE NOTIFICATION FORM (cf. Section 3.7 of detailed guidance CT-1)

*Please submit only relevant documents and/or when applicable make clear references to the new ones already submitted. Make clear references to any changes of separate pages and submit old and new texts. Tick the appropriate box(es).*

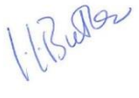
| | | |
|---|---|---|
| **I.1** | **Cover letter** | ☑ |
| **I.2** | **Extract from the amended document in accordance with Section 3.7.c. of detailed guidance CT-1 (if not contained in Part F of this form)** | ☐ |
| **I.3** | **Entire new version of the document[11]** | ☑ |
| **I.4** | **Supporting information** | ☑ |
| **I.5** | **Revised .xml file and copy of initial application form with amended data highlighted** | ☐ |
| **I.6** | **Comments on any novel aspect of the amendment if any:** | |

(11) Cf. Section 3.7.c. of the detailed guidance CT-1.

## J SIGNATURE OF THE APPLICANT IN THE MEMBER STATE

**J.1** I hereby confirm that/confirm on behalf of the sponsor that (delete which is not applicable)

- The above information given on this request is correct;
- The trial will be conducted according to the protocol, national regulation and the principles of good clinical practice; and
- It is reasonable for the proposed amendment to be undertaken.

| | | |
|---|---|---|
| **J.2** | **APPLICANT OF THE REQUEST FOR THE COMPETENT AUTHORITY** (as stated in section D.1): | ☑ |
| J.2.1 | Signature[12]: |  |
| J.2.2 | Print name: | Christopher Butler |
| J.2.3 | Date: | 19 February 2021 |

(12) On an application to the Competent Authority only, the applicant to the Competent Authority needs to sign.

| | | |
|---|---|---|
| **J.3** | **APPLICANT OF THE REQUEST FOR THE ETHICS COMMITTEE** (as stated in section D.2): | ☑ |

| | | |
|---|---|---|
| J.3.1 | Signature[13]: |  |
| J.3.2 | Print name: | Christopher Butler |
| J.3.3 | Date: | 19 February 2021 |

(13) On an application to the Ethics Committee only, the applicant to the Ethics Committee needs to sign.