PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Efficacy of pragmatic same-day ring prophylaxis for adult individuals exposed to SARS-CoV-2 in Switzerland (COPEP): protocol of an open-label cluster randomized trial
AUTHORS	Smit, Mikaela; Marinosci, Annalisa; Nicoletti, Giovanni; Perneger, Thomas; Ragozzino, Silvio; Andrey, Diego; Stoeckle, Marcel; Jacquerioz, Frederique; Lebowitz, Dan; Agoritsas, Thomas; Meyer, Benjamin; Spechbach, Herve; Salamun, Julien; Back, Moritz; Schaubhut, Carla; Fuchs, Simon; Decosterd, Laurent; Battegay, Manuel; Guessous, Idris; Chappuis, François; Kaiser, Laurent; Labhardt, Niklaus; Calmy, Alexandra

VERSION 1 – REVIEW

REVIEWER	Debbie Ford MRC Clinical Trials at UCL, London, UK
REVIEW RETURNED	15-Jun-2020

GENERAL COMMENTS	Abstract Line 46 missing word “repurposed drugs” Line 52 “asymptomatic” usually refers to someone with disease but no symptoms, here it includes individuals without the virus as well. I have said the abstract is incomplete as the description of the outcomes relies on definitions not available to the reader until the main paper. This is important but can be easily addressed as follows: Line 58 “incidence of COVID-19” should be clarified as “laboratory-confirmed COVID-19 with ≥1 symptom” or similar. The authors use “COVID-19” to mean symptomatic disease with lab-confirmation but this is not clear to a quick reader of the abstract. Introduction The use of a single dose of HCQ seems at odds with the treatment studies and other prevention studies – I realise more data are now available but at the time the protocol was written, why was a single dose considered? Methods Use of asymptomatic needs addressing as above. Use of COVID-19 to mean “laboratory-confirmed COVID-19 with ≥1 symptom” is not defined until line 175; this needs to be much earlier. The description of the primary endpoint (line 154) is much clearer in the supplementary material. Secondary outcomes are also better defined in the supplementary material, particularly as outcomes are described before measurements are defined. Inclusion criterion 1 (table 1 and lines 122-126) – this is not clear. The contact needs to be randomised within 48 hours of their contact with the confirmed case but the index case also needs to

	have tested positive within the last 48 hours I think. Is this correct? If so isn't the criterion "Documented close contact within the last 48 hours with an individual confirmed as PCR-confirmed SARS-CoV-2 positive also within the last 48 hours"? Recruitment is through households (possibly also work/social contacts who meet the definition although this is not clear) and through health care workers (line 129); it is unclear how the investigators expect participants to be divided between these two groups. This makes it difficult to know if other assumptions (see sample size) are reasonable. Sample size: • No references are given for the assumption of a 21-day incidence for COVID-19 of 20% or the 40% incidence of new SARS-CoV-2 infections among contacts. These seem high; there are household studies published in the literature and these should be referenced. • A relative risk reduction of 60% is very optimistic and there are no reasons given for assuming such a large treatment effect; particularly as the sample will be diluted for the primary endpoint by individuals who are already SARS-CoV-2-infected, where treatment may be too late. • The cluster size of 3 contacts (i.e. total of 4: the index case plus 3 contacts ≥18 years) seems high for Switzerland and certainly implies that most individuals will be recruited through households. • The design effect for the cluster design (1.1) is very small, and assumes that individuals within a household are close to independent in risk, which is unlikely. • In my view the trial is underpowered, but given there are other trials ongoing addressing these questions it may add to the combined literature and is worth publishing. Statistical analysis is well-described and seems appropriate. I did wonder why the investigators did not propose a mixed ordered logistic model for the outcome "severity of disease".

REVIEWER	Pradeesh Sivapalan Section of Respiratory Medicine, Herlev and Gentofte Hospital
REVIEW RETURNED	11-Jul-2020

GENERAL COMMENTS	This is a interesting protocol evaluating the efficacy of Hydroxychloroquine and lopinavir/ritonavir in adults exposed to severe acute respiratory syndrome coronavirus 2 I have a few comments: (a) This trial enrols adult individuals who have come into close contact with a confirmed case of SARS-CoV-2 infection. A close contact is defined as a person who spent >15 minutes in < 2 meter distance or shared closed space with a confirmed case for a prolonged period (e.g. more than 2 h) I think this definition is vague and should be elaborated Who reports the close contact to the cofirmed case of SARS-CoV-2 infection. Is it a healthcare professional or is it an infected person?

	(b) When hydroxychloroquine is used in rheumatologic doses, recommended control of: hemoglobin platelet count leukocyte and differential count Will these blood tests be taken during hospitalization? (c) The primary endpoint is the 21-day incidence of COVID-19 Why did you choose 21 days? The incubation time is shorter. (d) how many patients are expected to lost to follow-up and will this affect the sample size? (e) Is medicine compliance registered in CRF? (f) Page 19, line 107. Need to define COPEP the first time used (g) Under limitation you should mention that it is an unblinded study and that is great limitation. I think the trial will be substantially improved by making a dobbelt-blinded trial.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Debbie Ford
Institution and Country: MRC Clinical Trials at UCL, London, UK
Please state any competing interests or state 'None declared':None declared

Please leave your comments for the authors below
Abstract
Line 46 missing word "repurposed drugs"

Response:

Thank you, this has been corrected in the revised version.

Line 52 "asymptomatic" usually refers to someone with disease but no symptoms, here it includes individuals without the virus as well.
I have said the abstract is incomplete as the description of the outcomes relies on definitions not available to the reader until the main paper. This is important but can be easily addressed as follows: Line 58 "incidence of COVID-19" should be clarified as "laboratory-confirmed COVID-19 with ≥1 symptom" or similar. The authors use "COVID-19" to mean symptomatic disease with lab-confirmation but this is not clear to a quick reader of the abstract.

Response:

Thank you for the suggestions. The following changes have been made to the abstract to clarify these points:

"*Asymptomatic individuals may be either SARS-CoV-2 positive of negative. "*

"The primary endpoint is 21-day incidence of *laboratory-confirmed* COVID-19 *with ≥1 compatible symptom,* […]"

Introduction
The use of a single dose of HCQ seems at odds with the treatment studies and other prevention studies – I realise more data are now available but at the time the protocol was written, why was a single dose considered?

Response:

Since the first submission of this manuscript the study protocol has undergone an amendment which includes the removal of the HCQ arm, as such the revised manuscript does not address this point.

Methods
Use of asymptomatic needs addressing as above.
Use of COVID-19 to mean "laboratory-confirmed COVID-19 with ≥1 symptom" is not defined until line 175; this needs to be much earlier.
The description of the primary endpoint (line 154) is much clearer in the supplementary material.
Secondary outcomes are also better defined in the supplementary material, particularly as outcomes are described before measurements are defined.

Response:

Thank you. The following changes have been made to clarify the above:

"*Asymptomatic individuals may be either SARS-CoV-2 positive of negative. "*

"The main objective of COPEP is to assess prevention of *laboratory-confirmed* COVID-19 *with ≥1 compatible symptom,[…]"*

"The primary endpoint is the 21-day incidence of *laboratory-confirmed* COVID-19 *with ≥1 compatible symptom* in individuals exposed to SARS-CoV-2 who are asymptomatic *(either SARS_CoV-2 positive or negative)* at baseline."

Inclusion criterion 1 (table 1 and lines 122-126) – this is not clear. The contact needs to be randomised within 48 hours of their contact with the confirmed case but the index case also needs to have tested positive within the last 48 hours I think. Is this correct? If so isn't the criterion "Documented close contact within the last 48 hours with an individual confirmed as PCR-confirmed SARS-CoV-2 positive also within the last 48 hours"?

Response:

The inclusion criteria regarding the time window have been amended since submission of our original manuscript. Since the amendment individuals are eligible for inclusion in the study if they had a documented contact dating no more than 7 days since contact but no more than 72 hours since the index case was diagnosed, allowing to include index patients exposed to an index case during its asymptomatic phase.

The "48 hours since onset of symptoms" refer to the definition of the contact rather than the time window stipulated for the study. This has been clarified in the revised manuscript:

"This trial enrols individuals (≥*16* years) who have come into close contact with a confirmed case of SARS-CoV-2 infection. *Individuals are eligible to be enrolled if the contact occurred within the last 7 days but no more than 72 hours after the index case was diagnosed.* A close contact is defined, *as per the Swiss Federal Office of Public Health,* as a person who spent >15 minutes in < 2 meter distance or shared closed space with a confirmed case for a prolonged period (e.g. more than 2 hours) in the period extending from 48 hours before onset of symptoms (or before date of testing in absence of symptoms), or a person who had direct contact with the body fluids or laboratory specimens of a case without recommended personal protective equipment (PPE) or in case of failure of PPE.

Recruitment is through households (possibly also work/social contacts who meet the definition although this is not clear) and through health care workers (line 129); it is unclear how the investigators expect participants to be divided between these two groups. This makes it difficult to know if other assumptions (see sample size) are reasonable.

Sample size:

- No references are given for the assumption of a 21-day incidence for COVID-19 of 20% or the 40% incidence of new SARS-CoV-2 infections among contacts. These seem high; there are household studies published in the literature and these should be referenced.
- A relative risk reduction of 60% is very optimistic and there are no reasons given for assuming such a large treatment effect; particularly as the sample will be diluted for the primary endpoint by individuals who are already SARS-CoV-2-infected, where treatment may be too late.
- The cluster size of 3 contacts (i.e. total of 4: the index case plus 3 contacts ≥18 years) seems high for Switzerland and certainly implies that most individuals will be recruited through households.
- The design effect for the cluster design (1.1) is very small, and assumes that individuals within a household are close to independent in risk, which is unlikely.

• In my view the trial is underpowered, but given there are other trials ongoing addressing these questions it may add to the combined literature and is worth publishing.

Response:

The assumptions regarding the 20% and 40% incidence among contacts are based on observations made by the Swiss Office for Public Health (OFSP). The OFSP is responsible for contacting every index case and provide guidance on quarantine measures, perform detailed contact tracing and ensure close contacts also adhere to quarantine measures. According to the regional office of public health, 15-20% of contacts become symptomatic during quarantine (unpublished), thus in line with our assumptions for the sample size. The literature on positivity of contacts varied a lot, and this variation may also be context dependents. We preferred to base our sample size on our local data. Similarly, the cluster size is based on local information during the first wave, although since the first wave, we have also seen index cases in smaller households (1-3).

We thus acknowledge that our sample size may be underestimated under current epidemic parameters and thus result in an underpowered study. As highlighted by the reviewer, however, given other ongoing studies in this field, we believe that evidence from this trial will nevertheless contribute positively to emerging literature on this topic. Depending on the epidemic situation and options for additional financial support at the end of the planned recruitment period, the scientific steering committee will consider continuing recruitment to inflate the sample size.

Statistical analysis is well-described and seems appropriate. I did wonder why the investigators did not propose a mixed ordered logistic model for the outcome “severity of disease”.

Response:

Many thanks. Both methods can be used to analyse ordinal data. The Mann-Whitney assumes that the dependent variable is normally distributed, and it cannot be assumed that the severity of COVID-19 is normally distributed. The mixed ordered logistic model relies of more assumptions which cannot be guaranteed in this analysis of severity.

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Reviewer: 2
Reviewer Name: Pradeesh Sivapalan
Institution and Country: Section of Respiratory Medicine, Herlev and Gentofte Hospital
Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

This is a interesting protocol evaluating the efficacy of Hydroxychloroquine and lopinavir/ritonavir in adults exposed to severe acute respiratory syndrome coronavirus 2

I have a few comments:

(a) This trial enrols adult individuals who have come into close contact with a

confirmed case of SARS-CoV-2 infection. A close contact is defined as a person who spent

15 minutes in < 2 meter distance or shared closed space with a confirmed case for a

prolonged period (e.g. more than 2 h)

I think this definition is vague and should be elaborated
Who reports the close contact to the cofirmed case of SARS-CoV-2 infection. Is it a healthcare professional or is it an infected person?

Response:

The definition of a close contact is the official definition of the Swiss Federal Office for Public Health (OFSP). The regional offices of Public Health Office are responsible for doing the contact tracing for every index case, through the use of extensive telephonic interviews, using this definition. The details of any individuals identified as a close contact of an index case are forwarded by the OFSP to the study team, this ensures a homogeneity in the contact definition for this trial.

(b) When hydroxychloroquine is used in rheumatologic doses,
recommended control of:
hemoglobin
platelet count
leukocyte and differential count

Will these blood tests be taken during hospitalization?

Response:

Since the first submission of this manuscript the study protocol has undergone an amendment which includes the removal of the HCQ arm, as such the revised manuscript does not address this point.

(c) The primary endpoint is the 21-day incidence of COVID-19
Why did you choose 21 days? The incubation time is shorter.

Response:
The incubation period for SARS-CoV-2 is estimated to be 2 to 14 days and refers to the period between contracting the virus and the onset of symptoms. Positivity for SARS-CoV-2 can be picked up beyond the onset of symptoms. A Day 21 endpoint allows the study to pick up both a positive PCR (either on Day 21 or before as an additional PCR is done for every individual if they develops COVID-19 compatible symptoms during follow-up) and a positive serology (with studies indicating that seroconversion happens between 14-20 days post exposure). This is compatible with the aim of adequately detecting both the primary (incidence of COVID-19) and first of the secondary (incidence of SARS-CoV-2) endpoint. An endpoint beyond 21 days would risk picking up an infection that occurred via a new contact, once individuals have finished their 10-14 days quarantine, while an endpoint prior to Day 21 may risk not picking up an asymptomatic SARS-CoV-2 infection.

(d) how many patients are expected to lost to follow-up and will this affect the sample size?

Response:

We expect few LtFU for this study due to the study's extremely short follow-up period and the quarantine all conacts must adhere to. Participants self-report symptoms every day via an online questionnaire and participants who do not complete the online questionnaire for two consecutive days are contacted by the study team to encourage adherence to study protocol. So far, we have enrolled one third of expected participants and have had no LtFU.

(e) Is medicine compliance registered in CRF?

Response:

Yes. The online questionnaire asks every individual in the LPV/r arm whether they adhered to the drug schedule every day for the 5 days course (self-reported adherence) and on Day 21 participants are asked to return the vials and any pills not taken are counted an reported in the IMP log, as is standard GCP procedure for any study. Furthermore, every participant on LPV/r will provide a dried blood spot on Day 5, which will serve as an indicator to medicine adherence. These are described in the manuscript, with further clarification added to the revised manuscript:

"In addition, participants will be asked to provide on day 5 a capillary puncture on dried blood spot (DBS) to assess blood levels of LPV/r. Participants will be given the option of "self-test", or of a home-visit for this DBS procedure."

"The online questionnaire generates alerts when individuals report a symptom associated with COVID-19 and if participants do not complete the questionnaire for 2 consecutive days. The online questionnaire also serves as a reminder for those on the LPV/r arm, to take their daily medication up to Day 5."

"Participants on the LPV/r arm are asked to bring the vials which contained the medication to the Day 21 visit, so that the study team can record the number of returned pills, as per Good Clinical Practice standard."

(f) Page 19, line 107. Need to define COPEP the first time used

Response:

Thank you, this has been modified in the revised manuscript

(g) Under limitation you should mention that it is an unblinded study and that is great limitation. I think the trial will be substantially improved by making a dobbelt-blinded trial.

Response:

Thank you, this has been modified in the revised manuscript

VERSION 2 – REVIEW

REVIEWER	Debbie Ford MRC Clinical Trials Unit at UCL, London, UK
REVIEW RETURNED	12-Oct-2020

GENERAL COMMENTS	Check for typos Abstract: Need some consistency in use of plural/singular for LPV/r – maybe "LPV/r has been proposed as a combination of repurposed drugs …. COPEP aims at assessing its efficacy" Asymptomatic individuals may be either SARS-CoV-2 positive or negative (in a few places says "of" – would search – saw in Abstract and Methods) Strengths and limitations: mentions 2 prophylactic candidates – not sure this is quite right as LPV/r is being tested as one treatment option although it includes 2 drugs HCQ mentioned in acceptability endpoints

REVIEWER	Pradeesh Sivapalan Section of Respiratory Medicine, Herlev-Gentofte Hospital, Hellerup, Denmark
REVIEW RETURNED	10-Oct-2020

GENERAL COMMENTS	The authors responded satisfactorily to all comments. I have no further corrections.