

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol for the DisCoVeRy trial: multi-centre, adaptive, randomized trial of the safety and efficacy of treatments for COVID-19 in hospitalized adults
AUTHORS	Ader, Florence

VERSION 1 – REVIEW

REVIEWER	Justin Stebbing Imperial College, London
REVIEW RETURNED	16-Jun-2020

GENERAL COMMENTS	This is an excellent protocol which enhances our knowledge. Limitations are mentioned. 3 comments: 1. The controversy surrounding HCQ should be mentioned and, 2. The RT-PCR method including Ct cut off should be discussed - I presume however the WHO PCR protocols are adhered to. 3. I could find no evidence of sample collection.
-------------------------	--

REVIEWER	Andrea Cortegiani Policlinico Paolo Giaccone, Di.Chir.On.S. University of Palermo, Italy
REVIEW RETURNED	23-Jun-2020

GENERAL COMMENTS	This is the protocol of the DisCoVeRy trial which is one of the most anticipated multicentre randomized adaptive trials in COVID-19 patients. The manuscript is clear, well-written. All the relevant information are clearly explained. No comments to be addressed.
-------------------------	---

VERSION 1 – AUTHOR RESPONSE

Reviewers' Reports:

Reviewer: 1

Reviewer Name: Justin Stebbing

Institution and Country: Imperial College, London

Please state any competing interests or state 'None declared': none declared

This is an excellent protocol which enhances our knowledge. Limitations are mentioned.

We sincerely thank the reviewer for his kind words and comments that improved the protocol.

3 comments:

1. The controversy surrounding HCQ should be mentioned and,

We have indeed added a mention of the controversy surrounding the selection of HCQ as a candidate treatment:

Lines 725-734:

There have been controversies regarding the candidate treatments that should be selected for COVID-19 clinical trials and notably regarding hydroxychloroquine. Hydroxychloroquine was identified at the beginning of the pandemic as a candidate treatment based on preliminary data and quickly became the most tested treatment in the world for COVID-19.[40,41] However, many of the articles supporting hydroxychloroquine suffered from methodological shortcomings and were in fact non-informative.[42] Hydroxychloroquine has been widely promoted as soon as February 2020 as an effective drug by some scientists and politics[43], leading to difficulties in recruiting patients in randomized clinical trials such as DisCoVeRy.[44] This is why the ever-changing scientific background supporting the use of each candidate treatment should be clear, detailed and regularly updated and pragmatic, adaptive clinical trials should be encouraged.

2. The RT-PCR method including Ct cut off should be discussed - I presume however the WHO PCR protocols are adhered to.

Lines 426-429:

RT-PCR methods for SARS-COV-2 detection in participating centers are different but their performances were all validated by French National Reference Center for Viral Respiratory Infections and viral loads are determined using the specific French National Reference Center RT-PCR IP4.[31]

3. I could find no evidence of sample collection.

We guess that the reviewer is talking about a biobank with systematic sample collection. We have modified Table 1 to better highlight the biobank and added the following:

Lines 444-446:

A sample collection is constituted for each patient (biobank) including whole blood and plasma at baseline and plasma at days 3 (+/- 1 d), 5 (+/- 1 d), 8 (+/- 1 d), 11 (+/- 1 d), 15 (+/- 2 d) and 29 (+/- 3 d). The biobank will be used to conduct ancillary analyses that remain to be determined.

Line 704:

A biobank has also been planned to conduct further analyses that still remain to be determined.

Reviewer: 2

Reviewer Name: Andrea Cortegiani

Institution and Country: Policlinico Paolo Giaccone, Di.Chir.On.S. University of Palermo, Italy

Please state any competing interests or state 'None declared': None

This is the protocol of the DisCoVeRy trial which is one of the most anticipated multicentre randomized adaptive trials in COVID-19 patients.

The manuscript is clear, well-written. All the relevant information are clearly explained.

No comments to be addressed.

We sincerely thank the reviewer for these kind words and hope that the results of the trial will live up to expectations.