To: Participating Organisation

Subject: IRAS Number 281958; SA12 Notification of Amendment Category A, C

Dear Participating Organisation,

RE: IRAS Number 281958; PRINCIPLE; Amendment Reference – SA12

We are contacting you as a PRINCIPLE recruiter to update on the following three items (please see attached documents for further information):

1. Trial Intervention Summary – *Eligibility Summary*
2. Lack of capacity to consent – *Care Home Infographic*
3. Substantial Amendment 12 – *List of updated trial documents, located here for download* https://www.principletrial.org/health-professionals/substantial-amendment-12/.

1. Trial Intervention Summary

Thank you for your continued support of the PRINCIPLE trial!

We are pleased to confirm that we have just received approval from the REC, MHRA, the NIHR Urgent Public Health Group, and HRA to add Colchicine and Usual Care as a third treatment arm to the trial. We have also lowered the age group; people ill with COVID-19 who are 18 and over are now eligible for the Usual Care + Colchicine arm and Usual Care comparative group, PROVIDED they have either certain underlying health conditions or are experiencing shortness of breath as part of their COVID-19-like illness.

To note, the Usual Care + Budesonide arm continues to remain open only to those aged 50 – 64 with a certain **underlying health condition, or participants** aged 65 and over. A summary of the current arms and eligible age groups for each is provided in the table below.

Trial arms	Eligible Age Group (meeting inclusion criteria)
Usual Care	**18 and over**, with a certain underlying health condition, OR who have shortness of breath as part of their COVID-19-like illness
Usual Care + Colchicine	**18 and over**, with a certain underlying health condition, OR who have shortness of breath as part of their COVID-19-like illness
Usual Care + Budesonide	50 – 64 with a certain **underlying health condition** OR aged 65 and over

DUE TO TECHNICAL ISSUES, WE CAN CURRENTLY ONLY ENROL PATIENTS AGED 18-49 via the 0800 138 0880 FREEPHONE NUMBER. GPs conducting eligibility review via Sentry will only be able to randomise participants to Usual Care or Budesonide. We hope to have this fixed shortly and will update next week when we are able to recruit online, and will send updated promotional materials.

The inclusion and exclusion criteria for each trial arm is summarised in the attached **Eligibility Summary**. Further details for each treatment arm can also be found in the protocol Intervention Specific Appendices. Participants need to be eligible for Usual Care and at least one of the intervention groups, and assignment to a trial arm is automated by the online system and based on information provided at screening (completed by participant) and eligibility (completed by reviewing clinician).

2. Lack of capacity to consent

The PRINCIPLE trial has approval to recruit care home residents who lack capacity to consent, when a Legal Representative can be identified. Please see the attached **Infographic for Care Homes**, for further details.

3. Substantial Amendment 12

We have submitted and received REC, HRA and MHRA approvals (attached to this email) for an amendment for the PRINCIPLE study. A **List of Updated Documents** is attached and the documents can be downloaded directly from our website https://www.principletrial.org/health-professionals/substantial-amendment-12/. Please read the documents carefully as these provide information on how this amendment should be implemented, as well as what the amendment entails.

When will this amendment be implemented?
This amendment has been categorised as **category A, C** (see locked amendment tool for all changes and categorisations). In line with the Amendment Tool and UK wide policy on the handling of amendments, your site has **2** calendar days from the date of this notification to raise an objection about the amendment (does not apply to all UK nations). If we do not hear from you, we will assume that the amendment may be implemented at your site.

What is the impact on research activities at sites?
The main changes for attention are:

No.	Amendment	Rationale	Documents Updated
1	Addition of colchicine arm	The UK Therapeutics Task Force COVID-19 Advisory Therapeutics Committee and the Chief Medical Officers have recommended that the PRINCIPLE Trial evaluates colchicine. Colchicine is a drug already in widespread clinical use for treating acute gout, and is	• Protocol ISA • PIS appendix • Medication card • IMP label

		licensed in the United Kingdom. Colchicine was evaluated as a treatment for COVID-19 in the ColCorona trial, which found evidence that colchicine reduced hospitalisation and possibly death form COVID-19. The ColCorona trial did not assess the impact of colchicine on recovery. Not all findings were statistically significant. PRINCIPLE will assess colchicine as a potential COVOD-19 treatment looking at recovery and hospitalisation outcomes.	
2	Discontinuation of the doxycycline arm	Formal notification that the doxycycline arm has been discontinued (on 14th December 2020).	• Protocol
3	Inclusion criteria - to include those aged 18 or over, who have either certain underlying health conditions or shortness of breath	We now know that many people below the age of 50 can experience a severe, complicated or prolonged illness course. We do not know how younger people will be impacted upon by new virus variants. Inclusion criteria in the main protocol updated to now include **those aged 18 and over provided they have certain comorbidities or shortness of breath as part of their COVID-19 illness** **APPLIES ONLY TO THE USUAL CARE + COLCHICINE AND USUAL CARE ARMS OF THE TRIAL.** **THE BUDESONIDE ARM CONTINUES FOR THOSE AGED 50 OR ABOVE ONLY.**	• Protocol • Pictorial PIS • Colchicine documents: i) medication card, ii) PIS appendix and iii) IMP label • NHS testing wording • Recruitment poster • Pharmacy poster • Advert • Radio advert • Infographic script • Social media • Translated video script • Introductory letter • Scotland GP letter • Study partner letter • Patient recruitment letter

Is there any impact on funding/agreements?
This amendment **does not impact** the funding/agreement that have previously been agreed.

What is the HRA Approval status of the amendment?
All approvals have been received.

Kind regards
The PRINCIPLE Trial Team