Allegation of potential misconduct in research relating to a publication titled: "Preliminary meta-analysis of randomized trials of ivermectin to treat SARS-CoV-2 infection"

Report from the Screening Panel

Background

Complainant:

Mr Xavier Azalbert	President, BonSens.org a French citizen and civic association

Respondent:

Dr Andrew Hill	Senior Visiting Research Fellow in the Department of Pharmacology & Therapeutics (*Honorary University of Liverpool staff member*)

The focus of this investigation is on a number of potential research misconduct allegations raised in relation to the following publication:

"Preliminary meta-analysis of randomized trials of ivermectin to treat SARS-CoV-2 infection", published as a preprint (https://www.researchsquare.com/article/rs-148845/v1)

The concerns fall under the following categories of the University's Policy on Misconduct in Research:

- Reckless, negligent, or deliberate deviation from accepted good practice in carrying out research, including… failure to follow any protocols set out in the guidelines of appropriate recognised professional, academic, scientific and governmental bodies;
- Falsification;

- Misrepresentation of data and/or interests and or involvement; and
- Deception in proposing, carrying out or reporting results of research.

A full copy of the concerns can be found in *Appendix 1*.

The purpose of the Screening Panel has been to determine whether the allegation or apparent instance of misconduct warrants a Formal Investigation.

The Panel held two Panel meetings, and reviewed the following information:

- The allegations submitted by Complainant in an email on 25th March, 2021
- A response to the allegations submitted by the Respondent
- A response to additional questions posed by the Panel, submitted by the Respondent

Findings

The Panel did not find any evidence of misconduct in research which warrants a Formal Investigation.

Issues considered

Telephone transcript:

A telephone transcript was submitted by the Complainant as part of their evidence. Dr Hill states that he was unaware of the recording and did not give permission. The Panel's understanding (though the members acknowledge they are not legally qualified) is that such a recording is legal but may not be shared with third parties, though often done by e.g. journalists, with a public interest defence. The Complainant has not been forthcoming on this, other than to say that the full transcript which the Panel has not seen is currently being examined by a French magistrate. The Panel therefore agreed that it could not consider the transcript as part of the evidence.

Dr Hill's status:

Dr Hill is an honorary senior research fellow at the University of Liverpool, and not a paid employee, a post first appointed by Professor David Back with whom he was collaborating on HIV work; at the time, Dr Hill was employed by a major pharmaceutical company. The post has been renewed regularly since then.

Funding of the project:

Dr Hill acknowledges that the project which led to the preprint article was funded by Unitaid in a grant to his own company and, likewise, that the final article was funded by the Rainwater Foundation in a grant to his company; the University of Liverpool was not involved in either of these awards.

Methodological issues:

The Panel noted methodological issues with the preprint. These are listed in the following table:

Review process	Comment
Was the review question clearly defined?	Partially. No PICO table. Question is always clearer if explicitly written in terms of PICO.
Were appropriate sources searched?	Yes. PUBMED, EMBASE, MedRxiv and trial registries. Could have searched other databases but may not have found any more relevant studies.
Was the timespan of the searches appropriate?	No search dates stated for PUBMED, EMBASE or MedRxiv. Dates of searches specified for registries.
Appropriate search terms used?	Probably, but only three keywords stated.
Were the eligibility criteria appropriate to the decision problem?	RCTs were included if they compared an IVM-based regimen with a comparator or SoC for the treatment of COVID-19. Prevention/non-randomised/case-controlled studies were excluded.
Was study selection applied by ≥2 reviewers independently?	Not stated.
Was data extracted by ≥2 reviewers independently?	Yes. But no details were presented re how data discrepancies were resolved.

Appropriate criteria used to assess RoB and/or study quality?	Yes. Cochrane RoB tool was used (but non-standard summary words/lack of 'other bias' domain).
Was the quality assessment conducted by reviewers independently?	Not stated, but presumably yes (as data were reported to have been extracted by two reviewers independently and then cross-checked).
Were attempts to synthesise evidence appropriate?	All-cause mortality/survival data were synthesised using meta-analysis. Could have meta-analysed other outcomes? All other outcomes were narratively synthesised (text and tables). Very little detail presented re methods of MA.

Main concerns:

- Review is not reproducible from data available
- No PRISMA flow diagram or patient characteristics table
- Lots of inaccuracies/inconsistencies in the text/tables
- Sample size/analysis size not always clear from data in tables
- We are not confident that all relevant data from the original studies have been included in the analyses or that they have been reported without errors
- It is not easy to work out which studies have (not) been published; this means that it is not easy to work out which studies have (not) been peer-reviewed (authors do acknowledge that many of the studies have not been peer-reviewed)
- Risk of bias results have not been linked to outcomes (should have done this for MA where 4/6 included studies were assessed as limited (other two were fair and good)
- Needs more discussion re comparators (very mixed)

- Primary outcome (all-cause mortality from randomisation to the end of follow-up) not comprehensively described (no details of follow up periods in the text)
- Lots of text highlighting limitations/bias, especially around MA
- No analysis of adverse events
- List of authors and funding are a concern

Summary opinion:

Lots of errors, inconsistencies and lack of attention to detail - probably due to being written in haste by many authors. Do not think the results would change if more care with the reporting and analysis had been taken.

The Panel considered that the methodological flaws were a reflection of the rapidity of the publication of the paper, which was clearly a preprint without peer review and that many of the flaws had been corrected in the full publication. The Panel's view was that the public health importance of the data was such that rapid publication was entirely appropriate, even with the risk of such flaws. Furthermore, the study used unpublished data and un-peer reviewed data, identifying it clearly as such, and the data were updated as they became available – a laudable "living review". The Panel considered that the approach was acceptable and appropriate given the public health importance of the topic and that there is a need for caution in the interpretation of the results and in the conclusions that should be drawn.

The Panel had no strong criticisms of the methodological issues identified: the Panel found no evidence of inappropriate external influence and considered that the methodological flaws were not so severe as to amount to research misconduct or to require withdrawal of the preprint. The Panel considered the conclusions reached by the authors to be correct and appropriately cautious.

The Panel asked about the large number of authors on the preprint as the final article had far fewer authors. Dr Hill responded to this but acknowledged that he did not have documented proof that the people named as authors on the preprint had consented to and/or approved its publication. It seems likely that many of the authors on the preprint would not have fulfilled the International Committee of Medical Journal Editors (ICJME) expectations for authorship. The Panel considered this poor practice.

The Panel notes that screening this complaint has taken considerably longer than is expected from a University process perspective. The topic remains live and there are now several other reviews on this subject, most of which (though not all) agree with the cautious approach taken by Dr Hill and colleagues. This caution has been further reinforced within the past week by public criticisms of one particularly influential trial included in the Hill review, suggesting that the results of this trial were fraudulent.

Responses to individual issues remain as previously written in report of Panel meetings.

Concluding findings

The Panel found no evidence of deliberate misrepresentation, fraud or of poor practice amounting to research misconduct.

Appendices

Appendix 1: Email to Dr Andrew Hill from BonSens consultant

From: Lynden Alexander <Redacted>)
Date: Thursday, 18 March 2021 at 17:21
To: "<Redacted>" <Redacted>
Subject: Urgent Questions to Dr Andrew Hill

Dear Dr Andrew Hill

I refer you to my email, dated 11 March 2021, about which I have not yet received a response.

On 16 March 2021, I was instructed by the French citizens group BonSens.org to present the results of a forensic assessment of your preprint paper, 'Preliminary meta-analysis of randomized trials of ivermectin to treat SARS-CoV-2 infection' ("the Paper").

I have now carried out my preliminary assessment of the Paper. Prior to finalising my assessment report, which has highlighted a number of issues of concern, I would appreciate your clarification and response to the questions and comments that I set out below.

Please note, that if I do not hear from you, I will be finalising my report without the benefit of any input from you. My questions to you are as follows:

1. Please will you explain when the issue of regulatory approval became an objective in the Paper, such that it needed to be addressed in your conclusions?

2. Please will you explain your qualifications and relevant experience to form conclusions on the issue of the regulatory approval of ivermectin?

My research indicates that you do not appear to have any formal qualifications or relevant experience in assessing the evidence necessary for the regulatory approval of ivermectin. I therefore assume, pending clarification from you, that you are relying on the work of others to reach conclusions on this issue. Please will you identify the person or persons upon whom you have relied to make the conclusions on regulatory approval?

3. Please will you name, with the qualifications and relevant experience, all of the "shadow authors" who have contributed to the Paper?

My interim findings are that there is a non-native English speaker, who appears not to be a clinical scientist, who has contributed text to the Paper on the nature of the evidence base. There are also conclusions in the Paper that appear to be unsupported by the work included in it.

4. Why did you allow "shadow authors" to contribute text to the Paper?

5. Was any of the text from the initial draft of the Paper removed or significantly altered by the project sponsor Unitaid? Was any text removed or significantly altered by the "shadow authors" contributing to the Paper?

If so, please will you make the earlier draft of your paper available, so that there can be transparency about what are your views and what has originated from others?

6. Were any of the authors in the International Ivermectin Project Team consulted about the conclusions that appear to have been added to the Paper, after the draft of the Paper was shared with the project sponsor Unitaid? If not, why not?

Did you give any of these co-authors the opportunity to withdraw their names from the paper and did any take that opportunity?

7. Please will you provide me with the 'conflict of interest' statements made by yourself as the responsible author and by the co-authors in the International Ivermectin Project Team? Did you seek conflict of interest statements from the "shadow authors" assisting you with the Paper?

Conflict of interest statements are a standard element of scientific papers but are conspicuously absent from the Paper.

8. Please will you explain the role of the sponsor Unitaid in the drafting of your paper, as this is required by the PRISMA guidelines that you say apply to the production of the Paper?

The production of systematic reviews and meta-analyses is at the very heart of evidence-based medicine. Owing to their fundamental importance, the rules governing the production of these papers are detailed and clear.

9. What was the practical process by which the first draft of the Paper was revised? Were you given the opportunity to see the final version of the Paper before it was uploaded to the Research Square website?

10. With the upload of the Paper to the Research Square website, on or around (I assume) 12 January 2021 (please confirm the date of this upload), in your view, is the concurrent award of $40 million to the University of Liverpool by Unitaid on 12 January 2021 an issue that should have been disclosed under the PRISMA guidelines? and if not, why not?

I note that the award was in your discipline of infectious disease drug treatments. Will you be engaged in work in the new laboratories that are now funded? Was this award ever used as an overt or covert means to pressure you to alter your honestly held scientific views on the use of ivermectin in COVID-19?

11. Please can you confirm the methodology for assessing the risk of bias in the studies in your Supplementary Table 1?

The language used for assessing the risk of bias is ‘Limited’, ‘Fair’ and ‘Good’. I am unfamiliar with how these terms relate to the Cochrane Collaboration ‘risk of bias standardized assessment tool’.

12. Please will you explain why you did not carry out a GRADE assessment of your meta-analysis results?

Why do you criticise the evidence base of the meta-analysis without having graded the evidence?

13. Please will you explain how you reached your conclusions against 'the use' of ivermectin in the treatment of COVID-19 patients? Specifically, why did you fail to deal with the risk/benefit assessment that is required in respect of the emergency use of the drug?

Please explain which of the following criteria are not met by the synthesis of the clinical trial evidence in your meta-analysis (based here on FDA emergency use approval criteria):

1) COVID-19 is a serious or life-threatening disease or condition caused by SARS-CoV-2, as specified in the declaration of emergency; and/or

2) There are no adequate, approved, and available alternatives to the candidate product for treating this serious or life-threatening disease; and/or

3) Based on the scientific evidence available to the FDA, it is reasonable to believe that the known and potential benefits of ivermectin outweigh the known and potential risks of the drug for the treatment of suspected or laboratory confirmed COVID-19 in adults and children hospitalized with severe disease as defined above.

14. How is it ethical for you to present one set of conclusions in the Paper, while presenting different conclusions to an audience of treating physicians in South Africa? Surely, both cannot ethically co-exist when you are the responsible author of the Paper?

On 19 January 2021, the same day that the Paper became available on the Research Square website, you presented a webinar for the Ivermectin Interest Group ("IIG") in South Africa.

During that presentation and the question-and-answer session that followed, you presented information and expressed "personal" views that were contrary to the

conclusions of the Paper. This webinar was apparently attended by almost 1,000 physicians worldwide, with an interest in the use of the drug to treat COVID-19 patients.

Please explain this apparent conflict in the conclusions of the Paper versus your "personal" views expressed at the webinar.

15. In your estimation, how many lives have been avoidably lost by the delay in authorising the use of Ivermectin worldwide, since your interim provisional findings video released by WHO/Unitaid in late December 2020?

Has there been any indication in the emerging clinical trial data since 19 January 2020 to the present time that has indicated that your interim preliminary findings at the end of December 2020 would need to be significantly altered?

16. Several countries around the world have now authorised the rollout of Ivermectin as a treatment for COVID-19, the latest being South Africa on 17 March 2021. This is against the conclusions of the Paper but is aligned with your "personal" views expressed at the IIG webinar. Do you support SAHPRA's decision to authorise the use of ivermectin? or do you consider that evidence base is still not robust enough to allow for the emergency use of the drug?

17. What is your view on the conduct of further clinical trials in hospitalised patients?

Your public statements and written conclusions in the Paper are once again in conflict. You described the ethical position for further clinical trials in hospitalised patients as "very difficult" at the IIG webinar and yet recommended the continuation of trials in hospitalised patients and also advised on the design of new trials into the use of the drug.

How could any further clinical trials be run in hospitalised patients, when there is clear evidence of a statistically this significant increase in the survival of patients treated with ivermectin?

18. Why are you recommending clinical trials using a standard care placebo group simply to assess the best dose and regimen for ivermectin? Surely, the intelligent recommendation would be to select a commonly used regimen as the standard of care against which other regimens can then be tested?

Given the amount of clinical data we have on the progression of this disease in hundreds of thousands of COVID-19 patients, on what basis do you believe that we need to conduct more clinical trials? Couldn't virtual SOC placebo groups be created by medical statisticians instead, thereby avoiding the risk of avoidable death in the placebo groups of the further clinical trials that you envisage?

19. Why does the Paper continually seek to undermine the robustness of the evidence base, when on two occasions during your IIG webinar (when you were addressing the quality of the evidence) you emphasised to the audience that you were adopting only the "Gold Standard" of clinical evidence?

Why does your paper not detail your "personal" views about the objective nature of the endpoints that you have selected for analysis in the Paper? Additionally, why is the primary endpoint of survival placed at the end of your Results section, below the secondary subjective endpoints of clinical recovery and length of hospitalisation? Why do you focus the results section on the secondary endpoints of ivermectin's effect on inflammatory biomarkers and on viral clearance?

20. Why do you include the varying clinical trial designs, measurement criteria and SOC as 'limitations' of your meta-analysis, when in fact the varying nature of the included randomised placebo controlled trials into the use of ivermectin demonstrates consistent benefits in respect of the primary and secondary endpoints?

21. Why does the Paper not conclude on the safety of Ivermectin during its use in the 18 randomised controlled trials that are included in your meta-analysis?

Merck & Co have recently issued a statement questioning the efficacy and safety of ivermectin in the treatment of COVID-19. Have you found any evidence or reports of adverse events arising from the use of ivermectin during your extensive contacts with clinical trial investigators across the world?

22. What is your response to the UK Therapeutic Taskforce's use of the Merck & Co statement as the basis for its assessment of the safety of the use of ivermectin in the treatment of COVID-19 patients?

23. What is your "personal" view of the exclusion by the UK Therapeutics Taskforce of other (peer reviewed) systematic reviews and meta-analyses of the use of ivermectin in COVID-19 from its decision-making processes?