Numerous issues with the TOGETHER trial

Researchers and peer reviewers should strive for scientific integrity (rather than pseudoscientific malfeasance), especially given that COVID mortality remains unacceptably high.

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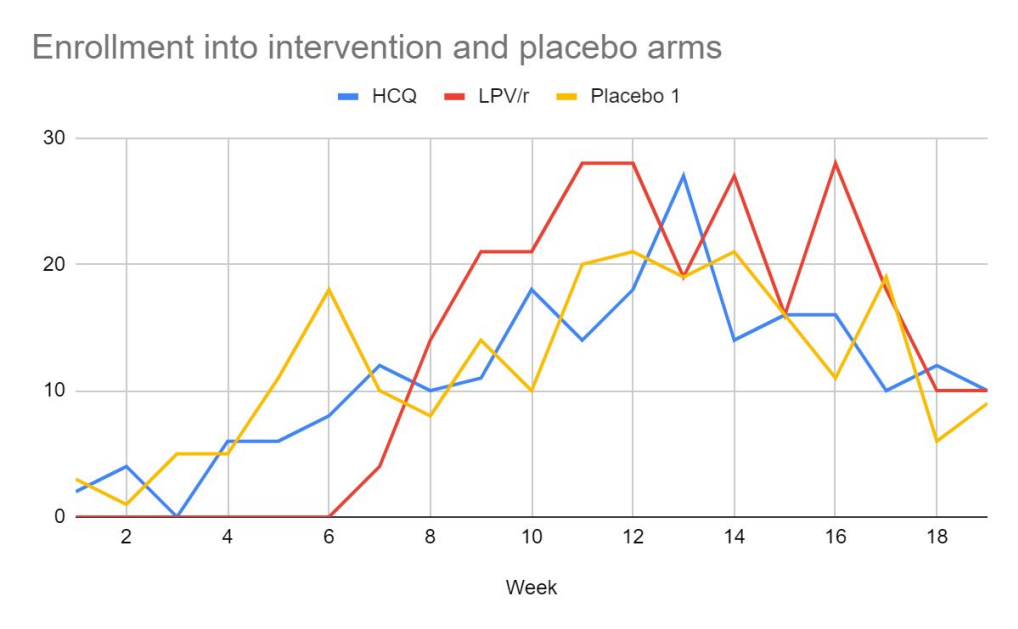
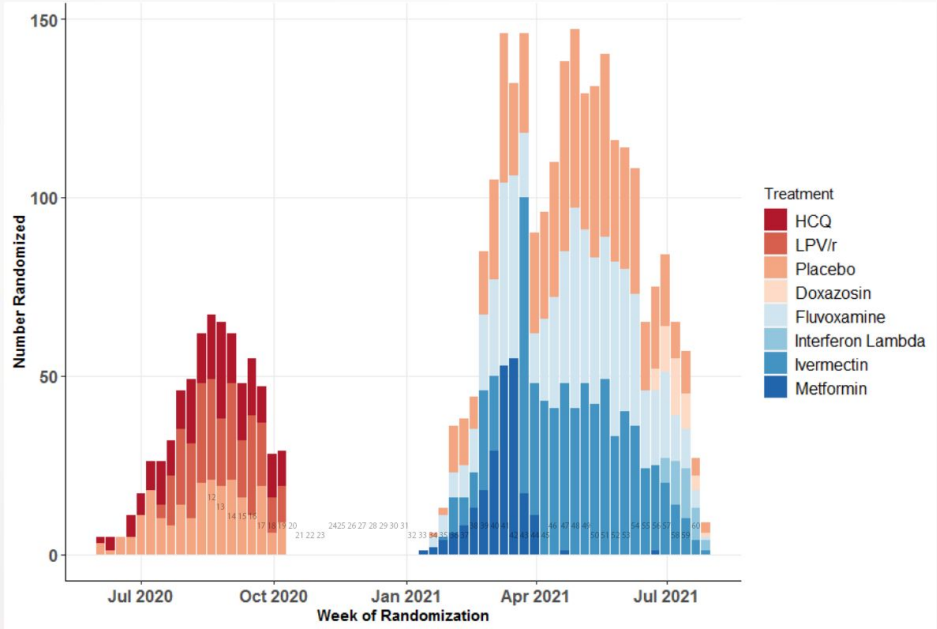


The TOGETHER trial has a history of *unusual* intervention/placebo group assignment. In the first set of trials, enrollment into the LPV/r intervention was delayed. Then, “catch up” enrollment occurred so that all 3 arms of the trial would have roughly the same number of participants.

HCQ = 214, LPV/r = 244, Placebo = 227

Also see the published paper on this trial: https://doi.org/10.1001/jamanetworkopen.2021.6468



Data in this presentation has been calculated from page 17 of the presentation PDF used by Edward Mills, available at

https://dcricollab.dcri.duke.edu/sites/NIHKR/KR/GR-Slides-08-06-21.pdf

https://rethinkingclinicaltrials.org/news/august-6-2021-early-treatment-of-covid-19-with-repurposed-therapies-the-together-adaptive-platform-trial-edward-mills-phd-frcp/

How the methodology was reported

The study's paper (doi:10.1001/jamanetworkopen.2021.6468) described the trial as a "Randomized Clinical Trial".

> **Interventions and Randomization**
>
> We randomized patients to the hydroxychloroquine, lopinavir-ritonavir, and placebo groups at 1:1:1. Randomization was stratified by site, age (aged 50 years or older vs less than 50 years), and time of onset of flulike symptoms (at least 5 days vs less than 5 days). Patients, investigators, health care practitioners, and sponsors were masked to the study drug assignment. The randomization schedule was prepared by a masked statistician and provided to site-level pharmacists.

The paper describes the randomization as "1:1:1". That could be compared to saying that the Titanic maiden voyage was 'mostly' non-fatal. It fails to describe the totality of events.

A pattern of misrepresenting questionable trial design decisions

The paper states that a talc placebo was used:

> A sample size of 492 patients per group was chosen for each experimental group to achieve 80% power with α = .05, 2-sided type 1 error for a pairwise comparison against the control (talc) to detect minimum treatment efficacy defined by 37.5% relative risk reduction of preventing hospitalization assuming a control event rate of 20%.

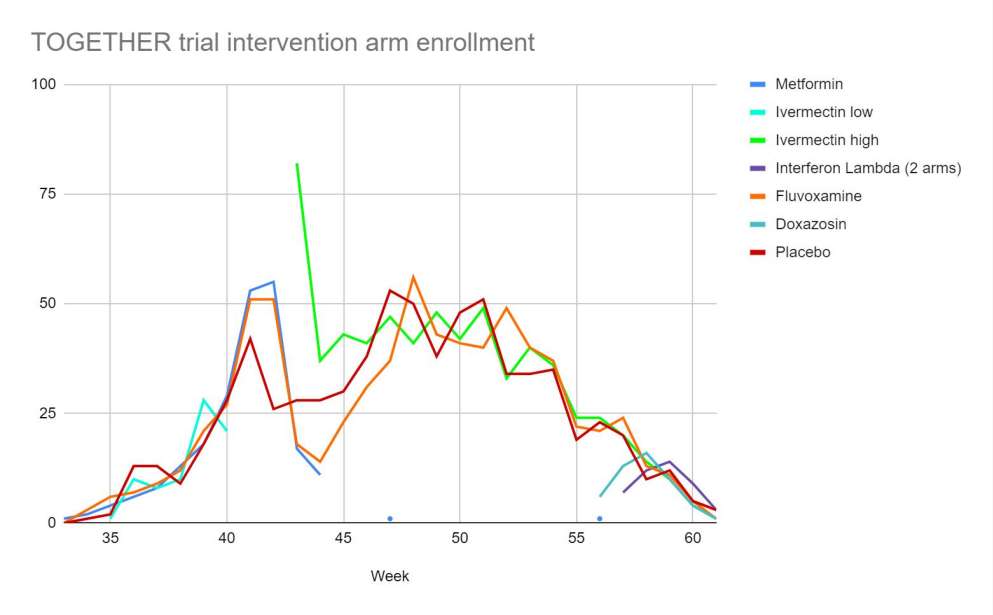
Yet the supplemental content document labelled “Trial Protocol” describes an “ascorbic acid” placebo that was also used in the trial.

3.2.5. *Rationale for Ascorbic Acid Control as a Comparator*

In healthy adults, COVID-19 disease is likely to present as an upper respiratory viral infection, characterized by a febrile disease with cough and fatigue.[30] Symptom reporting may vary based on participants' perception as to whether they are taking investigational antivirals or ascorbic acid, but the primary study endpoints of LRTI and viral shedding are not affected. There is no rigorously-proven therapy for individuals with outpatient COVID-19 disease, although multiple therapies are under investigation.

Because there is not established therapy, use of a control is acceptable and ethical both for participants' health and safety as well as ensuring the most rigorous trial design to evaluate an intervention for COVID-19 disease caused by SARS-CoV-2. As there are multiple intervention regimens with different dosing schedule and route, full blinding for patients and clinicians will not be feasible. Participants will be blinded to their allocation to the extent possible.

The dose of ascorbic acid chosen for this protocol is considered to be safe and well tolerated. All participants, regardless of assigned group, will be able to take additional ascorbic acid (e.g., over the counter vitamins, or through food) should they choose, as there is no known maximum daily safe dose of ascorbic acid. Clinical trial evidence has demonstrated that ascorbic acid, alone or in combination with other micronutrients, does not substantially reduce the risk of upper respiratory infections or severe consequences of infectious processes; thus, ascorbic acid is not expected to have a prevention effect for SARS-CoV-19 and is considered a placebo-equivalent product for this study.



Unusual intervention/placebo group assignment continued into the second round of TOGETHER trials. The ivermectin arm was stopped and replaced by a higher-dose ivermectin arm. "Catch up" enrollment may have occurred in the high-dose ivm group (in neon green) judging by its initial high rates of assignment.

The timing differences between placebo and intervention are ignored. The published paper inappropriately describes the placebo group as a "control". It is not a pure control group.

Multiple placebo groups are sometimes inappropriately described as a single placebo group

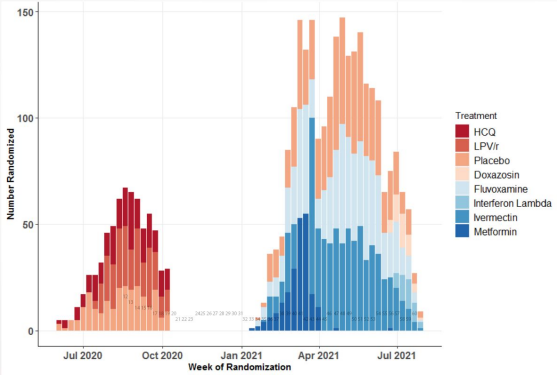
During the TOGETHER trial, there were **multiple** placebo groups as each intervention arm had a corresponding placebo. This is described in NCT04727424. Participants and their clinicians were aware that may have been receiving one of the interventions but knew that the patient was NOT receiving the other interventions being tested at the time.

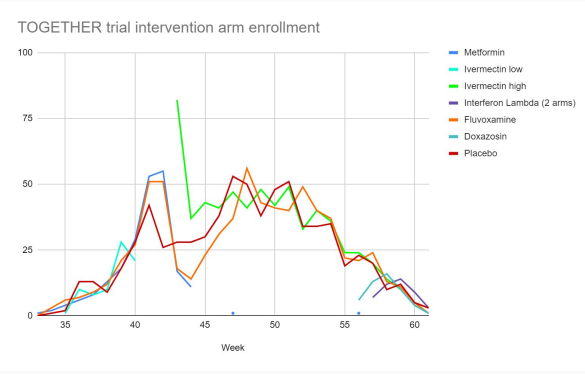
Secondly, trial protocol did not seem to preclude enrollment of patients with prior ivermectin use as ivermectin was not one of the exclusion criteria. Previous trial protocol documents may suggest that such patients would be assigned to a non-ivermectin intervention/placebo arm, e.g. into a metformin intervention or metformin-placebo group.

Given numerous discrepancies between the intervention and placebo groups (e.g. timing differences, ivermectin use, and differences in placebo effect with its associated adverse event vigilance), it is inappropriate to assume that all of the placebo cohorts are valid controls for the intervention group.

Ivermectin patients were inexplicably dropped from the intervention cohort

The NEJM paper (doi:10.1056/NEJMoa2115869) states that **679** patients were in the ivermectin intervention group. Yet data from the presentation slide mentioned earlier (below, left) indicates that **78** patients were assigned to the low-dose ivm group and **636** patients were assigned to the high-dose ivm group. It is inappropriate for the NEJM paper to state that the trial was “pre-registered” when data analysis protocol and trial design were determined *after the fact*.





A call for honest, reliable science

It is not ideal when the outcome of a clinical trial can be predicted by reading the social media activity and media interviews of the principal investigators. Editorial content (e.g. the HCQ editorial briefly highlighted on TogetherTrial.com, commentary regarding ‘paramedical groups’) should not telegraph trial outcomes. Science should be performed with an open mind, tolerant of results that go against the investigators’ original hypotheses.

A call for honest, reliable science (continued)

Secondly, there may be some usefulness in the TOGETHER trial data. If inappropriately placebo cohorts are excluded, it may be possible randomized controlled trial data exists (where the intervention group is several times larger than the placebo group).

While such data will face accusations of bias and poor methodology, it may add to our knowledge regarding ivermectin's in vivo (in)effectiveness. There may be salvageable data. The non-reporting of such data could potentially create publication bias in the ivermectin literature.

Given the likely bias of the principal investigators, one might speculate that the unreported results trend towards favouring ivermectin. It would be in humanity's interest for a reliable analysis of this data to be published.

“However, the medical research community's response to COVID-19 has arguably been inefficient and wasteful, with an overwhelmingly large number of clinical trials having been registered and done **with questionable methodological quality**.”

- Jay Park, **Edward Mills** et al.

How COVID-19 has fundamentally changed clinical research in global health

https://doi.org/10.1016/S2214-109X(20)30542-8

I would **concur** with Edward Mills regarding the importance of methodological quality - **we should all strive to do better**. Thank you.