# Forensic Communication Assessment:

## Supplementary Report

1. **Preliminary meta-analysis of randomized trials of ivermectin to treat SARS-CoV-2 infection [Preprint] by Dr Andrew Hill (on behalf of the International Ivermectin Project Team) – 19 January 2021**

2. **Meta-analysis of randomized trials of ivermectin to treat SARS-CoV-2 infection by Dr Andrew Hill *et al* – 6 July 2021**

**Lynden Alexander (Forensic Communication Consultant)**

**6 October 2021**

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## Author: Professional Details

Lynden Alexander is a forensic communication consultant practising from 7 Bell Yard, London WC2A 2JR.

He has 24 years of professional experience, providing advice and professional development services to corporate clients and independent expert witnesses. His expertise is focussed on assisting experts and professional witnesses in communicating technical expertise in a clear, concise and reliable manner, suitable for the UK's (predominantly) non-specialist judiciary.

For over 20 years, an important focus of his expertise has been the assessment of expert and professional evidence. The medico-legal domain of litigation has been a particular area of interest, leading to the publication of a co-authored professional guide (with the barrister Giles Eyre) on the writing of medical evidence in the UK civil courts. The first edition of *Writing Medico-Legal Reports in Civil Claims* was published in 2011, with an expanded second edition in 2015.

Since March 2020, he has committed himself to a research project focussed on the medical response to the COVID-19 pandemic and specifically the co-ordination of the global medical response by the World Health Organization, its partners and funders.

He maintains a wide professional network of scientific, professional and technical experts, both in the UK and internationally.

# 1.0 Instructions

## 1.1 Instructions Received from Bon Sens

1.1.1 I was first instructed on 15 March 2021 by Bon Sens, a civic group based in France, to provide a forensic communication assessment of the preprint paper 'Preliminary meta-analysis of randomized trials of ivermectin to treat SARS-CoV-2 infection', by Dr Andrew Hill and the 'International Ivermectin Project Team', pre-published on Research Square on 19 January 2021 (1). ("Preprint Paper")

1.1.2 I received an additional oral instruction on 22 September 2021 to address in a Supplementary Report the subsequent published paper (later withdrawn) 'Meta-analysis of randomized trials of ivermectin to treat SARS-CoV-2 infection' by Dr Andrew Hill *et al* published in *Open Forum Infectious Diseases* on 6 July 2021. (2) ("Published Paper")

1.1.3 Specifically, I was asked to provide an assessment of what, if any, additional conclusions concerning Dr Hill's Preprint Paper 'Preliminary meta-analysis of randomized trials of ivermectin to treat SARS-CoV-2 infection' could be drawn in the light of Dr Hill's Published Paper.

## 1.2 Supplementary Report

1.2.1 This Supplementary Report is an advisory report (as defined by the UK Civil Justice Council) and provides advice for the use of Bon Sens in its activities in relation to public health policy in France.

1.2.2 This Supplementary Report and my original Forensic Communication Assessment dated 19 March 2021 on which it is based are confidential and may only be reproduced with the prior written permission of the author.

1.2.3 The author and Professional Solutions (Forensic Consulting) Limited accept no liability whatsoever for the use of these reports by any person, organisation or party other than Bon Sens and its legal team.

1.2.4 The Forensic Communication Assessment of Dr Hill's work issued on 19 March 2021 and this Supplementary Report have been produced with reasonable skill and care and are based on the identified materials available to the author at the relevant dates.

1.2.5 As such, the conclusions are subject to revision should further relevant information become available at a later stage.

## 2.0 Approach to the Forensic Communication Assessment

### 2.1 Dr Hill's Published Paper

2.1.1 In this Supplementary Report, the Published Paper (later withdrawn) from Dr Hill and his co-authors, 'Meta-analysis of randomized trials of ivermectin to treat SARS-CoV-2 infection' published in *Open Forum Infectious Diseases* on 6 July 2021 will be used as a basis for a comparison with Dr Hill's Preprint Paper.

2.1.2 For this work, I will compare the two papers to identify any differences that do not arise "naturally" from the expanded meta-analysis in the Published Paper, which includes additional studies on the use of ivermectin up to the new search date of 12 May 2021.

### 2.2 Identification of Issues

2.2.1 My explanations of the differences between the Preprint Paper and the Published Paper rely upon my making reasonable assumptions and deductions based on my analysis of the text and where possible cross-checking these against the evidence available from other sources.

2.2.2 Therefore, my explanations for the factual matters arising in this Supplementary Report should be treated with some caution and would be best used to assess the weight to be given to other available evidence and to provide a basis for further investigations into the production of Dr Hill's Preprint Paper. My explanations should not be taken as a definitive account of how the Preprint Paper came to be in its present form, as I do not have the evidence that I would require to achieve that level of certainty.

2.2.3 In the event that more documentation becomes available to me, I will review all such documentation and reserve the right to revise my conclusions. Of particular importance is an earlier version of Dr Hill's Preprint paper, at the point when it was first provided to the project sponsor Unitaid, probably in early January 2021.

2.2.4 I have not contacted Dr Hill in respect of the content of this Supplementary Report, as communication with him broke down in mid-March 2021, with his failure to respond to any of my questions regarding his Preprint Paper.

2.2.5 My original email correspondence with Dr Hill is included in **Appendix 1** and my questions on his Preprint Paper, which were sent to Dr Hill on 18 March 2021 ("My Questions"), are included in **Appendix 2**.

# 3.0 My Comparison of Dr Hill's Papers

## 3.1 Overview of the Published Paper

3.1.1 In this section, I will summarise the key findings of the Forensic Communication Assessment I carried out in March 2021 and will then explore how these issues have (or have not) been carried forward into the Published Paper.

3.1.2 A basic textual analysis of the Preprint and Published Papers indicated that these papers were written by an educated native English speaker, who has a good command of English grammar and punctuation and the fundamental disciplines of scientific writing. I assume that this was the work of Dr Hill or one of the native English-speaking assistants identified in these papers, or a combination of Dr Hill and an assistant.

3.1.3 In the UK, it is common practice for senior academic scientists and professionals in private practice to delegate the initial drafting of scientific papers to experienced junior colleagues or assistants. The "lead" scientist or professional then brings the paper into its final form, by making any necessary amendments, once the initial draft of the paper has been completed.

3.1.4 It would, therefore, be unsurprising to find that someone on the team other than Dr Hill was responsible for the initial drafting the text.

## 3.2 Authors of the Paper

3.2.1 The authors of the Preprint Paper were identified as 'Andrew Hill on behalf of the International Ivermectin Project Team'. The 'International Ivermectin Project Team' seems to have been made up of Dr Hill himself in the final position as the responsible author, members of his research team (two of whom are identified in the main text as being the 'independent reviewers'[1]) and the names of what appear to be 32 physicians or clinical scientists, who are the authors of the underlying clinical trials on the use of ivermectin to treat COVID-19 patients. These clinical trials form the basis of the meta-analyses presented in the Preprint and Published Papers.

3.2.2 It was unclear what role, if any, these co-authors had in the production of the Preprint Paper. No information was included to indicate whether these co-authors agreed the content of the Preprint Paper prior to its issue and it was also unclear the extent to which these co-authors were able to influence the content of the Preprint Paper.

3.2.3 In the Published Paper, reference to the 'International Ivermectin Project Team' has been removed and with it all the physicians or clinical scientists who carried out the underlying clinical trials, which were the basis of the full meta-analysis.

[1] Preprint Paper Page 7 – first paragraph

3.2.4 It is likely that Dr Hill and the remaining 9 co-authors of the Published Paper were the team responsible for the meta-analysis in the Preprint paper. The 32 co-authors were involved in the preliminary meta-analysis, but in apparently disposable supporting roles.

3.2.5 The role of the now removed co-authors of the 'International Ivermectin Project Team' in the production of the Preprint Paper was raised with Dr Hill in My Questions nos 6 & 7.

### 3.3 Funding for the Published Papers

3.3.1 In the Preprint Paper, Unitaid is identified as the funding source for the meta-analysis.[2] In the Acknowledgements of the Published Paper, the funding source is identified as the Rainwater Foundation.

3.3.2 Although Unitaid funded Dr Hill's work on repurposed drugs from early in the pandemic[3], Unitaid has been excluded as a funding source in the Published Paper. Therefore, the published statement is not a true reflection of the role of Unitaid in funding the majority of the project and does not meet the descriptive statement on the role of funders indicated in the PRISMA Checklist.

3.3.3 Therefore, the funding statement in the Published Paper does not reflect the actual funding arrangements for this project. The majority of the project was conducted under a funding arrangement with Unitaid, probably as part of Unitaid's wider funding arrangement with the University of Liverpool.[4] [5]

3.3.4 Owing to the importance of systematic reviews and meta-analyses in clinical decision making, there is clear guidance on the content of these papers. The PRISMA Checklist is a useful tool for authors of systematic reviews and meta-analyses to check that they have carried out the project appropriately and to the appropriate standard.

3.3.5 Dr Hill's Preprint and Published Papers refer to either the 'PRISMA guidelines'[6] or the 'PRISMA checklist'[7], or both. The Preprint Paper did not include any details of how the PRISMA guidelines were used in the production of the paper.

3.3.6 The Published Paper includes the PRISMA Checklist (as Supplementary Table 1) but truncated at item 14, rather than including the full 27 items. The full PRISMA Checklist from 2009[8] is included in **Appendix 3**.

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[2] Preprint Paper Page 2
[3] As described in his presentation during the International Ivermectin Group webinar, on 19 Jan 2021
[4] Both Unitaid's and the University of Liverpool's logos were included on Dr Hill's PowerPoint presentation used in the Ivermectin Interest Group webinar, as well as the 'ACT accelerator' logo
[5] The details of Dr Hill's or the University of Liverpool's funding arrangement with Unitaid are not in the public domain.
[6] Preprint Paper Page 7 – paragraph 1
[7] Published Paper Page – paragraph 4
[8] A revised PRISMA Checklist dated 2020 was available but was not used for the Published Paper and presumably not used for the Preprint Paper (although this is not addressed in the text).

3.3.7 There appears to be no reason why items 15-27 of the PRISMA Checklist would be excluded from the Published Paper's Supplementary Table 1. The possible explanations for this are a simple production error by the authors of the Published Paper, or a drafting decision that the entire PRISMA Checklist was in some way not relevant (although this drafting decision would need to be explained), or it was an attempt to avoid highlighting the need for a statement to describe the role of funders of the project.

3.3.8 A screenshot of PRISMA Checklist Item no.27 is included below:

| | | | |
|---|---|---|---|
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | |

3.3.9 The issue of Unitaid's role as a funder of the project was included in My Question no. 8.

## 3.4 Stated Objective of the Published Paper

3.4.1 In the Published Paper, the stated *'objective'* is to *'combine available results from published and unpublished randomized trials of ivermectin in SARS-CoV-2 infection, to inform current guidelines.'* [9] This singular objective deals with the project work that Dr Hill is qualified to carry out, based on his experience and expertise working as an infectious disease specialist.

3.4.2 I would expect that this research 'objective' would lead logically to conclusions on the results of the meta-analysis in respect of the efficacy of early treatment and hospitalized treatment with ivermectin, as well as the essential question of the safety of the drug in the treatment of hospitalised COVID-19 patients.

3.4.3 Dr Hill does not identify these as specific research questions that the paper will address, as would normally have been indicated by item 4 in the PRISMA Checklist below:

| | | | |
|---|---|---|---|
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | |

3.4.4 Additional information about the objective of the Published Paper is provided in the Search Strategy and Selection Criteria section, which states the *'primary outcome was all-cause mortality from randomization to the end of follow-up'*, with a brief discussion of an expanded list of secondary outcome measures. These include: time to viral clearance; PCR negativity at day 7; clinical recovery; time to clinical recovery; mechanical ventilation; duration of hospitalization; and number of hospitalisations. [10]

[9] Published Paper Page 4 - para 2
[10] Published Paper Page 5 - para 4

3.4.5 The expanded list of secondary outcomes reflects the more extensive sub-group analyses carried out in the Published Paper.

## 3.5 "Shadow Author" Interference in the Preprint Paper

3.5.1 In my Forensic Communication Assessment of the Preprint Paper, issued on 19 March 2021, I found multiple instances of interference (additional text added to the paper) from what I termed a "Shadow Author".

3.5.2 I subsequently concluded that this interference may have been the work of more than one individual, as there appeared to be both interference in the text and interference in the technical assessment of the studies used in the meta-analysis and that these instances of interference were not consistent. (See for example, Preprint Paper 'Evaluation of Studies'[11] where the text added into the section and the non-standard methodology introduced into Supplementary Table 1 did not align in terms of terminology and counts.)

3.5.3 In addition, there was text written by a native English speaker that was dissonant with the structure and content of the paper, which could possibly have been added by an additional "Shadow Author" or were an attempt by a legitimate author to respond to an outside influence or instruction regarding the required content of the Preprint Paper.

3.5.4 I concluded that one common feature of these interventions was that they occurred after the initial drafting of the Preprint Paper. This conclusion was based on the nature of the added content, its positioning within the structure of the Preprint Paper, and the added content reflected a poor understanding of fundamental scientific writing disciplines.

3.5.5 I also concluded that these changes were introduced without Dr Hill and his core team having the opportunity to review them in a formal "edit and sign off" procedure, as no credible science professional would have allowed such text into a formal preprint of a meta-analysis to be published under his name.

3.5.6 I raised the issue of the "Shadow Author" in My Questions nos 3, 4 and 5 (second part). However, given the lack of response from Dr Hill, these conclusions remained provisional, pending further investigation.

## 3.6 "Shadow Author" Interference in the Published Paper

3.6.1 In the Published Paper, Dr Hill and his co-authors omit 7 instances of text that I had previously identified as "Shadow Author" interference, they also revise the "shopping list" of criticisms of the meta-analysis (included in the Limitations section of the Preprint Paper) and the methodology related to the Risk of Bias assessments.

[11] Preprint Paper Page 11- final paragraph

3.6.2 These omissions and revisions are presented in **Appendix 4**. I provide brief explanations of these changes below:

**"Shadow Author" – Grammatical Failings**

3.6.3 In the example below, the chaotic "run on" structure of this sentence does not appear elsewhere in the initial drafting of the Preprint Paper. The "Shadow Author" also has an issue with the use of the definite article in noun phrases and with subject-verb agreement.

3.6.4 For the purposes of illustration, I have presented the corrected text in ***bold italicised*** text, within square brackets, though I have not sought to amend the phrase structure of the sentence:

> *'[**The**] Limitations of [**the**] current analysis is [**are**] important [**,**] as it is being [**was**] performed with secondary data from a wide variety of different trials in many different parts of the world with designs that were not originally meant to be compatible. Further refined analysis, including direct data examination are [**is**] warranted.'* [12]

> *'Further evaluation [**of the included studies**] with access to [**the**] original data from the trials is warranted[**,**] to increase [**the**] quality of [**the**] evidence.'* [13]

3.6.5 I addressed questions about the contributions of a "Shadow Author" in My Questions nos 3 & 4.

**"Shadow Author" - Technical Failings**

3.6.6 In the Preprint Paper, aside from the structural, grammatical and stylistic failings of the interference in the text by the "Shadow Author", there were also obvious technical failings.

3.6.7 The Cochrane Risk of Bias Tool does not include any methodology for assessing the quality of the studies and their impact on the meta-analysis. This would require both a GRADE assessment and detailed sub-group analyses. This work was not presented in the Preprint Paper. Nevertheless, the text provided an assessment of the quality the underlying studies:

> *'Of the 18 trials [**included in the meta-analysis**], 11 were of poor quality and seven of fair or high quality.'* [14]

3.6.8 The counts and terminology in this sentence did not match the content of the right-hand column in the Preprint Paper's Supplementary Table 1. The alteration to the Cochrane Risk of Bias Tool reflected a non-standard methodology, which was not explained or justified by the authors of the Preprint Paper.

3.6.9 The addition of the right-hand column into Supplementary Table 1 allowed an attack on the quality of the underlying randomised controlled trials, but without carrying

[12] Preprint Paper Page 6 - final two sentences of the Introduction section.
[13] Preprint Paper Page 11 – final paragraph
[14] As above

out the necessary professional work to ensure that this attack was supported by evidence.

3.6.10 In the Published Paper, the non-standard methodology has been removed and a standard Risk of Bias assessment appears to have been carried out. None of the language used in the right-hand column in the Preprint Paper's Supplementary Table 1 is included in the Published Paper's Supplementary Table 3A.

3.6.11 I addressed the misuse of the Cochrane Risk of Bias Tool in My Questions nos 11 & 12.

**"Shadow Author" – Unsupported Criticisms**

3.6.12 In the Preprint Paper, the authors set out the findings of the meta-analysis in the first paragraph of the Discussion section:

> *'This systematic review of 18 RCTs (n = 2282) showed ivermectin treatment reduces inflammatory markers, achieves viral clearance more quickly and improves survival compared with SOC. The effects of ivermectin on viral clearance were stronger for higher doses and longer durations of treatment. These effects were seen across a wide range of RCTs conducted in several different countries.'*

3.6.13 These important findings, where no other early or hospitalised treatment for COVID-19 had shown such a significant effect on survival, were immediately qualified in the same paragraph by the following criticisms:

> ***'However, the data should be interpreted carefully in the context that meta-analyses are highly prone to confounding bias****, and current viral* ***PCR assays have several important limitations****. Many of the studies assessed have not been peer-reviewed.'* [15] (Emphasis Added)

3.6.14 This was then followed, still in the same paragraph, by the opinion:

> *'Larger, appropriately controlled randomized trials are needed before [a] rigorous evaluation of the clinical benefits of ivermectin can be undertaken.'* [16]

3.6.15 In 25 years of practice, I have never seen the authors of a study combine a summary of their findings, with a series of criticisms of the underlying data, and an admission that the entire study was not rigorous, and to do so in the first paragraph of a Discussion section.

3.6.16 This highly unusual drafting strategy was amplified by the nature of 2 of the 3 criticisms that proceeded the opinion (emboldened in the quotation above). Both criticisms would pose fundamental questions about the WHO's 'Living Guidelines' approach for clinical trial evidence (which uses meta-analyses as the basic tool of assessment for the efficacy and safety of medications) and the WHO's assessment

[15] Preprint Paper Page 11 - first paragraph

[16] As above

criteria for the use of therapeutic agents in the treatment of COVID-19 (which uses PCR testing to confirm viral clearance).

3.6.17 In the Published Paper, the second half of this first paragraph of the Discussion section (containing the criticisms and the opinion) is omitted. There are no criticisms of the meta-analysis included until the appropriate section heading 'Limitations', which is placed after the Discussion section.

## 3.7 Limitations of the Meta-Analysis

3.7.1 In the Preprint Paper, the Dr Hill and the co-authors presented the limitations of the meta-analysis as a list of issues, unsupported by factual or expertise-based analysis:

> ***Limitations***
> *'Key limitations to this meta-analysis include the comparability of the data, with studies differing in dosage, treatment duration, and inclusion criteria. Furthermore, the SOC used in the background treatment differed between different trials. Additionally, ivermectin was often given in combination with doxycycline or other antimicrobials. Individual trials may not have power to detect treatment effects on rare endpoints such as survival. Outcome measures were not standardized; viral clearance was measured in most trials, but at different time points and with different PCR cycle thresholds. The reliability of PCR tests for quantification purposes has been the subject of substantive debate. Most studies were conducted in populations with only mild/moderate infection and some trials excluded patients with multiple co-morbidities.'* [17]

3.7.2 In the Published Paper, these limitations are still included, but the discussion has more balance, as an assessment of the significance of these limitations is now provided to add clinical context:

> *'A key limitation to this meta-analysis is the comparability of the data, with studies differing in dosage, treatment duration, and inclusion criteria. Furthermore, the standard of care used in the control arm differed between trials.* ***In this meta-analysis, trials that used active controls such as hydroxychloroquine or lopinavir/ritonavir were combined together with those that used placebo or standard care. However, lopinavir/ritonavir and hydroxychloroquine have shown no overall benefit or harm in large randomized trials and meta-analyses.*** *[7, 59-61]* ***Furthermore, additional analyses in this paper separating trials by subgroups of standard care/ placebo and active control showed no significant difference between groups.'*** (Emphasis Added)

## 3.8 Conclusions Section

3.8.1 In the Preprint Paper, the first paragraph of the Conclusions section presented the findings of the preliminary meta-analysis of 18 randomised controlled trials. These findings showed a 75% improvement in survival, faster time to clinical recovery, and signs of a dose-dependent effect on viral clearance for patients given ivermectin over control.

[17] Preprint Paper Page 12 – last paragraph

**Efficacy and Safety of Ivermectin**

3.8.2 The findings on efficacy would have created an immediate problem for the "Shadow Author", whose role it was to transform the conclusions of the Preprint Paper to justify a WHO recommendation against the use of ivermectin in the treatment of COVID-19 patients, outside of clinical trials.

3.8.3 The possible mechanisms for the interference in the text include direct action by a "Shadow Author" without the knowledge of Dr Hill and the co-authors, co-operation between one of the authors and a "Shadow Author", or direct pressure on Dr Hill and the co-authors to make changes to the Preprint Paper themselves.

3.8.4 As there were no evidential reasons for failing to address the risk/benefit assessment that would have been intrinsic to an emergency use authorisation for ivermectin, it seems probable that the Conclusions section was substantially altered to exclude this fundamental issue.

3.8.5 The conclusions of the Preprint Paper did not deal with the essential question of the safety of ivermectin in the treatment of COVID-19 patients. This would have been a standard assessment to be included in a meta-analysis for a repurposed drug, as recording adverse events or other signals on safety would have been fundamental to the design of the clinical trials included in the meta-analysis.

3.8.6 Therefore, the conclusion that a "Shadow Author" was empowered to add text to the Preprint Paper (by whatever means or method), for the purpose of undermining a positive evidence-based conclusion on the efficacy and safety of ivermectin, seems the most likely explanation for the interference in the Preprint Paper.

3.8.7 Similarly, the removal of text could also have been used to create a false basis for recommending against the use of ivermectin, through the removal of information supportive of its use. This would also seem to be an obvious strategy for a"Shadow Author" to adopt, as there would be no obvious trace of the deleted text remaining in the Preprint Paper.

3.8.8 The absence of a conclusion on safety meant that there could be no conclusion on the essential risk/benefit assessment for the treatment of hospitalised patients with ivermectin.

3.8.9 Addressing the risks and benefits of the use of ivermectin would, in turn, have been essential to support any recommendation for an emergency use authorisation to be considered by national regulators[18].

[18] The WHO has no legal power to authorise or approve any drug, but during the COVID-19 pandemic national regulators in the G7 nations (and beyond) have rapidly aligned with WHO guidance.

**"Parachuted" Conclusion on Regulatory Approval**

3.8.10 The second paragraph of the Conclusions section rules out *'the use or regulatory approval'* of ivermectin, as the evidence base was insufficiently 'robust'. This conclusion was unsupported by a GRADE assessment of the underlying clinical trials or by detailed sub-group analyses to establish the contribution of studies at a higher risk of bias to the overall synthesis of clinical trial results, for both primary and secondary endpoints.

3.8.11 The compound conclusion against 'the use or regulatory approval' of ivermectin defied the clinical evidence presented in the Preprint Paper:

> *'Despite the encouraging trend this existing data base demonstrates, it is **not yet a sufficiently robust evidence base to justify the use or regulatory approval** of ivermectin…'* (Emphasis Added)

3.8.12 The second sentence in the second paragraph of the Conclusions section then 'stacks' a series of contentions, one upon another, using a cascade of adjectives and adverbs (unquantified descriptive language, rarely used in scientific writing).

> *'**However**, the **current** paucity of **high**-quality* evidence ***only** highlights the **clear** need for **additional, higher**-quality and **larger**-scale clinical trials, warranted to investigate the use of ivermectin **further**.'* (Emphases added)

3.8.13 This was an attempt to hammer home (using the same drafting approach seen in the first paragraph of the Discussion section) a conclusion that was unsupported by any assessment of the quality of the evidence in the meta-analysis:

3.8.14 In essence, the objection to the use of ivermectin in the treatment of COVID-19 patients was not based on the results of the preliminary meta-analysis, but rather on the WHO's stated preference (and by extension, Unitaid's which it hosts) for institution-led large-scale clinical trials. The inherent delays and mass avoidable mortality resulting from such a policy does not seem to impinge on the WHO's policy preferences.

3.8.15 By failing to address the question of the risk/benefit assessment that underlies an emergency use authorisation, Dr Hill and the co-authors (or "Shadow Author") avoided having to provide any professional rationale for the stated compound conclusion that rejected the use of ivermectin to treat COVID-19 patients on regulatory grounds.

**Further Clinical Trials**

3.8.16 The final paragraph of the Conclusions section sought to set an agenda for the concluded need for further clinical trials:

> *'The maximum effective dose of ivermectin needs to be clarified and new clinical trials should use a consistent multi-day dosing regime, with at least 0.4mg/kg/day. The appropriate dose and schedule of ivermectin still requires evaluation and the current randomized clinical trials of ivermectin need to be continued **until ready for rigorous review by regulatory agencies**.'* (Emphasis Added)

3.8.17 This conclusion did not arise from a stated objective of the meta-analysis and was simply "parachuted" into the Preprint Paper to bolster an unsupported conclusion for the non-use of ivermectin outside of clinical trials.

3.8.18 The conclusion on the review of regulatory agencies could not have been properly made by Dr Hill and the co-authors and would not typically be addressed in a meta-analysis of randomised controlled trials.

3.8.19 There was no evidence that indicated that any of the authors had regulatory experience. There was no information on the regulatory approval process for repurposed drugs included in the Preprint Paper or in Dr Hill's subsequent Ivermectin Interest Group webinar in South Africa, on 19 January 2021.

3.8.20 I addressed questions about the expertise and experience of Dr Hill and the co-authors in respect of the regulatory requirements of repurposed drugs in the COVID-19 pandemic in My Questions nos 1 & 2.

3.8.21 In the Preprint Paper, no evidence was presented that contradicted the efficacy of ivermectin in the treatment of COVID-19 patients and no evidence was presented to indicate that there was a safety issue with the use of the drug. The quality assessments were based on a non-standard methodology that was not explained in the paper.

3.8.22 Therefore, there was no clinical basis for Dr Hill and his co-authors to have concluded against the use of ivermectin in the treatment of COVID-19 patients, based on the 'best evidence' available at the time.

**Omission of the Conclusions Section in the Published Paper**

3.8.23 In the Published Paper, the entire Conclusions section is omitted. Dr Hill and his co-authors offer no conclusions on efficacy, on safety, on the risk/benefit assessment of use, on regulatory approval, or on clinical trial design in future trials.

3.8.24 The closest I can identify as a conclusion to the Published Paper is the final paragraph of the Limitations section:

> *'Several other repurposed medications have shown promise in early smaller trials for example* ***sofosbuvir/daclatasvir, colchicine and remdesivir*** *but the benefit was not seen later in larger trials. This meta-analysis of 24 RCTs in 3328 patients showed a 56% improvement in survival, faster time to clinical recovery and signs of a dose-dependent effect of viral clearance for patients given ivermectin versus control treatment.* ***This benefit needs to be validated in larger confirmatory trials.'*** (Emphasis Added)

3.8.25 The inclusion of remdesivir as a justification for recommending further clinical trials in ivermectin is nonesense. The first randomised controlled trial of remdesivir in China during February and March 2020 was led by (amongst others) Professor Peter Horby (the Chief Investigator of the RECOVERY trial). The trial was stopped early

because of a lack of efficacy and remdesivir treatment was stopped because of a lack of enrollment and adverse events in 12% of patients in the treatment group:

> Between Feb 6, 2020, and March 12, 2020, 237 patients were enrolled and randomly assigned to a treatment group (158 to remdesivir and 79 to placebo); one patient in the placebo group who withdrew after randomisation was not included in the ITT population. Remdesivir use was not associated with a difference in time to clinical improvement (hazard ratio 1·23 [95% CI 0·87–1·75]). Although not statistically significant, patients receiving remdesivir had a numerically faster time to clinical improvement than those receiving placebo among patients with symptom duration of 10 days or less (hazard ratio 1·52 [0·95–2·43]). Adverse events were reported in 102 (66%) of 155 remdesivir recipients versus 50 (64%) of 78 placebo recipients. Remdesivir was stopped early because of adverse events in 18 (12%) patients versus four (5%) patients who stopped placebo early. (3)

3.8.26 During February to April 2020, there was limited benefit of remdesivir treatment identified in a clinical trial in the United States, where the findings indicated a shorter period to clinical recovery, but found no statistically significant decrease in mortality:

> Our data show that remdesivir was superior to placebo in shortening the time to recovery in adults who were hospitalized with Covid-19 and had evidence of lower respiratory tract infection. (4)

3.8.27 The WHO's large-scale SOLIDARITY trial later found that there was no mortality or shorter period of recovery from the use of remdesivir in the hospitalised treatment of COVID-19 patients:

> These remdesivir, hydroxychloroquine, lopinavir, and interferon regimens had little or no effect on hospitalized patients with Covid-19, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay. (5)

3.8.28 As such, there had never been a strong signal of reduced mortality with remdesivir treatment in hospitalized COVID-19 patients. The SOLIDARITY trial did not extinguish a strong signal of clinical benefit, it simply demonstrated that the relatively minor claims for the efficacy of the drug were not found in the large-scale trial.

3.8.29 Putting aside the continued clinical use of remdesivir in Europe and the United States, despite its lacklustre clinical trial performance, a rationale that uses the established lack of efficacy of remdesivir as a justification for refusing to act on the findings of a substantial mortality benefit from ivermectin was flawed.

3.8.30 There was no basis for comparison between the clinical trial results from these drugs and no basis to use this comparison as a justification for recommending confirmatory clinical trials.

**WHO's Public Position on Ivermectin**

3.8.31 In the absence of any conclusions on the risk/benefit analysis (of the use and safety of ivermectin in the treatment of COVID-19 patients), the WHO leadership team were able to issue public statements about the quality of the data for ivermectin and the need for a comprehensive review.

3.8.32 On 5 February 2021, at a WHO Virtual Press Conference in Geneva, Dr Maria Van Kerkhove, the WHO's technical lead on COVID-19 gave the following (prepared) response to a question about the use of ivermectin[19]:

> "Currently, we [the WHO] haven't made a recommendation on the use of ivermectin, but we're closely following the research that is ongoing related to this drug, which has shown some promising results in some trials for the treatment of COVID-19.
>
> We are aware that there is currently data available of about 1500 study patients, slightly less than that, from 11 studies, and there's data expected from up to more than 7000 patients in 56 studies. And these studies are of varying quality.
>
> So, we have a WHO steering committee that is tracking these studies, and closely looking at them in order to trigger the guidance, and when we have enough information to look at guidance and updating our guidance to change policy. This may begin in the coming weeks, **so any of the changes that come from WHO recommended treatments follow an expedited but an incredibly comprehensive review**, which will be shared with the public at the earliest time that we can." (6) (Emphasis Added)

3.8.33 The proper interpretation of "an expedited but an incredibly comprehensive review" will require further investigation to establish, in the context of the blatant interference in Dr Hill's Preprint Paper.

3.8.34 It also appears that the interference in the Preprint Paper was executed in a hurry, as the corruption of the core text was executed in an amateurish manner. The method and means by which this interference took place remain unclear, pending further investigation.

[19] The complete answer from the WHO team present at the virtual press conference is included in **Appendix 5**.

# 4.0 Supplementary Conclusions Following a Review of the Published Paper

## 4.1 My Questions Posed to Dr Hill on 18 March 2021

4.1.1 I set out below a summary table of My Questions (See **Appendix 2**) sent to Dr Hill by email on 18 March 2021, during an ongoing email exchange between us:

| Question No. | Topic | Published Paper |
|---|---|---|
| 1. | Inclusion of regulatory approval as a study objective | All content regarding regulatory approval omitted |
| 2. | Regulatory approval expertise and experience of authors | All content regarding regulatory approval omitted |
| 3. | Identity of "Shadow Authors" | Most content identified as "Shadow Author" omitted |
| 4. | Basis for allowing "Shadow Authors" | 32 co-authors removed from author list, with no new additions to the list |
| 5. | Role of Unitaid and "Shadow Authors" in drafting the Preprint Paper | All content related to Unitaid omitted. |
| 6. | Consultation with co-authors in the Ivermectin Project Team on new text | Ivermectin Project Team (32 co-authors) removed from author list |
| 7. | Conflict of Interest Statements from co-authors and "Shadow Authors" | No information provided |
| 8. | PRISMA declaration regarding role of the sponsor Unitaid | All references to Unitaid omitted |
| 9. | Revision of the paper after submission to Unitaid | All references to Unitaid omitted |
| 10. | Concurrent award of USD 40m to University of Liverpool by Unitaid | All references to Unitaid omitted |
| 11. | Use of Non-Standard Risk of Bias Methodology | Standard methodology adopted with sub-group analyses |
| 12. | Absence of GRADE assessments of the clinical trial evidence | No explanation provided. Criticism of the quality of the trials revised |
| 13. | Explanation for conclusion against use / failure to address risk/benefit for EUA | Conclusion against use omitted / no attempt to address risk/benefit for EUA |
| 14. | Ethics of publishing a preprint with different conclusions to IIG webinar | Conclusions against use omitted / call for larger confirmatory trials maintained |
| 15. | Avoidable mortality in COVID-19 from the undermining of the meta-analysis | No information provided |
| 16. | Conditional approval of ivermectin in South Africa – support or not? | No discussion of the successful use of the drug in South Africa, India, Bangladesh… |
| 17. | Conflict between Preprint paper and IIG presentation on more clinical trials | Recommendation for more clinical trials maintained (and promoted on Twitter) |
| 18. | Recommendation for more clinical trials against placebo despite efficacy | Recommendation for more clinical trials maintained (and promoted on Twitter) |
| 19. | Reason for undermining the quality of the evidence contrary to IIG assertions | Recommendation for more clinical trials maintained (and promoted on Twitter) |
| 20. | Differences between studies described as "limitations" | Revised discussion of limitations with supportive reasoning |
| 21. | No conclusion on safety from 18 studies and 2282 participants | No conclusion on safety from 24 studies and 3328 participants |

| | | |
|---|---|---|
| 22. | Use by UK Therapeutics Committee of Merk & Co press release on safety | No conclusion on safety from 24 studies and 3328 participants |
| 23. | View on sole reliance by UK Therapeutics Committee on Preprint | No discussion of other meta-analyses and no conclusions included |

4.1.2 The issues identified by My Questions were omitted from the Published Paper in 9 of 23 instances[20]; were substantially revised in 5 of 23 instances[21]; remained unaddressed in 6 of 23 instances[22]; or were maintained unchanged in 3 of 23 instances[23].

4.1.3 14 of 23 of the issues raised in My Questions lead to a substantial revision of the Published Paper, without stimulating a formal response from Dr Hill.

## 4.2 Communication Issues in the Published Paper

**Unitaid as the Major Funder of the Project**

4.2.1 The removal of any reference to Unitaid from the Published Paper is an unacceptable breach of the PRISMA Guidelines and Checklist. Despite Unitaid's role as the funder for most of the duration of the project, Dr Hill and the co-authors have sought to obscure the role of Unitaid in the project.

4.2.2 The PRISMA Guidelines and Checklist include a statement from the authors of the Preprint Paper about the role of the funders of the research, precisely because meta-analyses have a profound effect on medical practice and the treatment of patients.

4.2.3 The publication of a truncated PRISMA Checklist in Supplementary Table 1 of the Published Paper, excludes the item of a descriptive statement about the role of the funder of the meta-analysis. This only adds to the impression that Dr Hill and the co-authors were actively seeking to distance their work from Unitaid.

4.2.4 In addition, the failure of Dr Hill to declare in his Conflicts of Interest statement Unitaid's announcement on 12 January 2021 of an award of $40 Million in direct funding for the University of Liverpool's Centre of Excellence for Long-acting Therapeutics (CELT) remains open to question.

4.2.5 The CELT project appears to offer opportunities in scientific research in which Dr Hill would be able to participate. There appears to be no good reason why this award was not declared in the Published Paper, even if Dr Hill was unaware of the pending announcement, during the production of the Preprint Paper. (7)

[20] Questions 1-6 & 8-10
[21] Questions 11-14 & 20
[22] Questions 7, 15-16, 21-23
[23] Questions 17-19

**"Shadow Authors"**

4.2.6 Dr Hill did not add to the authors list to reveal who had added text to the Preprint Paper. Instead, he removed 32 co-authors from the author list included in the Preprint Paper. It remains unclear in what way, if any, the 32 co-authors of the Preprint Paper were able to influence the content of the Preprint Paper or on what basis these co-authors were subsequently removed from the Published Paper.

4.2.7 In the Published Paper, 7 instances of "Shadow Author" interference were omitted. This included the omission of instances of interference in the Abstract, Introduction, Discussion, Evaluation of Studies, Limitations and Conclusions sections. (See **Appendix 4**)

4.2.8 In addition, the Limitations section was revised, with the inclusion of important clinical context, and the Risk of Bias methodology was returned to its standard form. The inclusion of more detailed subgroup analyses also improved the evidence presented in the Published Paper. (See **Appendix 4**)

## 4.3 The Removal of the Conclusions Section in the Published Paper

4.3.1 The conclusions of the preliminary meta-analysis would have been expected to provide strong support for a recommendation for the use of ivermectin in the treatment of hospitalised COVID-19 patients. The addition of further studies, which also produced positive findings for the use of ivermectin, enhanced the preliminary meta-analysis.

4.3.2 In this context, the absence of any conclusions in the Published Paper arising from a meta-analysis of 24 randomised controlled trials into the use of ivermectin is very difficult to explain based on the evidence presented in the Preprint Paper.

**Safety of Ivermectin**

4.3.3 Dr Hill and his co-authors maintained their silence on the safety of ivermectin despite its unparalleled safety record and Dr Hill's previous statements at the International Ivermectin Group webinar on 19 January 2021 that he would want his own brother to take the drug if he were infected with COVID-19.

4.3.4 The unwillingness of Dr Hill and the co-authors to address the issue of the safety of ivermectin in the treatment of COVID-19 patients, in a meta-analysis of 24 clinical trials with over 3,000 participants, defies a clinical or scientific explanation.[24]

**Risk/Benefit Assessment for Emergency Use of Ivermectin**

4.3.5 The continuing failure of Dr Hill and his co-authors to offer any conclusions on the risk/benefit implications of the use of ivermectin defies a clinical or scientific explanation.

[24] This allowed the UK Therapeutics Taskforce to rely on a statement issued by Merck & Co (who were concurrently promoting two alternative proprietary therapies) questioning the safety of the use of ivermectin in the treatment of COVID-19 patients. Source: Personal Correspondence

4.3.6 This was a meta-analysis specifically commissioned to identify repurposed drugs for the treatment of COVID-19 patients. The efficacy and safety of ivermectin were essential questions to be addressed in the conclusions of the Published Paper. There is no question that Dr Hill and the co-authors had access to the data.

4.3.7 The subgroup analyses added to the Published Paper provided essential confirmation of the efficacy of ivermectin in the treatment of COVID-19 patients across multiple studies in multiple countries and yet this finding does not apparently warrant any conclusion on efficacy, on safety, or on the risk/benefit analysis of use or on an emergency use authorisation[25].

**Regulatory Requirements for Approval of Ivermectin**

4.3.8 The conclusions on the evidential requirements for regulatory approval of ivermectin "parachuted" into the Preprint Paper were omitted in the Published Paper.

4.3.9 In the Preprint Paper, the failure of Dr Hill and his co-authors to carry out GRADE assessments of each of the studies enabled a "Shadow Author" to fabricate a quality of evidence assessment attached to the Cochrane Risk of Bias Tool in Supplementary Table 1, and to use this fabrication to reject the whole body of studies in the meta-analysis on the basis of the quality of the studies and issues with regulatory approval.

4.3.10 The omission of the conclusions on the quality of the clinical trials in the Published Paper provides additional evidence that supports my concerns that Dr Hill and the co-authors lacked expertise in regulatory matters. This also removes an obstacle to Dr Hill and the co-authors reaching conclusions on the efficacy and safety of ivermectin in the treatment of COVID-19 patients.

**Dr Hill's Ethical Position After His Ivermectin Interest Group Webinar**

4.3.11 On the same day that the Preprint Paper was published on the Research Square website (19 January 2020), Dr Hill expressed a different set of "personal" conclusions supporting the use of ivermectin to over 1,000 physicians, who were attending the Ivermectin Interest Group webinar hosted in South Africa. (8)

4.3.12 The physicians in attendance were treating COVID-19 patients in South Africa and in countries across the world. Dr Hill's presentation and answers to questions clearly influenced the treatment of COVID-19 patients, as shortly thereafter the South African Health Products Regulatory Authority (SAHPRA) was taken to court by physicians and civic groups over the legality of ivermectin use in South Africa. (9)

4.3.13 Dr Hill has never explained his conduct in allowing interference in his Preprint Paper, but the unavoidable conclusion is that Dr Hill did not have the strength of character or ethical commitment to present conclusions that he believed were correct, based on the 'best evidence' available to him at the time.

[25] A Conditional Marketing Authorisation (CMA) in the UK, an Autorisation Temporaires D'Utilisation (ATU) in France, or an Emergency Use Authorization (EUA) in the United States

4.3.14 In his Published Paper, Dr Hill refuses to reach any conclusions on over 6 months of research. In a gesture worthy of Pontius Pilate, he simply washes his hands of the responsibility of presenting evidence-based conclusions.

## 4.4 Potential Motivation of Unitaid in Suppressing Ivermectin Treatment

4.4.1 It is a matter of public record that during January 2021, Unitaid was seeking funding in the region of $28 Billion for its COVID-19 pandemic response plan. Ivermectin, a cheap, effective and widely available generic drug would have profoundly undermined its corporate funding goals. (10)

4.4.2 An evidence-based decision that produced a positive risk/benefit assessment for ivermectin or a recommendation for an emergency use authorisation for the drug would also have been devastating to the strategic and commercial interests aligned with the WHO's global pandemic response plan.

4.4.3 Unitaid and the WHO had a strong motive for ensuring that Dr Hill's meta-analysis concluded against the use of the drug, with recommendations for a new clinical trial programme that would inevitably take many months or years to complete and whose results could be "shaped" by clinical trial design and specification decisions to achieve a result supportive of the WHO's policy priorities.

4.4.4 A detailed forensic investigation of Dr Hill's communication with Unitaid and WHO staff and with other institutional scientists aligned with Unitaid's corporate goals remains an urgent priority.

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## Appendix 1: Email Communication with Dr Andrew Hill

A1.1.1 I wrote to Dr Hill during the late afternoon on Friday, 12 February 2021, as follows (emboldening per original email):

---

*Dear Dr Hill*

*Thank you for posting online the [pre-print] meta-analysis of the clinical trial data into the use of Ivermectin in the treatment of COVID-19 patients.*

*I have 2 questions about your (and your colleagues') conclusions:*

*"This meta-analysis of 18 RCTs in 2282 patients showed a **75% improvement in survival, faster time to clinical recovery and signs of a dose-dependent effect of viral clearance for patients given ivermectin versus control treatment**. Despite the encouraging trend this existing data base demonstrates, **it is not yet a sufficiently robust evidence base to justify the use or regulatory approval of ivermectin**. However, the current paucity of high-quality evidence only highlights the clear need for additional, higher-quality and larger-scale clinical trials, warranted to investigate the use of ivermectin further." (Emphases Added)*

*Given that the effect of ivermectin is so large (75% improvement in survival) and that the potential side-effects arising from the use of the drug are minimal (while concurrently taking on board your use of remdesivir as a comparison of the required sample size in your "interim findings" WHO video and the relatively small 'real difference' arising from its use, along with its recognised potential for serious side effects to manifest, particularly in respect of kidney damage), please would you explain:*

1. *the basis for your recommendation against 'the use' of ivermectin? Specifically, was it your intention with your use of the words '**it is not yet a sufficiently robust evidence base to justify the use … of ivermectin'** to recommend against even an Emergency Use Authorization for ivermectin?*

2. *If you did intend, by your use of the phrase 'to justify the use', to (effectively) recommend against the issuance of an EUA for ivermectin, please would you explain which of the "eligibility criteria" below are in your opinion not met and why? (Below, I quote by way of example the EUA from the FDA for remdesivir, issued on 16 April 2020)*

***Eligibility of the Product for an EUA***

- *COVID-19 is a serious or life-threatening disease or condition caused by SARS-CoV-2, as specified in the declaration of emergency.*

- *There are no adequate, approved, and available alternatives to the candidate products for treating this serious or life-threatening disease.*

- *Based on the scientific evidence available to FDA, it is reasonable to believe that the known and potential benefits of RDV 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.*

*I am fully onboard, at this stage, with the requirement for further evidence in respect of a full approval, but your conclusions seem to rule out the issuance of an EUA for ivermectin. If this was your intention, then your conclusions would potentially impact the treatment of many thousands of COVID-19 patients with moderate to severe COVID-19 over the coming months.*

*I am sure that I do not need to remind you of the great responsibility you hold in this matter and would welcome a rapid response to my questions.*

*Kind regards*

*Lynden Alexander*
---

A1.1.2 Dr Hill replied to my email the next morning on Saturday 13 February 2021:

---
*Dear Lynden,*

*Thanks for your message. We are working with regulatory authorities on a combined analysis of available and emerging evidence from randomised clinical trials of ivermectin. There are several clinical trials with results emerging in the next 4-6 weeks which will be included in the overall evaluation.*

*Best Wishes,*

*Andrew*
---

A1.1.3 I reached out to Dr Hill again on 20 February 2021, to seek clarification of his expected timeline, as follows:

---
*Dear Andrew*

*Thanks for your reply – apologies for my late response, the week has been extremely busy.*

*I think NIH has taken a neutral stance on ivermectin since 11 Feb, which is progress. Is MHRA or EMA looking at this or is this part of the living guidelines process at WHO? I am not quite sure what the process it on this.*

*When is the next look at the evidence with regulators happening?*

*Best wishes*

*Lynden*
*---*

A1.1.4 Dr Hill responded on the same day, as follows:

*---*
*Dear Lynden,*

*Thanks for your message. I am not sure about the review of the data with regulatory authorities. We should know more at the end of March, after several large randomised trials have generated results.*

*Best Wishes,*

*Andrew*
*---*

A1.1.5 On Thursday, 11 March 2021, I wrote to Dr Hill, as follows:

*Dear Andrew*

*I trust you are well.*

*I have been booked by a South African radio station to do a feature on the clinical trials, systematic reviews and meta-analyses on the use of ivermectin, before the ivermectin court case there in the last week of March.*

*I have found some inconsistencies in the preprint on Research Square, which I need to address. I would like to do this informally with you, if at all possible, as the document as presented would not stand up to forensic scrutiny.*

*My deadline is early next week, so if we could speak soonest, I think that would be the best approach.*

*Best wishes*

*Lynden*

## Appendix 2: Formal E-Mail Request for Information to Dr Andrew Hill

A2.1.1 On 18 March 2021, I emailed Dr Hill to request specific information about his preprint paper:

---

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 2021 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 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?**

Given the importance of the Paper to the medical community, treating physicians, and to patients currently suffering with COVID-19 all around the world, I look forward to your early response to these fundamental questions. If you require any clarification of these questions, I am very happy to assist you.

I also ask you to consider the immediate withdrawal of the Paper, while these essential questions are addressed, so that reliable scientific evidence can be the focus of national decision making on the use of ivermectin in the treatment of COVID-19 patients.

Your sincerely

Lynden Alexander

**Lynden Alexander**
**Forensic Communication Consultant**

# Appendix 3: PRISMA 2009 Checklist

## PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | |

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(Cont.)

## PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

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## Appendix 4: "Shadow Author" Omissions and Revisions

**Omissions**
The following text was omitted in the Published Paper:

1. Abstract (Page 3: final paragraph)

*Many studies that were included were not yet published or peer- reviewed and meta-analyses are prone to confounding issues. Furthermore, there was a wide variation in standards of care across trials, and ivermectin dose and duration of treatment was heterogeneous. Ivermectin should be validated in larger, appropriately controlled randomized trials before the results are sufficient for review by regulatory authorities.*

2. Introduction (Page 6: final paragraph, sentences 2 & 3)

*Limitations of current analysis is important as it is being performed with secondary data from a wide variety of different trials in many different parts of the world with designs that were not originally meant to be compatible. Further refined analysis, including direct data examination, are warranted.*

3. Evaluation of Studies (Page 11: final paragraph)

*An evaluation of the quality of the studies included in this meta-analysis was conducted according to the Cochrane Collaboration tool to assess the risk of bias. Of the 18 trials, 11 were of poor quality and seven of fair or high quality. Further evaluation with access to original data from the trials is warranted to increase quality of evidence. [Supplementary table 1]*

4. Discussion: (Page 12: first paragraph, sentences 4-6)

*However, the data should be interpreted carefully in the context that meta-analyses are highly prone to confounding bias, and current viral PCR assays have several important limitations. Many of the studies assessed have not been peer-reviewed. Larger, appropriately controlled randomized trials are needed before rigorous evaluation of the clinical benefits of ivermectin can be undertaken.*

*5.* Limitations: (Page 13: second paragraph, sentence 2)

*The evidence from this first set of studies will require validation in larger RCTs evaluating fixed dosing schedules, preferably using higher doses for between 3-5 days*.

6. Conclusions (Page 15: fourth paragraph)

*Despite the encouraging trend this existing data base demonstrates, it is not yet a sufficiently robust evidence base to justify the use or regulatory approval of ivermectin. However, the current paucity of high-quality evidence only highlights the clear need for additional, higher-quality and larger-scale clinical trials, warranted to investigate the use of ivermectin further.*

7. Conclusions (Page 15: final paragraph)

*The maximum effective dose of ivermectin needs to be clarified and new clinical trials should use a consistent multi-day dosing regime, with at least 0.4mg/kg/day. The appropriate dose and schedule of ivermectin still requires evaluation and the current randomized clinical trials of ivermectin need to be continued until ready for rigorous review by regulatory agencies.*

**Revisions**

8. Limitations (Page 12: final paragraph)

Key limitations to this meta-analysis include the comparability of the data, with studies differing in dosage, treatment duration, and inclusion criteria. Furthermore, the SOC used in the background treatment differed between different trials. Additionally, ivermectin was often given in combination with doxycycline or other antimicrobials. Individual trials may not have power to detect treatment effects on rare endpoints such as survival.

Published Paper (Page 12: paragraphs 1&2)

*A key limitation to this meta-analysis is the comparability of the data, with studies differing in dosage, treatment duration, and inclusion criteria. Furthermore, the standard of care used in the control arm differed between trials.* ***In this meta-analysis, trials that used active controls such as hydroxychloroquine or lopinavir/ritonavir were combined together with those that used placebo or standard care. However, lopinavir/ritonavir and hydroxychloroquine have shown no overall benefit or harm in large randomized trials and meta-analyses. [7, 59-61] Furthermore, additional analyses in this paper separating trials by subgroups of standard care/ placebo and active control showed no significant difference between groups.***

*Another limitation is that ivermectin was given in combination with doxycycline in three trials. Individual trials may not have power to detect treatment effects on rare endpoints such as survival.*

9. Supplementary Table 1 (Preprint Paper)

**Supplementary table 1. Assessment of Risk of Bias**

Graded low, high or unclear risk of bias on the bases of the prespecified criteria set out in the Cochrane Risk of Bias Tool

| Study | Random Sequence Generation | Allocation Concealment | Blinding of Participants and Personnel | Blinding of Outcome Assessment | Incomplete Outcome Data | Selective Reporting | Overall Quality of Evidence |
|---|---|---|---|---|---|---|---|
| Mahmud et a l [R2] | Low | Low | Low | Low | High (*21% of patients randomized not included in the analysis*) | Unclear | **Limited** |
| Mohan et al [R14] | Unclear | Unclear | Low (*Unblinded but objective outcome measure (PCR and viral load)*) | Unclear | Unclear | Low | **Limited** |
| Chowdhury [R15] | High (*Odd/Even randomization based on registration numbers*) | Unclear | Unclear | Unclear | Low | Low | **Limited** |
| Rezai et al [R13] | Low | Low | Low | Low | Low | Unclear | **Fair** |
| Spoorthi et al [R10] | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | **Limited** |
| Raad et al [R11] | Unclear | Unclear | Low | Low | Unclear | Unclear | **Limited** |
| Asghar et al | Unclear | Unclear | Unclear | Low | High (*5% (control) vs 18% (ivermectin) attrition rate between arms*) | Low | **Limited** |
| Podder et al [R6] | High (*Odd/Even randomization based on registration* | Unclear | High (*Open Label + primary endpoint symptoms resolution (subjective element)*) | High (*Open Label + primary endpoint symptoms resolution* | Unclear | Unclear | **Limited** |

35

Published Paper

**Supplementary table 3. Assessments of Risk of Bias**

Graded low, some concerns, or high risk of bias on the bases of the prespecified criteria set out in the Cochrane Risk of Bias Tool

Supplementary Table 3.a: Summary of risk of bias assessment: Primary outcome

| | Randomization | Intended interventions | Measurement of outcome | Missing data | Reported Results | Overall |
|---|---|---|---|---|---|---|
| **Ahmed** | Low risk | Low risk | Low risk | Low risk | Low risk | **Low risk** |
| **Babalola** | Low risk | Low risk | Low risk | Low risk | Low risk | **Low risk** |
| **Chaccour** | Low risk | Low risk | Low risk | Low risk | Low risk | **Low risk** |
| **Elgazzar** | Low risk | Low risk | Low risk | Low risk | Low risk | **Low risk** |
| **Niaee** | Low risk | Some concerns | Low risk | Low risk | Low risk | **Low risk** |
| **Lopez-Medina** | Low risk | Low risk | Low risk | Low risk | Low risk | **Low risk** |
| **Fonseca** | Low risk | Low risk | Low risk | Low risk | Low risk | **Low risk** |
| **Rezai** | Low risk | Low risk | Low risk | Some concerns | Low risk | **Low risk** |
| **Petkov** | Low risk | Low risk | Low risk | Low risk | Low risk | **Low risk** |
| **Kirti** | Low risk | Low risk | Low risk | Some concerns | Low risk | **Some concerns** |
| **Krolewiecki** | Low risk | Some concerns | Low risk | Some concerns | Low risk | **Some concerns** |
| **Mahmud** | Some concerns | Low risk | Low risk | Some concerns | Low risk | **Some concerns** |
| **Mohan** | Some concerns | Low risk | Low risk | Some concerns | Low risk | **Some concerns** |
| **Okumus** | Some concerns | Some concerns | Low risk | Some concerns | Low risk | **Some concerns** |

## Appendix 5: WHO Transcript Virtual Press Conference 5 Feb 2021

[…]

**00:44:23**

FC [Fadela Chaib] Thank you, Dr Ryan. I would like now to invite Isabel Sacco from EFE to ask the next question. Isabel, can you hear me?

IS [Isabel Sacco] Yes, good afternoon. Thank you very much, Fadela. My question is on [unclear] on treatment. This [unclear] is being widely used in many available countries as treatment for COVID patients and in several countries - for example in Latin America - is advised by the health authorities even if its efficacy is not completely proven, or its safety.

Many many people, plain people [?] are using this [unclear] also as a preventive. I would like to know what is the position of the WHO on this issue and when do you expect to have results from the [unclear] involving [unclear] in the Solidarity trial? Thank you.

FC Isabel, the last sentence was not very clear. Is it okay?

IS The question regarding all that I said is I would like to know the position of WHO regarding Ivermectin [?] and when do you expect to have results from the trial involving this drug in the Solidarity trial?

FC Thank you, Isabel. Dr Van Kerkhove will take this question.

**00:45:58**

MK [Dr Maria Van Kerkhove] Yes, I will start and Soumya's going to answer the second part of the question. Currently we haven't made a recommendation on the use of Ivermectin but we're closely following the research that is ongoing related to this drug, which has shown some promising results in some trials for the treatment of COVID-19.

We're aware that there's currently data available of about 1,500 study patients, just slightly less than that, from 11 studies and there's data expected from up to more than 7,000 patients in 56 studies and these studies are of varying quality.

We have a WHO steering committee that is tracking these studies and closely looking at them in order to trigger the guidance and when we have enough information to look at guidance and updating our guidance to change policy. This may begin in the coming weeks.

So any of the changes that come from WHO-recommended treatments follow an expedited but an incredibly complex review which will be shared with the public at the earliest time that we can. Do you want to cover the second part? Thanks.

**00:47:07**

SS [Dr Soumya Swaminathan] Thanks, Maria. Just to clarify that Ivermectin was not prioritised for inclusion in the Solidarity trial. As you know, we have an expert committee that looks at which drugs should go into the Solidarity trial and we're just in the process of finalising the next set of drugs that would be tested in the Solidarity trial but Ivermectin is not part of it.

Just to add to what Maria was saying, we have this process of the living guidelines update which means that we're tracking all the developments in the treatment of COVID-19 in the different clinical trials that are going on all over the world and we do living updates of the meta-analysis so as every trial gets completed it gets added on and it adds to the weight to the evidence and then the guideline developing group actually looks at the evidence and then makes a recommendation and then that gets updated on the living guideline platform.

They're now looking at aisle [sic] six inhibitors, they're looking at Heparin-like anti-thrombotic agents, they're looking at Ivermectin the next couple of weeks and then at a few other drugs. So we'll keep updating the guideline but it's really based on examining all the evidence from all the clinical trials.

00:48:26

The problem is there are many small trials which sometimes give you misleading results and people get either very excited or very depressed about a result which is actually scientifically not valid. So we have to be very careful when we interpret results from these small trials and we need to really review the evidence as a whole. Thank you.

MR [Dr Mike Ryan] Again very often in situations like this - and this is where we need all of science to work together - we often see observations when you'll see it written in the newspapers in vitro you can demonstrate that a particular drug can kill the virus or inhibit the virus in vitro. That means in a test tube or on a dish. That doesn't necessarily mean in a human body and there are all kinds of issues there.

Also astute clinicians over the years often observe that a drug that's been used in one disease, for one indication can potentially be used in another and they make observations on that and often they publish what's called a case study or a clinical series. They publish and say, look, I've observed this, I've treated a few patients, I think this might work.

**00:49:37**

That's then often picked up and put into small-scale clinical studies where you do prospective; you wait to get the patient, you use the drug and you collect your data. The difficulty we have with that situation is that can often, as Soumya said, lead to conflicting information; many, many small studies; one says it might work; others say it doesn't.

What you need are large-scale clinical studies that can definitively answer the question. It doesn't mean the drugs are bad or good. It just means we cannot give a definitive answer on that but it is important to recognise too that all of these drugs - and you will hear people say, oh, these drugs are safe or they're well-tolerated. Most drugs are but all drugs have side-effects so therefore it's really important that we have evidence that shows that the benefit of taking a drug outweighs any risk of taking that drug. So the widespread use of a drug on the basis of a hunch is not necessarily the best way forward.

Having said that, it's really important that physicians and doctors and nurses are out there observing because very often breakthroughs come from unusual observations so we want to see that continue but we also want to bring all of that data together in a way that it can drive long-term policy.