Canadian Covid Care Alliance
Alliance canadienne pour la prévention et prise-en-charge de la covid

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Analysis of the TOGETHER Trial's Ivermectin Arm Results

The TOGETHER Trial is a complex and ambitious clinical study that seeks to evaluate efficacy of multiple established medications against COVID-19. It uses a novel adaptive trial design that seeks to provide data in a more streamlined manner, is able to test multiple treatment candidates in parallel, and utilizes a common control group. This could potentially save valuable time and money.

The TOGETHER trial is the result of a partnership between health researchers in Brazil, Canada and several other countries. Besides trial locations in Brazil, the trial has expanded to South Africa and Pakistan (the ivermectin arm of the trial took place only in hospitals in the Minas Gerais region of Brazil).

Total of 11 interventions have been evaluated so far with some arms already completed or stopped and some still ongoing. Results for hydroxychloroquine, lopinavir/ritonavir, metformin, fluvoxamine and ivermectin have already been published. Based on public statements, trial results for another intervention, peginterferon lambda, are positive but this data has not yet been published in a scientific journal.

This trial has sparked an extensive interest and discussions in the medical and scientific community around the world as is also evident by a number of high-impact publications that resulted from the trial.

The TOGETHER trial is one of only a few high-profile trials that seek to evaluate the potential of established medications against COVID-19 (*i.e.*, drug repurposing). Established medications are typically more available and much less expensive than newer patented drugs. A well-conducted trial in this area can thus have an enormous public health impact not only for the treatment of COVID-19 itself, but can also guide the design and execution of future clinical trials. **The integrity of a trial such as the TOGETHER trial is therefore paramount.**

It is beyond the scope of this communication to analyze all the published data from the trial to date. We want to focus specifically on the most recently published data from the trial's ivermectin arm (published in the New England Journal of Medicine (NEJM) on March 30th 2022; *Effect of Early Treatment with Ivermectin among Patients with Covid-19*). Ivermectin's potential use in the treatment of COVID-19 has received widespread coverage and the drug has been used extensively by many medical professionals who are treating patients on the frontlines. The debate over drug's utility has been, however, highly polarized and reminds one more of poisonous tribalism than scientific rigor, critical thinking and empathy.

While the TOGETHER trial had potential to bring more clarity to this debate, we conclude that it achieved the very opposite; it only obfuscates things further. **Based on the publication process, media coverage, extensive conflicts of interests and the published data itself, we have deep concerns about the publicized conclusions of trial's ivermectin arm.**

Numerous groups and researchers have analyzed the presented and published results from the trial over the past month. In fact, trial results were publicized by the media in an incorrectly simplified way weeks

before the actual paper came out in the NEJM illustrating a concerning tendency to communicate "science by press release" – *for links to these analyses see the end of the document.*

The issues surrounding this trial are so extensive that it is difficult to list them all here. Some are highly technical and deal with the study and statistical analysis protocols – *see the included links.*

The Canadian Covid Care Alliance (CCCA) would like to share at least our main concerns with the study protocol and data analysis.

List of identified concerns

Study protocol issues

- Treatment was underdosed
- Prior ivermectin use was not an official exclusion criterion of the trial
- This was NOT an early treatment trial on a high-risk population
- 25% of participants were hospitalized before finishing treatment
- Potential problems with randomization and blinding
- Vaccination and natural immunity status of trial participants was unclear
- Ivermectin was studied as a monotherapy

Potential conflicts of interest

- Private companies with potential conflicts of interest involved
- Data and Safety Monitoring Committee (DSMC) was not independent

Results reporting issues

- Unexplained publication delay and paper modifications
- NEJM publication quality is questionable
- Superficial discussion of study's limitations
- Bayesian probability of ivermectin superiority is hidden in the Supplement
- Three different conclusion statements are given
- Main study author acknowledges that the study showed some treatment benefit
- Trial data is not available for independent analysis

Each of these is addressed below. A conclusion is provided at the end of this document.

Study protocol issues

Treatment was underdosed

The ivermectin arm of the trial initially administered only a single dose of the drug and was changed to a 3-day regimen of 0.4 mg/kg only after complaints from the outside medical and scientific community (77 patients had already been recruited to the arm prior to this change; they are not included in the data analysis).

Additionally, one crucial aspect of the used dosing is completely absent from the whole paper. Participants were given ivermectin according to their weight only up to 90 kg weight. Everybody heavier got only 36 mg dose without further increase based on their weight. This is absolutely crucial, because obesity is a well-established risk factor of COVID-19, meaning that those most at risk of progressing into severe disease were most undertreated.

Moreover, *"Patients were advised to take the pill on an empty stomach."* Yet, it is known that ivermectin is fat soluble and its administration with meals can lead to higher absorption. This was absolutely unaddressed in the main text and was largely downplayed in the Supplement. In effect, ivermectin was substantially underdosed to an undetermined extent.

Prior ivermectin use was not an official exclusion criterion of the trial

While some of the other medications tested in the TOGETHER trial generally require prescription, ivermectin is widely available over the counter in Brazil. Prior use of the drug was, however, not one of the formal exclusion criteria in the trial. This indicates that some of the placebo patients may have also been exposed to the drug. The authors claim that trial participants were extensively screened, but how this was done is unclear. NEJM publication contains many instances of missing data, indicating that the trial had difficulties with recording even such a simple information as age. Moreover, news reports from the trial period show that use of ivermectin in the Minas Gerais region was highly elevated.

This was NOT an early treatment trial on a high-risk population

The trial design sought to be a double-blind, randomized and placebo-controlled, adaptive platform trial involving symptomatic SARS-CoV-2–positive adults with symptoms of COVID-19 for up to 7 days. Concerns exist that due to medication delivery, patients up to 8 days from symptoms onset may have been included in the trial. This can hardly be considered an early treatment. It is widely known that the initial viral phase of COVID-19 progresses into the inflammatory and coagulation stage around day 8 and with some aggressive variants, such as the Brazilian gamma variant, dominant during much of the trial, even sooner. For comparison, participants in trials for the widely publicized patented drugs Molnupiravir and Paxlovid were included only within 5 or 3 days of symptoms onset, respectively. Ideally, considering the apparent late entry of participants in this arm, confirmation that the participant was in the early phase of the illness should have been done using markers of inflammation.

The trial aimed at focusing on high-risk adults, but this claim is questionable. Median age of participants was 49 years (IQR 38–57). Participants were overweight, but no more than a third had additional risk factors (See Table 1 in the paper). Women, who are known to be at lower risk than men, were somewhat overrepresented. Based on the well-established knowledge of who is at the greatest risk of severe outcomes this patient population appears suboptimal for determining the true therapeutic effect of the studied medication.

25% of participants were hospitalized before finishing treatment

The publication states: *"Primary-outcome events in the trial happened a median of 5 days (interquartile range, 3 to 7) after randomization."* ***"****The primary composite outcome of this study was hospitalization due to COVID-19 within 28 days after randomization or an emergency department visit due to clinical worsening of COVID-19 (defined as the participant remaining under observation for >6 hours) within 28 days after randomization."* This means that 25% of participants ended up in hospital before finishing the treatment. This further supports the fact that this was not an early treatment trial.

Potential problems with randomization and blinding

As already mentioned, the trial initially investigated a single dose of the drug and switched to a 3-day regimen of a higher dose only later *"on the basis of feedback from advocacy groups."* This created anomalies in patient randomization into the ivermectin arm. It appears that time differences existed between the treatment and placebo arm, indicating a risk of multiple biases and potential unblinding. Moreover, the publication states *"The active drug and placebo pills were packaged in identically shaped bottles and labeled with alphabetic letters corresponding to ivermectin or placebo."* However, it is unclear if ivermectin and placebo tablets themselves were visibly different. Authors have not addressed these issues.

Vaccination and natural immunity status of trial participants was unclear

Those that were previously COVID-19 vaccinated were accepted in the study, but distribution of vaccinated and unvaccinated individuals in the ivermectin-treated and placebo groups was not provided. Nor were the participants evaluated with serological tests for possible prior exposure to SARS-CoV-2, which would have also reduced the severity of COVID-19 acquired during the study period and hospitalization rates.

Ivermectin was studied as a monotherapy

While it is common to study single drugs in trials, COVID-19 is a multifaceted disease. Healthcare professionals treating COVID-19 patients have been instead using multiple drugs and nutraceuticals in combination to target various aspects of the disease. Drugs used in isolation are inadequate for achieving maximal treatment success. Trial's senior author, Professor Mills, admitted in August 2021 that *"…the next steps for the TOGETHER trial are going to be getting into combinations. And, you know, those of you*

working in infectious diseases, know that almost all the time, it is combinations of treatments that give us the best return, and I suspect that is going to be the case here." (see 58 min here).

Potential conflicts of interest

Private companies with potential conflicts of interest involved

"The trial was coordinated by Platform Life Sciences, and Cardresearch conducted the trial and collected the data."

"Personnel at Cytel performed all the analyses." Cytel is a statistical modeling company that helps pharmaceutical companies get approvals — it receives payment from and works closely with Pfizer. Cytel's software and services are used by the top 30 pharmaceutical companies.

The trial is associated with MMS Holdings, whose mission includes helping pharmaceutical companies get approval and designing scientific studies that help them get approval. One of their clients is Pfizer.

One of the trial's senior investigators, Dr. Craig Rayner, is senior vice-president of Integrated Drug Development at Certara. Their website states: "*Since 2014, our customers have received over 90% of new drug and biologic approvals by the FDA*." One of their clients is Pfizer. Dr. Rayner had previously publicly criticized the use of ivermectin for treatment of COVID-19.

Data and Safety Monitoring Committee (DSMC) was not independent

Professor Thorlund is Vice President of the contract research organization (CRO, *i.e.*, Cytel), employee of the CRO, professor at the sponsoring university, author of the TOGETHER protocol, and at the same time also the non-voting chair of the DSMC for the trial. Professors Mills and Thorlund have over 100 shared publications, and co-founded MTEK Sciences together. Another DSMC member, Dr. Haggstrom has also a relationship with MTEK and Cytel. More can be found here.

Results reporting issues

Unexplained publication delay and paper modifications

The ivermectin arm of the trial ended in early August 2021, at the same time as the fluvoxamine arm. The fluvoxamine preprint was published shortly after, and its official Lancet Global Health paper was published on October 27th. According to the authors, the ivermectin manuscript was submitted to NEJM in September, but for unknown reasons, it took 6 months to publish. As described below, despite this delay, the publication had numerous issues and was further modified on April 5th, 2022, without explanation.

NEJM publication quality is questionable

The main body of the publication has 11 pages and appears intentionally unclear and deflecting. Three pages of the paper describe methods, but important information is missing. Subgroups in the subgroup

analysis provided differ from those provided in the other TOGETHER trial publications, and no explanation for this was provided. Bayesian probability of superiority and reference to several study limitations are hidden in the Supplement with no or minimal mention in the main text. Tables in the main text include numerous numerical inconsistencies. While some of these appear to be typos and have been corrected in the April 5th update of the paper, many numerical inconsistencies in the main tables remain unaddressed.

Superficial discussion of study's limitations

Main body of the paper largely only lists methods and numerical results. Discussion of limitations is minimal, and many important limitations listed here are not stated at all or are relegated into the Supplement – such as reasons of chosen dosing and its impact or appropriateness of study population. The impact of the changing disease burden and changing viral variants with different severity during the trial are also completely overlooked in the paper. The rapidly progressing gamma variant in particular was prevalent during a portion of the trial.

Bayesian probability of ivermectin superiority is hidden in the supplement

The Bayesian probability of drug's efficacy summary graphic is included in the Figure S6 of the Supplement with no reference to this figure in the main text of the paper. Legend of the Figure S6 states: *"The probability that the event rate was lower in the ivermectin group compared to placebo was 79.4% for the intention-to-treat population, 81.7% for the modified intention-to-treat population, and 63.4% in the per-protocol analysis."* This is clearly favourable for the ivermectin treatment arm. The same summary graphic is included in the main body of the papers for metformin and fluvoxamine arms of the trial. It is very hard to imagine that this obfuscation was not done on purpose.

Three different conclusion statements are given

While the paper's abstract states: *"Treatment with ivermectin did not result in a lower incidence of medical admission to a hospital due to progression of Covid-19 or of prolonged emergency department observation among outpatients with an early diagnosis of Covid-19."*

Discussion begins with the statement: *"We did not find a significantly or clinically meaningful lower risk of medical admission to a hospital or prolonged emergency department observation (primary composite outcome) with ivermectin administered for 3 days at a dose of 400 µg per kilogram per day than with placebo."*

And the paper concludes with: *"In this randomized trial, the administration of ivermectin did not result in a lower incidence of medical admission to a hospital or prolonged emergency department observation for Covid-19 among outpatients at high risk for serious illness."*

The differences in these statements may be subtle to some, they are however highly relevant. None of the statements mentions important limitations of this study – treatment given on empty stomach and limited dosage given to participants over 90 kg, among other issues.

Main study author acknowledges that the study showed some treatment benefit

NEJM publication and its coverage in media largely distorted the statistical findings of the trial and claimed no benefit of ivermectin; yet one of the main study authors, Professor Mills, on one occasion, admitted that a signal of benefit could have been more apparent if the study was larger (for insightful discussion see his comments and additional comments on interpreting statistics here – 28-35 min) and on another occasion even states *"… I actually think it is quite positive. …"*.

Trial data is not available for independent analysis

A transparent trial must be able to provide the anonymized patient-level data that were used to generate the published results for an independent scrutiny. The trial registration states that data was to be available at termination and upon request, but this seems to have changed. Professor Mills now states: "*We are providing all data sets to ICODA*" [International COVID-19 Data Alliance]. "*Applicants can then propose an analysis to ICODA and, if they approve it, can get access to the data*." The authors have not yet responded to data requests even though this trial arm was concluded more than 8 months ago.

No adverse event differences between the treatment and control group identified

Despite all these identified concerns, it is also interesting to note that this is yet another trial that confirms a very good safety profile of ivermectin, which is also recognized by Professor Mills. Media and some government agencies have been discouraging people from taking ivermectin, citing safety concerns, yet based on the available evidence, these concerns have been clearly vastly exaggerated.

Alexandros Marinos concluded one of his analyses very poignantly: "*As we try to make sense of the anomalies, we're forced to confront the dilemma of whether this is the result of lack of competence or its presence. Given that many of the authors of the TOGETHER papers are deeply involved in the evolution of the concept of an adaptive platform trial, and have much experience designing clinical trials for large pharmaceutical companies, neither conclusion is without serious implications.*

The medical use of pharmaceutical products, as the root word pharmakon denotes, implies the knowledge of how to cure, but also the knowledge how to poison. After all, it is the dose that makes the difference. Likewise, with the experts involved in the TOGETHER trial, we must know if the result we saw is a case of application of expertise towards non-obvious ends, or perhaps in the midst of a raging pandemic, honest mistakes were made.

The razor that will distinguish the intertwined hypotheses is the response of the TOGETHER team to the publication of this analysis and others like it. I sincerely hope they respond with more transparency, openness to third party analysis of the data, and a willingness to acknowledge the things that did not go as expected. In contrast, doubling down and making it even harder to get answers will tip the balance in favor of those who believe that whatever mistakes were made, were not, in fact, honest."

Conclusion

Due to the numerous concerns with the study protocol and authors' analysis, we question the validity of the published results and their interpretation.

Despite the above, based on our analysis, the underpowered, methodologically flawed TOGETHER trial showed that even treatment with underdosed ivermectin as a monotherapy later in the disease had a clinical benefit.

It is not our intention to pick on this specific trial. Similar weaknesses can potentially be identified in other drug trials when closely scrutinized. The extent of concerns with the ivermectin arm of the TOGETHER trial is, however, staggering. Science requires transparency and rigor, or it is no science at all. The evidence-based medicine has been hailed as a cornerstone of modern science-based decision making in public health. It primarily relies on double-blind, placebo-controlled studies published in top medical journals. NEJM is undoubtedly considered one such journal. If this publication represents the broader evidence base that our healthcare is built on, we fear the extent of scientifically unfounded practices in modern medicine.

Please review provided links for additional concerns with this study.

Further analyses:

https://c19ivermectin.com/togetherivm.html
The problem with the TOGETHER trial - by Alexandros Marinos (substack.com)
Misconceptions about ivermectin dosing - by Joomi (substack.com)
Whoops! The TOGETHER trial actually showed that ivermectin worked. (substack.com)
The can't add TOGETHER trial - by Phil Harper - The Digger (substack.com)

This document was drafted by Ondrej Halgas, PhD. on April 17th, 2022, with additional editorial input from the members of The Scientific and Medical Advisory Committee of the Canadian Covid Care Alliance (CCCA). Author contact: ondrej.halgas@mail.utoronto.ca

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