COPCOV - Frequently Asked Questions from Sites

CONTINUED RATIONALE FOR THE STUDY

Q) Several studies have indicated that hydroxychloroquine may not be an effective treatment for COVID-19 and concerns have been raised around safety. Why are you continuing the COPCOV trial?

A)

- COPCOV is a pre-exposure prophylaxis trial.
- Almost all antiviral treatments work much better the earlier they are given. A good example is HIV prophylaxis which can prevent infection if given pre-exposure or up to three days post exposure but can only ever control, not cure HIV infection.
- The post-exposure trials with hydroxychloroquine for COVID-19 have been too small, and drug has been given too late in most participants but there are indications that given early enough hydroxychloroquine may prevent COVID-19.
- Safety concerns were raised by an observational study based on a large, probably fraudulent, commercial data base which was published in the Lancet during May and which has since been retracted.
- Results of large treatment trials such as RECOVERY using doses of hydroxychloroquine much larger than in COPCOV have confirmed the long-established excellent safety and tolerability record of hydroxychloroquine.
- Rheumatology specialists are familiar with using hydroxychloroquine and may be good local advocates or PIs for the study.

Q) Rates of COVID-19 are currently low in the UK. Shouldn't we wait to set the study up until rates increase?

A)

- Rates generally are low but healthcare workers have COVID-19 rates up to 10x higher than the general population.
- Where there are local outbreaks, healthcare workers continue to catch COVID-19.
- With current levels of immunity a further increase in COVID-19 rates is expected in the UK as has been seen elsewhere in Europe especially as autumn and winter arrive.
- We are looking to set up 20-25 sites to run COPCOV by the end of October 2020 so that we are fully ready to deliver recruitment to the trial over the winter months.

Q) There is currently limited capacity to take on this study as we are under pressure to recruit to other COVID studies and restart non-COVID research.

A)

- NIHR have re-confirmed the importance of the COPCOV trial and its status as an Urgent Public Health priority trial
- COPCOV is the only Urgent Public Health badged study addressing how to protect healthcare workers from COVID-19
- COPCOV is the only Urgent Public Health study looking at a non-vaccine prevention strategy.
- In this light we hope sites will prioritise COPCOV over non-UPH studies and over UPH studies in domains such as treatment if they are already running competing trials.
- Participants in COPCOV may co-enrol into SIREN and this makes recruitment more efficient for research teams delivering the two studies.

SITE IDENTIFICATION	
When is the site set up due to start?	We are actively setting up sites in August and September. We would like to have a good spread of sites - aiming for at least 20 open by the end of October anticipating increasing case numbers of COVID-19 as the autumn starts
How quickly can sites be set up after expression of interest?	As soon as local agreements in place.
Where should EOIs be submitted?	Via TV&SM LCRN SSS email (studysupport.crnthamesvalley@nihr.ac.uk)
We are setting up SIREN which recruits healthcare workers. How does this affect COPCOV?	People who have antibodies to COVID-19 are not eligible for COPCOV. We have agreed with the SIREN investigators that participants who are antibody negative can co-enrol in COPCOV and SIREN. This makes it easy for sites to run both studies side by side and recruit as many participants as possible to both studies with minimal additional burden to participants.
Given the high level of COVID in London are you interested in any London sites?	Yes, we are interested in centres all over the UK. Even in London it is likely that only a minority of people have yet been infected with COVID and so staff working at London hospitals are definitely eligible to participate
Which sites should take part?	Any acute NHS trust is eligible to take part. The Expression of interest form sets out details of what resources are required
How can healthcare workers access the study?	The study website COPCOV.org has a participant expression of interest and enrolment-check form which healthcare workers can complete. Alternatively they can go via their local research team. The study provides templates for a poster and emails to staff which can be localised with contact information for the study team at each site.
Would you consider sites with an initial target of 200. As a formal MH trust that has recently merged with a Community Trust we SHOULD have the numbers, but we are still developing research links between the two organisations so we are not 100% sure how recruitment will proceed?	We have not set any hard limits but expect most sites will be able to recruit well if all eligible staff are encouraged to consider taking part. The study is open to a very wide range of staff and to healthcare workers at local ambulance and community trusts should they wish to enrol.
Can sites who have already expressed an interest resubmit EOIs if circumstances have changed?	Yes happy to receive
Can sites act as a PIC to signpost to another trust for the study?	Sites do not need to be set up as a PIC to advertise the study to their staff. We have prepared a range of advertising templates so that recruiting sites can contact local healthcare providers and ask them to make their staff aware of the study.

Is there a deadline for EOIs?	No but the sooner the better.
Will there be an SIV? If not, what are the training requirements for the study?	A full set of SIV slides are available to sites to view. We will offer online training / Q+A sessions to sites as required. We hold a monthly teleconference for site investigators to catch up with each other about study progress and share learning
Will there be training in the following: -The way that swabs should be taken - BDS from venous draw - Centrifuge - Dispensing of medicines for pharmacy	Swabs in the study are 'self taken' by participants. They will be directed to NHS advice on self taking swabs for COVID which is available here:https://www.gov.uk/government/publications/covid-19-guidance-for-taking-swab-samples/how-to-use-the-self-swabbing-kit-for-a-combined-throat-and-nose-swab-video Information about sample handling and dispensing of IMP is included in the SIV slides and SOPs which are all available on COPCOV.org
We are wondering if we can run the study across 2 sites to give staff options for study visits is this possible?	Yes. Substantial Amendment 4 which is under review currently (Aug 19) will make it easier for a single Trust to run the study across more than one site.
Looking at the information can a nurse or pharmacist prescribe the medication after the PI has confirmed eligibility?	This will be dependent upon the Trust. As long as the eligibility of a participant has been checked by a clinician who has been trained on the study this is ok but some site Prescribing committees have said they still require a medic to prescribe.
PROTOCOL	
Exclusion criteria – need to consider including; pregnant / breastfeeding women, renal impairment – eGFR or CrCl? This protocol says to exclude CrCl<10ml/min, but The Renal Database advises caution for those with CrCl<30ml/min.	Exclusion criteria are as per the protocol. Although hydroxychloroquine is widely used safely in pregnancy in the Trial the MHRA have asked us to exclude pregnant women or women who are trying to become pregnant. There is no requirement to avoid pregnancy or have a negative pregnancy test. Participants may be excluded at the PI or their delegates discretion if they have, among other pre-existing conditions CKD. As used within the Trial HCQ is safe in participants with CrCl down to 10ml/ml. the MHRA have approved the trial on the basis of its current protocol.
CONTRACTING AND PATIENT REIMBURSEMENT	
Site funding available	1: £10,000 upon full execution of the site agreement 2: 100 participants enrolled £2,500 3: 200 participants enrolled £2,500 4: 300 participants enrolled £2,500 5: 400 participants enrolled £2,500 6: Over 400 participants enrolled £10,000

Is there reimbursement to participants e.g. to cover travel expenses for the baseline and follow-up visits etc.?	a. No, the administrative burden to do this would be too great for this number of participants.
Whether the above funding would apply in full or, at least, in part as a PIC.	Participants can include those working outside of the participating sites, but their employing organisations would not be set up as a PIC. Posters may be displayed in those organisations or people working there may see the trial advertised nationally or express interest via the website, but only secondary care sites would be participating and no PICs will be set-up.
When will contracts be circulated with the local pack	These are available now to site which express an interest
Does the study team envisage any excess treatment costs?	Yes, The SoECAT is available from the COPCOV.org website
DATABASE, RECRUITMENT, RANDOMISATION, FOLLOW-UP AND STUDY PROMOTION	
How can healthcare workers access the study?	The study website COPCOV.org has a participant expression of interest and enrolment-check form which healthcare workers can complete. Alternatively they can go via their local research team. The study provides templates for a poster and emails to staff which can be localised with contact information for the study team at each site.
Is this study open to Primary Care or primary care staff? Also, would research staff (eg. research nurses) be able to take part?	It is open to all healthcare staff working in a place where patients could have COVID-19 (so not exclusively front-line staff, also clerical staff for example) AND to staff that don't necessarily work in a place (eg ambulance crew) but who are in contact with patients because of their job.
Is ethnicity data being collected for this study?	Yes this will be gathered in the CRF
What about other studies recruiting the same population?	As of today COPCOV is the only non-vaccine prophylaxis study currently badged by DHSC as a UPH study. Sites should not recruit to a competing non- UPH badged study.
Are there GI side effects of a loading dose, which means staff have to be off work?	This is very unlikely. GI side-effects are only really expected with the first loading dose and should be mild and short lived. In the BOULWARE study of post-exposure prophylaxis which used larger loading doses less than half the participants even guessed correctly whether they were taking HCQ or placebo.

Nurse follow up on whether people have confirmed they are ok each day via the app.	The App will feed into a spreadsheet each day to the study team at the sites. If people report they are unwell or do not report this is flagged up on a continuous basis to the study team. Participants given all contact details of the study team, participants also provide email address and mobile phone number.
Regional recruitment centres, should we be encouraging HCP to travel to other centres?	This is really up to sites. Many sites are able to recruit participants from outside without bringing people into clinical areas of the hospital.
Can accruals be counted?	Yes
What is the proposed recruitment end date?	Competitive recruitment UK 10,000 globally 40,000. We expect recruitment to finish by the end of March 2021
Are the staff recruited going to be tested for antibodies, to check if they have already had the virus, to cover those that were asymptomatic?	All participants are tested for antibodies in blood taken at baseline and the end of the study but this testing is all done at the end of the study. Where participants have had a positive test e.g. as part of staff screening they are NOT ELIGIBLE to join COPCOV. If a staff member has been symptomatic or self-isolating before and yet tested negative they ARE eligible to take part
Is it only for staff delivering care at the time of the study or can recruitment be retrospective?	Participants should fulfil enrolment criteria at the time they join the study not retrospectively.
What is the window to see eligible participants after confirmation and referral to site?	There is no set window but clearly the sooner the better. In any case eligibility is rechecked at the enrolment visit.
What is the inclusion criteria for suspected COVID-19 cases? Are they still able to participate if the diagnosis was not confirmed?	Yes only a proven diagnosis of COVID 19 precludes participation. This is expected to be on the basis of a positive throat swab. Many healthcare staff have had respiratory tract infections over the last three months and in many cases this will NOT have been COVID 19 so we would definitely encourage such staff to take part
Why does the protocol not require baseline ECGs? Can the CI offer any reassurance as to why the ECG is not required?	Hydroxychloroquine prolongs the ECG QT interval but as used in the trial there is no need to do a baseline ECG. The MHRA has approved on this basis. The doses we are using in this trial (much lower than in treatment trials) are widely used for other conditions (e.g. rheumatological conditions) where routine ECG monitoring is not required, and no safety concerns have been raised. Modest QT-prolongation has not been associated with adverse cardiovascular events and these drugs have been used as antiarrhythmics. A baseline QTc, and degree of prolongation have not

	been established which warrant exclusion from the study. The exclusion criteria ensure participants are not at risk of harm from QT prolongation. In selected patients a local PI may choose to do an ECG rather than automatically exclude certain participants and detailed advice about this is contained in the study training documents.
Are employees from Social Care/Care Homes eligible to take part in the study?	Yes
is there a window +/- to see participants for their follow ups?	Yes -3/+1 Days for visits
Would District/Community Nursing Staff be eligible?	Yes as above as their work brings them into contact with patients who may have unsuspected COVID-19 infection
We are in the process of collecting expressions of interest from sites and several of the sites that we have spoken to have indicated that the target of 400 may not be achievable. Do you know if sites in England also feel that the target is high? We are wondering if any sites in the UK will be capable of achieving such a high target?	We think that at medium to large trusts with many thousands of employees given the wide range of areas and staff types involved in care of patients with COVID 19 that this should be possible. Given the recruitment window now runs across the winter these numbers should be achievable
Could you confirm with the study team whether pharmacy will also be blinded in this study, as it would be useful to be able to recruit pharmacy staff.	Yes blinding is done centrally so all site staff are blinded
Is co-enrolment with other CTIMP studies allowed?	No, participants may not co-enrol in another CTIMP. There is a 6 week wash-out period from COPCOV before participants are able to enter another study. Of note COPCOP participants can join other observational studies and can co-enrol in the SIREN study
DOCUMENTATION AND SITE SUPPLIES & SAMPLING	
Will a site file be provided?	Documents will be shared via email, the website or other electronic means for sites to print according to an ISF index we will provide. A physical file cannot be provided at this time and sites will be required to create their own file form the documents provided.
How will the study documents be shared – on a website or emailed?	They are all available on the study website.
What vendor is being used for the eCRF?	Axiom

Will they be providing thermometers and a site file.	Yes thermometers are provided along with swabs, pre-paid return (to Oxford) postage for swab transport and filter papers for dried blood spots.
Do you provide the nose or throat swab kit if participants get COVID-19 during the trial?	Yes
If the patients have been tested positive via standard practice they will have to isolate. Will you post the kits to the participants home with SAE to post back the sponsors lab?	Yes. Sites will be supplied with swabs and prepaid return (to Oxford) labels. Sites will need to purchase specific packaging and postage to send to participant. Info about how to do this is in the SIV materials.
Do you provide a dried blood spot (DBS) sample kit?	Yes we provide DBS kits.
Can you clarify if you provide the EDTA sample tubes?	No these are standard EDTA tubes all hospitals use. Sites will need to supply lab consumables for spinning, aliquoting and storing blood samples.
How often will you want sites to courier the samples to your labs? Do you arrange the courier to ship the samples?	We can ship at intervals to work with your lab depending on space and yes we will arrange this
How will the finger prick samples be stored?	We will supply reagents for the finger prick samples – little cassettes that are similar to the Guthrie cards all kids get at birth.
I can see storage information for the EDTA but not the filter paper only that it will be in individual plastic bags?	Once taken they need no special storage just in their boxes. We supply labels for all this.
We only have a minus 40 freezer on site. My question is can we put the samples in the minus 40 initially and then transfer within a day or so of that?	Yes that's fine. The only real need for -80 is the respiratory samples which are now to go direct to the trials unit from each participant.
What is the time frame for taking bloods, centrifuge and being stored in a freezer.	A couple of hours on ice is fine so that samples can go from the clinic to the local lab at intervals
IMP SOURCING AND PHARMACY CONSIDERATIONS	
What pharmacy storage is needed?	At least 400 doses of drug. This is 8 boxes of 353MM X 400MM X 236MM. Ambient temperature. Locked cupboards
What research laboratory capabilities are needed?	Immediate processing (spinning) storage -20C and transport of baseline and end of study blood samples.
How will the IMP be shipped, dispensed and what is expected for returns? Is there a process in place for ordering this and is it via IMMFORM by pharmacy departments directly?	IMP will be shipped in one or two batches and dispatched in one go to the participants via a pharmacy at the start of study. IMP will require onsite destruction at the end of the study

Will the sponsor be supplying a pharmacy HRA assessment?	No, not at this time.
What are the individual patient medication package sizes?	The boxes of 50 kits are 353mm x 400mm x 236 mm – you will receive 8 of these boxes. I don't know the size of the per patient carton.
How are other sites dealing with the need to receive returns? Our preference would be that for the duration of the study we do not accept returns, particularly from high-risk areas/participants.	We would only expect returns at the end of the study for destruction. Note these are healthy staff members not patients with COVID19. If sites cannot accept returns please let us know and we will find an alternative solution.
Are there recommendations for film covered tablets to ensure that participants are not unblinded due to the bitter taste of the medication?	Both active and placebo are overcoated to make them physically identical.