Articles Explaining the Shortcoming of the ACTIV-6 Study Protocol for Ivermectin and other alternative treatment options to the SARS-Cov-2 "vaccine" options

Compiled by Duane G. Leet, PhD

Introduction

The ACTIV-6 protocol has been used in several high profile studies of alternative treatments for Covid-19. I provide two articles describing some of the identified problems with relying on the conclusions of papers publishing the results of studies using this protocol:

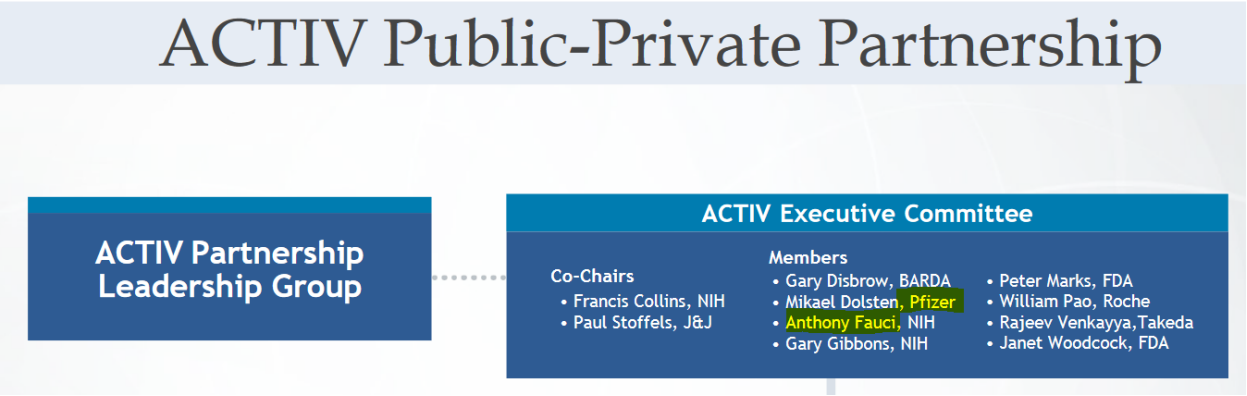
I have taken the liberty of reformatting the original articles, which were in web format, with typical font-types and figure formatting, that don't translate well to printed form. I did this by importing the articles into Word and creating a legible, printed version. I've also added a footnote or two, with my initials following the footnote. DGL

22-11-01 ACTIV-6 Dosing & Timing: A Fox In The Henhouse

Author: Alexandros Marinos, published

Background

Trying to understand what I learned in my conversation with the ACTIV-6 patient[1], I looked at who is actually responsible for the ACTIV trials. It turns out that ACTIV is a "Public-Private" partnership, with several pharmaceutical companies having representatives on its executive committee:



[1] This article is the next section DGL

Beyond J&J, Roche, and Takeda, there is also representation from Pfizer, which—in Paxlovid—has a direct competitor to all the repurposed drugs being tested by ACTIV-6. And let's not forget that Anthony Fauci, also on the executive committee, has made statements of this nature:

Is this someone we'd trust to lead an organization that will answer the question of ivermectin's Covid-19 efficacy for us?

If you're wondering whether the trial was sabotaged by lack of funding, you can rest assured that was not the case. The trial was provided with an initial $155 million, working out to more than $11,000 per patient:

Monday, April 19, 2021

Large clinical trial to study repurposed drugs to treat COVID-19 symptoms

Using an ACTIV master protocol, the trial will focus on potential interventions for mild-to-moderate illness.

The National Institutes of Health will fund a large, randomized, placebo-controlled Phase 3 clinical trial to test several existing prescription and over-the-counter medications for people to self-administer to treat symptoms of COVID-19. Part of the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) public–private partnership, the ACTIV-6 trial aims to provide evidence-based treatment options for the majority of adult patients with COVID-19 who have mild-to-moderate symptoms and are not sick enough to be hospitalized. NIH will provide an initial investment of $155 million in funding for the trial.

So, whatever the reason was that they could not serve patients over the weekend—in our trial participant's experience—lack of money was not it.

Most nurses and doctors have been taught the "five rights" of medication use

- the right patient,
- the right drug,
- the right time,
- the right dose,
- and the right route.

So let's see how timing and dosing affected this trial:

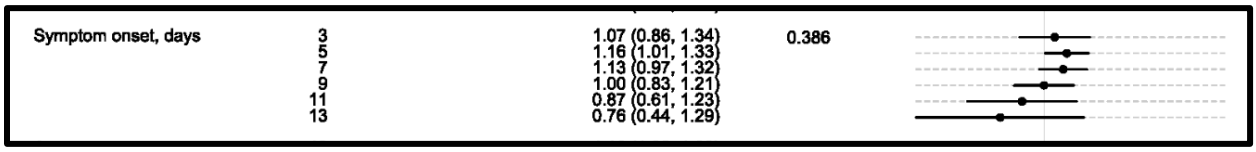
Was The Timing Right?

Antivirals are like a parachute. If you open them too late, you're going to get hurt, badly. This doesn't mean the parachute didn't work. It means that you didn't open it in time. Very similarly, if an antiviral is taken too late to effectively check the replication of the virus, any effect will be suboptimal, to say the least.

This is, of course, is very well understood by the people who test antivirals. For instance, the EPIC-HR trial—that led to Paxlovid's approval—as well as the MOVE-OUT trial—that led to Molnupiravir's approval—excluded patients that were over five days from symptom onset. MOVE-OUT had 50% of patients with less than three days from symptom onset. For EPIC-HR that was 68%. ACTIV-6 on the other hand, only had 25% of ivermectin patients with less than five days from symptom onset. As absurd as it may sound, 75% of the patients in ACTIV-6 for ivermectin would have been rejected from the Molnupiravir and Paxlovid trials for having the disease in too advanced a stage.

And let's not forget that based on what we learned from the ACTIV-6 patient I spoke to, the drug was shipped on the first day of participation in the trial, which means most likely we should add an extra day to all the ACTIV-6 numbers above. Based on the literature review I did in this previous article, the ACTIV-6 trial for ivermectin treated its patient later than all the trials describing themselves as "early treatment" in the *New England Journal of Medicine.*

Using the same formula I used in that article, the ACTIV-6 ivermectin 400 trial would be described as having a maximum of 15 days from onset of symptoms and a median of 8 days (IQR [6-9]), until the patients were actually treated. Here's what the trial tells us about results in subgroups:



In short, this trial does not fit any definition of early treatment. Even so, there's a clear trend towards a timing-response relationship.

Was The Dose Right?

According to the trial publication, the patients got approximately 400 µg/kg of ivermectin for three days.[2]

> **Interventions**
>
> A central pharmacy supplied ivermectin or placebo to participants via direct home delivery. Ivermectin was supplied as a bottle of 15 7-mg tablets. Participants were instructed to take a prespecified number of tablets for 3 consecutive days based on their weight for a daily dose of approximately 400 µg/kg (**Supplement 1**). Packaging for matched placebo was identical to that of ivermectin. Packaging for other contributing placebo was identical to that of the associated study drug.

[2] This paper was written with a 400 microgram / 3 day administration protocol in mind. One of the papers recommended by Dr. Simmons has a 600 microgram / 6 day administration protocol, which was intended by the researchers to address this criticism. Nevertheless, the comments that follow are legitimate criticisms of protocols similar to this. DGL

What does “approximately” mean? Let’s find out! Naturally, for this, we must read the protocol:

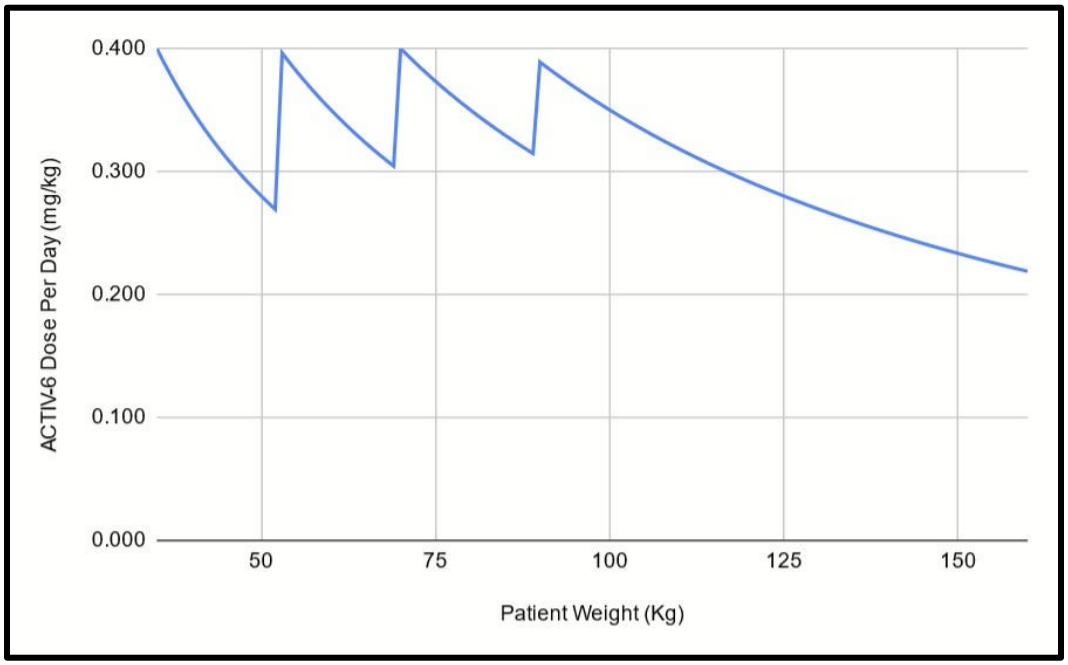
16.3.3. Dosing and Administration

Ivermectin should be taken on an empty stomach with water (30 minutes before a meal or 2 hours after a meal). Each participant will receive a bottle of fifteen 7-mg tablets and will be instructed to take a pre-specified number of tablets for 3 consecutive days based on their weight (see **Table 4**) for a daily dose of approximately 300-400 µg/kg.

Table 4: Ivermectin 400 Dosing Schedule

Weight (kg)	Day 1 (# of 7-mg tablets)	Day 2 (# of 7-mg tablets)	Day 3 (# of 7-mg tablets)	Daily Dose (µg/kg)
35-52	2	2	2	269-400
53-69	3	3	3	304 -396
70-89	4	4	4	315-400
>90	5	5	5	≤389

This looks like the sort of thing that would look good on a chart:



Well, that is… interesting. You see, the 400µg/kg is actually the maximum dose per kg of bodyweight, which would be given only to patients weighing exactly 35, 53, and 70kg. (That’s 77, 117, and 234 lb respectively, for my friends of the imperial persuasion.) Everyone else gets underdosed to a smaller or greater extent. My best estimate—taking the data the authors gave us—is that the average dose was about 343µg/kg, or 14% less than advertised. This is a naive average, because I assume every weight in the range has the same probability of appearing, but it’s OK for a first estimation.

Even assuming that there is a perfectly reasonable explanation for why the authors chose to dose ivermectin this way, nobody forced them to claim they gave 400µg/kg instead of whatever the average or median was. Scientific integrity demands that they be precise in describing the experiment they ran. The fact that they failed in such an easily verifiable way inspires little trust. For me, accurately describing dosing is the brown M&M test, and ACTIV-6 failed it (as have so many others before it).

But that isn't all. You see, when we cross beyond 90kg (198.4 lb) the dose/kg decreases as weight increases. And weight is also highly correlated with increase in BMI:

Weight-Height Relationships and Body Mass Index: Some Observations From the Diverse Populations Collaboration

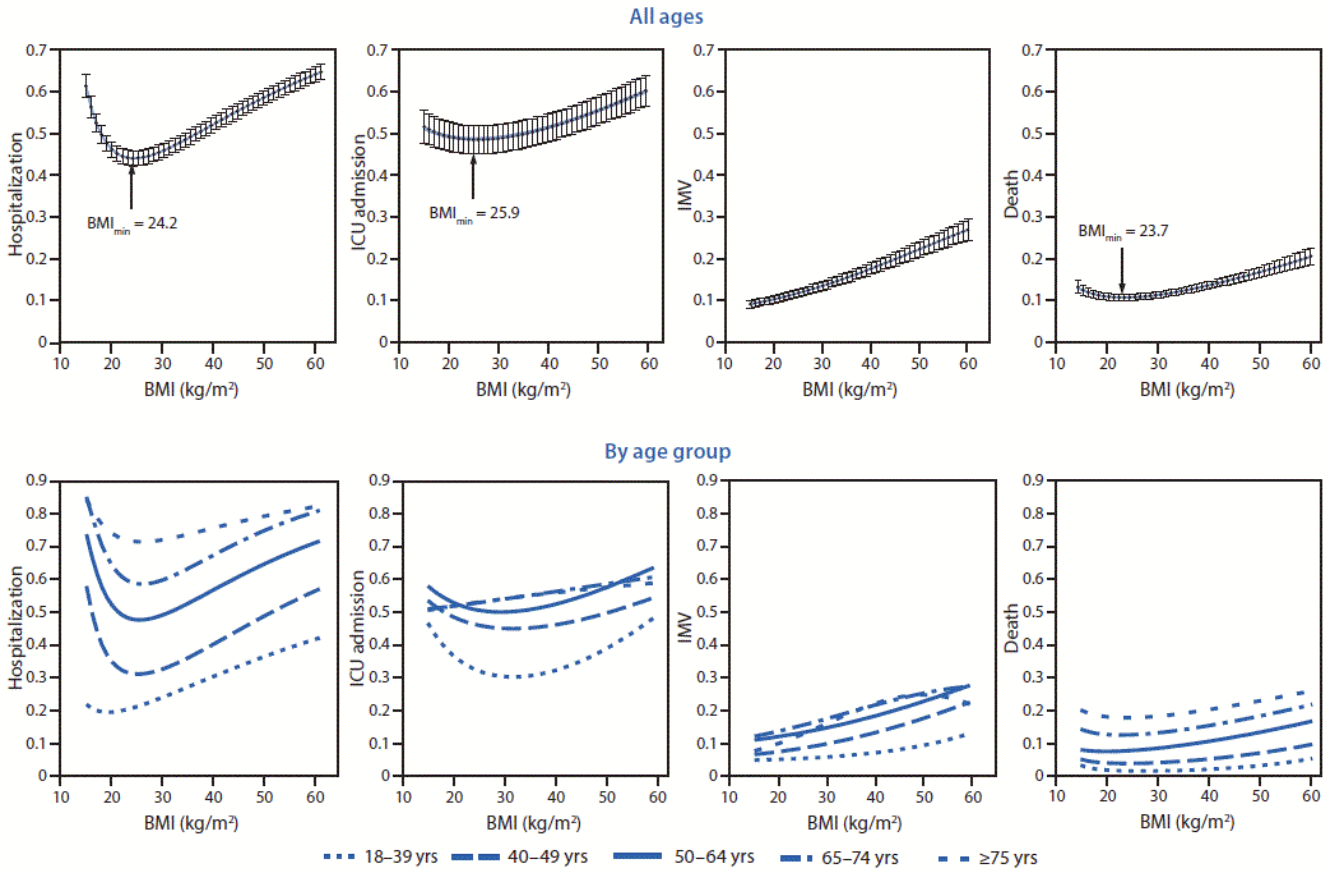
Diverse Populations Collaborative Group*

Department of Statistics, Florida State University, Tallahassee, Florida 32306-4330

KEY WORDS height; weight; body mass index; anthropometrics; obesity

ABSTRACT Body mass index (BMI, weight (kg)/height $(m)^2$) is the most widely used weight-height index worldwide. This universal use of BMI assumes that the rationale for its use is universally applicable. We examine two possible rationales for using BMI as a universal measure. The first rationale is that BMI is strongly correlated with weight, but is independent of height. The second rationale is that BMI correctly captures the relationship between weight and height, which implies that the slope of log weight regressed on log height is 2. We examined the weight-height relationship in 25 diverse population samples of men and women from the US, Europe, and Asia. The analysis included 72 subgroups with a total of 385,232 adults aged 25 years and older. Although BMI was highly correlated with weight in all studies, a significant, negative correlation between BMI and height was found in 31 out of 40 subgroups of men ($r = -0.004$ to -0.133) and 32 of 32 groups of women ($r = -0.016$ to -0.205). When log weight was regressed on log height, the 95% confidence intervals (CI) of the slopes did not include 2 in 25 out of 40 male subgroups. The summary estimate of the slopes across studies of men was 1.92 (95% CI, 1.87–1.97). For women, slopes were lower than 2 in 28 of 32 subgroups with a summary estimate of 1.45 (95% CI, 1.39–1.51). In most of the populations, BMI is not independent of height; weight does not universally vary with the square of height; and the relationship between weight and height differs significantly between males and females. The use of a single BMI standard for both men and women cannot be justified on the basis of weight-height relationships. Am J Phys Anthropol 128:220–229, 2005.

BMI is also a serious risk factor for COVID. Risk of death doubles for patients with the highest BMI:



All this goes to show that the ACTIV-6 trial didn't just underdose patients in a random fashion. It underdosed its most at-risk patients the most. As such, the risk-adjusted underdosing is substantial in the highest weight/BMI patients.

How Was The Dose Decided?

You may have seen Tweets like these going around, by ACTIV-6 author Dr. David Boulware:

> David Boulware, MD MPH @boulware_dr
> @richardemoe @GidMK @EdoajoEric Also, so you are aware, I consulted on the IVM dosing with a prominent FLCCC member when ACTIV-6 was designed. They thought the dosing was "totally reasonable." Subsequently in Oct 2021, (after the TogetherTrial results were available), FLCCC have changed their dosing rec.

Three assertions here:

1. Dr. Boulware consulted a prominent member of the Front Line Covid-19 Critical Care Alliance (FLCCC).
2. This prominent member thought the dosing was "totally reasonable."

3. FLCCC changed their dosing recommendation in October 2021.

The internet can be an incredible place sometimes. For instance, we found that very email exchange, in said prominent FLCCC member Dr. Pierre Kory's Substack:

From: David Boulware <>
Date: Thursday, May 13, 2021 at 8:19 AM
To: Pierre Kory <>
Subject: Re: Positive Mongolia study on fluoxetine (Prozac) for COVID

Pierre,

What's a reasonable dose for ivermectin for early mild disease?

RCTs are testing 400 mcg/kg/day x 3 days.

Reasonable? Too low? Too high?

David

On May 27, 2021, at 8:46 PM, Pierre Kory <> wrote:

400mcg for 3 days is totally reasonable.. but I would go 5 if they did not have a sufficient response/resolution by day 3 . My issue with RCT's is that they treat too late by definition in almost all acute illness models – for every day later you treat, you need to be more aggressive. ***So 400mcg is fine for me as a doc when a patient calls me or I get word someone is sick.***. but by the time a sick patient is enrolled in an RCT who knows

Other issue is I believe any further placebo controlled RCT's are unethical – but understand others don't see the world that way.. not a surprise - Pierre

Pierre Kory, MD, MPA

President & Chief Medical Officer

Front-Line Covid-19 Critical Care Alliance

I'll leave it up to the reader if this qualifies as "consulted with."

Note that Dr. Boulware doesn't even say he's asking as part of trial design. For all Dr. Kory knows, Dr. Boulware might be asking for a relative and mentioning the RCTs[3] as a reference point.

Also note that Dr. Boulware explicitly asks for **early & mild** disease. As we have already discussed, the trial doesn't qualify as early treatment. It also describes itself as a study of "mild & moderate" patients, so that, too, is incorrect.

Dr. Kory's first sentence in response is:

400mcg for 3 days is totally reasonable.. but I would go 5 if they did not have a sufficient response/resolution by day 3 .

So, first of all, Dr. Kory makes clear that this regimen is shorter than he would personally use. HOWEVER:

My issue with RCT's is that they treat too late by definition in almost all acute illness models – for every day later you treat, you need to be more aggressive. So 400mcg is fine for me as a doc when a patient calls me or I get word someone is sick.. but by the time a sick patient is enrolled in an RCT who knows

Here he makes it clear that the regimen is fine *for him* as a doctor when a patient calls—which is usually on day 1 or 2 of symptoms—but not for an RCT which, structurally enroll patients later.

Why does Dr. Kory say that RCTs enroll patients late? Let me count the ways:

RCTs often require positive PCR tests to confirm infection, which themselves take a few days and are subject to pandemic and demand-related bottlenecks.

Other times, trials ask for not one, but two symptoms besides a PCR test (like ACTIV-6 does, actually—the man really is a prophet), which would tend to add to the overall time to initiation.

In general, there is a large amount of paperwork that needs to be done. For one, enrollment may take time. For another, many trials actually initiate treatment a day after the patient has been randomized—since there is so much data gathering that needs to be done—even after the patient has been enrolled.

Finally, due to pandemic precautions, some trials will send the drugs to the patients using a delivery service like FedEx. Some trials won't ship drugs over the weekend. If

[3] RCT = Randomized Control Trial DGL

you think I'm talking about some random trial in a far away land, reader, I assure you, I'm talking about ACTIV-6 again.

But let's go back to a little comment that may have gotten lost in the noise:

for every day later you treat, you need to be more aggressive.

This sounds pretty important. I wonder if that part of the consultation with FLCCC was incorporated into the ACTIV-6 protocol somewhere. I haven't read the whole thing yet, so if an author could kindly point me in the right direction, I would love to be delighted.

Other issue is I believe any further placebo controlled RCT's are unethical – but understand others don't see the world that way.. not a surprise - Pierre

Pierre Kory, MD, MPA

This last line may seem out of place, but in fact, it is historical testimony to the same line of ethical thought we've seen at a similar point in time from someone like Dr. Thomas Borody. It goes to show that this wasn't something being said for effect in the media, but a deeply held principle that was conveyed in private to anyone who seemed like he wanted to listen.

The representation of the email is entirely misleading, and I lack the legal background to determine if the Tweet meets the standard of libel. If, however, Dr. Boulware stands by the fact that he "consulted" with the FLCCC, the least Pierre Kory can do is to send him an invoice.

There is another, bigger problem, though.

What Did 400 µg/kg Mean For FLCCC?

The FLCCC—with its v10 protocol, which was current at the time of Boulware's email—already recommended 0.4mg/kg dosing for treatment after the fifth day of symptoms, or for patients dealing with aggressive variants:

I-MASK+

PREVENTION & EARLY OUTPATIENT TREATMENT PROTOCOL FOR COVID-19

Page 1/2

PREVENTION PROTOCOL

Ivermectin[1]	***Prevention for high risk individuals*** 0.2 mg/kg per dose (take with or after meals) — one dose today, repeat after 48 hours, then one dose weekly*
	Post COVID-19 exposure prevention[2] 0.2 mg/kg per dose (take with or after meals) — one dose today, repeat after 48 hours*
Vitamin D3	1,000–3,000 IU/day
Vitamin C	500–1,000 mg twice a day
Quercetin	250 mg/day
Zinc	30–40 mg/day
Melatonin	6 mg before bedtime (causes drowsiness)

EARLY OUTPATIENT PROTOCOL[3]

Ivermectin[1]	0.2–0.4 mg/kg per dose (take with or after meals) — one dose daily, take for 5 days or until recovered* Use upper dose range if: 1) in regions with more aggressive variants; 2) treatment started on or after day 5 of symptoms or in pulmonary phase; or 3) multiple comorbidities/risk factors.
Fluvoxamine	50 mg twice daily for 10–14 days. Add to ivermectin if: 1) minimal response after 2 days of ivermectin; 2) in regions with more aggressive variants; 3) treatment started on or after day 5 of symptoms or in pulmonary phase; or 4) numerous comorbidities/risk factors. Avoid if patient is already on an SSRI.
Nasopharyngeal Sanitation	Steamed essential oil inhalation 3 times a day (i.e. vapo-rub) and/or chlorhexidine/benzydamine mouthwash gargles and Betadine nasal spray 2–3 times a day
Vitamin D3	4,000 IU/day
Vitamin C	500–1,000 mg twice a day
Quercetin	250 mg twice a day
Zinc	100 mg/day
Melatonin	10 mg before bedtime (causes drowsiness)
Aspirin	325 mg/day (unless contraindicated)
Pulse Oximeter	Monitoring of oxygen saturation is recommended (for instructions please see page 2 of this file)

For **optional medicines** and an overview of the developments in prevention and treatment of COVID-19, please visit www.flccc.net/optional-medicines.

* The dosing may be updated as further scientific studies emerge.

[1] The safety of ivermectin in pregnancy has not been established. A discussion of benefits vs. risks with your provider is required prior to use, particularly in the 1st trimester.

[2] To use if a household member is COVID-19 positive, or you have prolonged exposure to a COVID-19 positive patient without wearing a mask

[3] For late phase — hospitalized patients — see the FLCCC's MATH+ Hospital Treatment Protocol for COVID-19 on www.flccc.net

Please regard our **disclaimer** and further information on page 2 of this document.

flccc.net

Behavioral Prevention

WEAR MASKS

Must wear cloth, surgical, or N95 mask (without valve) in all indoor spaces with non-household persons.

Must wear a N95 mask (without valve) during prolonged exposure to non-household persons in any confined, poorly ventilated area.

KEEP DISTANCE

Until the end of the Covid-19 crisis, we recommend keeping a minimum distance of approx. 2 m / 6 feet in public from people who are not from your own household.

WASH HANDS

We recommend, after a stay during and after outings from home (shopping, subway etc.), a thorough hand cleaning (20–30 sec. with soap), or also to use a hand disinfectant in between.

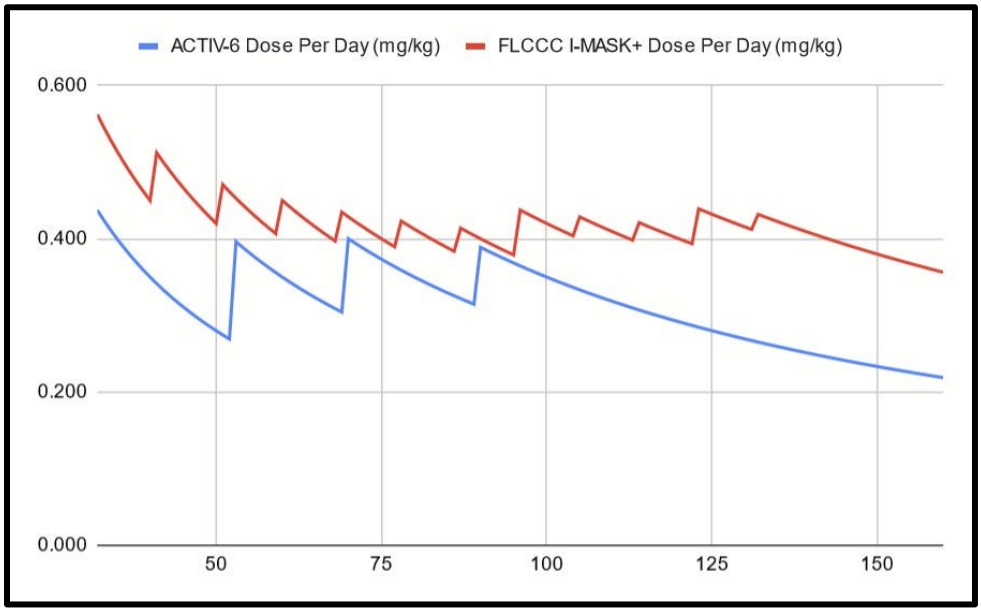
This effectively covers all the patients in the ACTIV-6 trial, who were not only overwhelmingly beyond five days of symptoms, but also were dealing with Delta—a more aggressive variant than Alpha—which was dominant at the time of Boulware's email to Kory.

In addition, the FLCCC protocol was always very specific about how it implemented that recommendation:

Body weight conversion (kg/lb) for ivermectin dose in prevention and treatment of COVID-19

Body weight **Conversion (1 kg ≈ 2.2 lbs)** (doses calculated per upper end of weight range)		**Dose** **0.2 mg/kg ≈ 0.09 mg/lb** (Each tablet = 3 mg; doses rounded to nearest half tablet above)	
70–90 lb	32–40 kg	8 mg	(3 tablets = 9 mg)
91–110 lb	41–50 kg	10 mg	(3.5 tablets)
111–130 lb	51–59 kg	12 mg	(4 tablets)
131–150 lb	60–68 kg	13.5 mg	(4.5 tablets)
151–170 lb	69–77 kg	15 mg	(5 tablets)
171–190 lb	78–86 kg	16 mg	(5.5 tablets)
191–210 lb	87–95 kg	18 mg	(6 tablets)
211–230 lb	96–104 kg	20 mg	(7 tablets = 21 mg)
231–250 lb	105–113 kg	22 mg	(7.5 tablets=22.5 mg)
251–270 lb	114–122 kg	24 mg	(8 tablets)
271–290 lb	123–131 kg	26 mg	(9 tablets = 27 mg)
291–310 lb	132–140 kg	28 mg	(9.5 tablets=28.5 mg)

So how does that superimpose on the ACTIV-6 dosing if we compare the 400µg/kg versions? It looks something like this:



The FLCCC doses in a way that makes 400 µg/kg the minimum—not the maximum.

Even if Dr. Boulware was not enamored with the FLCCC, by using what was recommended in their protocol at the time, he would have had a defensible position, if his intention was to say that he followed the recommendation of the FLCCC. All this was knowable at the time, if only Dr. Boulware had visited the FLCCC website and downloaded their protocol.

So how do the two implementations differ? The naive average here across the 40-140kg weight range is 324 µg/kg for ACTIV-6 vs. 421 µg/kg for FLCCC—**a 23% average drop for the ACTIV-6 implementation from the FLCCC baseline**. If I use the weight IQR information offered in the ACTIV-6 paper—with some generous assumptions—I can bring the relative drop to just under 20%.

As if that wasn't enough, the ACTIV-6 trial explicitly instructed patients to take ivermectin on an empty stomach, whereas FLCCC instructs them to take it with or after a meal. According to Merck's package insert for stromectol, “Administration of 30 mg ivermectin following a high-fat meal resulted in an approximate 2.5-fold increase in bioavailability relative to administration of 30 mg ivermectin in the fasted state.” In other words, FLCCC's weight-adjusted dose is boosted to the equivalent of 843µg/kg, **making the ACTIV-6 effective dose 60% lower than the FLCCC effective dose**. Let's keep in mind that we're still comparing two protocols that both nominally administer 400µg/kg.

And somehow, it gets worse. Much of the risk of deterioration is within the overweight patients. What's more, the higher the weight, the more severe the underdosing. So just calculating the amount of underdosing doesn't reflect the degree to which the results would have been affected. I've been trying to quantify this compounding of risk, but the precise version of this work will have to wait for another article. **I expect the risk-adjusted dosing of ACTIV-6 might look like 70-80% lower than the dose the FLCCC recommended.**

Let’s go back to the original tweet:

> David Boulware, MD MPH @boulware_dr
> @richardemoe @GidMK @EdoajoEric Also, so you are aware, I consulted on the IVM dosing with a prominent FLCCC member when ACTIV-6 was designed. They thought the dosing was "totally reasonable." Subsequently in Oct 2021, (after the TogetherTrial results were available), FLCCC have changed their dosing rec.
>
> 2:22 PM · Jun 14, 2022

We can now see that:

The question Dr. Boulware asked did not match the trial that was executed.

Even if it did, the response is deceptively summarized.

Even if it wasn't, the dosing implemented is very different from what FLCCC recommended at the time.

Further, the claim that the protocol was updated in October 2021 is false. The first version mentioning an even higher dose was in August 2021.

Did The Patients Even Take The Medicine?

Can it get worse than that? Well, of course it can! Dr. Boulware said the following to me on Twitter:

> David Boulware, MD MPH @boulware_dr
> @alexandrosM @AviBittMD @JoshuaG19367959 And this is designing a platform trial in Feb 2021, not knowing what the future may hold. But knowing the history that HCQ became politicized, with then people be unwilling to enroll into clinical trials (as people strongly believed hcq worked or absolutely did not work).

While the author admits the fear of politicization, the paper does not deign to inform us how many patients actually took the drugs they were given. Is it hard to believe that patients may have had reluctance about taking the "horse dewormer paste" drug? Especially when the FDA is putting out Tweets[4] ~~like this fine specimen of messaging?~~

The only other major US clinical trial on ivermectin that ran during a similar time period reported that only 85% of the patients took more than 70% of the doses they were offered.

This means that beyond the underdosing and late treatment issues, the trial may also have had an adherence issue. We're simply not told. If the ACTIV-6 authors had an approach to resolving this issue, it would be good to hear about it—which they can document by telling us how many patients adhered to the trial dosing. In addition, clinical trials tend to offer a "per-protocol" analysis, which focuses the results on the patients that did, in fact, take the drug as instructed. Neither COVID-OUT nor ACTIV-6 have offered such analyses.

Dr. David Boulware is an investigator on both.

To Sum It All Up

By underdosing the most at-risk patients, treating patients late, and not telling us how many patients even took the medication, the authors create substantial room for doubt. This is a trial in which other drugs—like Paxlovid—would almost certainly have failed. Separately, the attempt to offload bad decisions to the FLCCC reeks of dishonesty and

[4] At this point, the author shows a tweet of the horse-wormer add. I deleted that tweet because it is really old news.

is not something that should be acceptable within the scientific community. And that's before we bring the blatant conflicts of interest that members of the ACTIV executive committee had in relation to early treatment medicines.

From <https://doyourownresearch.substack.com/p/activ-6-dosing-and-timing-a-fox-in>

The Story Of A Real ACTIV-6 Patient

ALEXANDROS MARINOS

OCT 30, 2022

Introduction

This could only have happened in the era of Twitter: when I posted my previous article on the ACTIV-6 trial on ivermectin, I came in contact with a participant from the ACTIV-6 trial. You heard that right. The contents of this article are coming… straight from the horse's mouth.

The ACTIV-6 patient confirmed much of what we suspected about the trial:

The participant contacted the trial staff within 5 days after symptoms started. They were enrolled in the trial 7 days after initial symptoms. Official "day 1" in the trial was 10 days after symptom onset. The medicine arrived a full 11 days after symptoms started.

The patients were taken at their word that they had a positive test; a self-administered rapid antigen test was sufficient.

Most patients never saw the trial staff, and didn't speak to them on the phone after the first few days.

Patients were asked which drug they preferred to randomize for, opening real questions with regard to the validity of the randomization process.

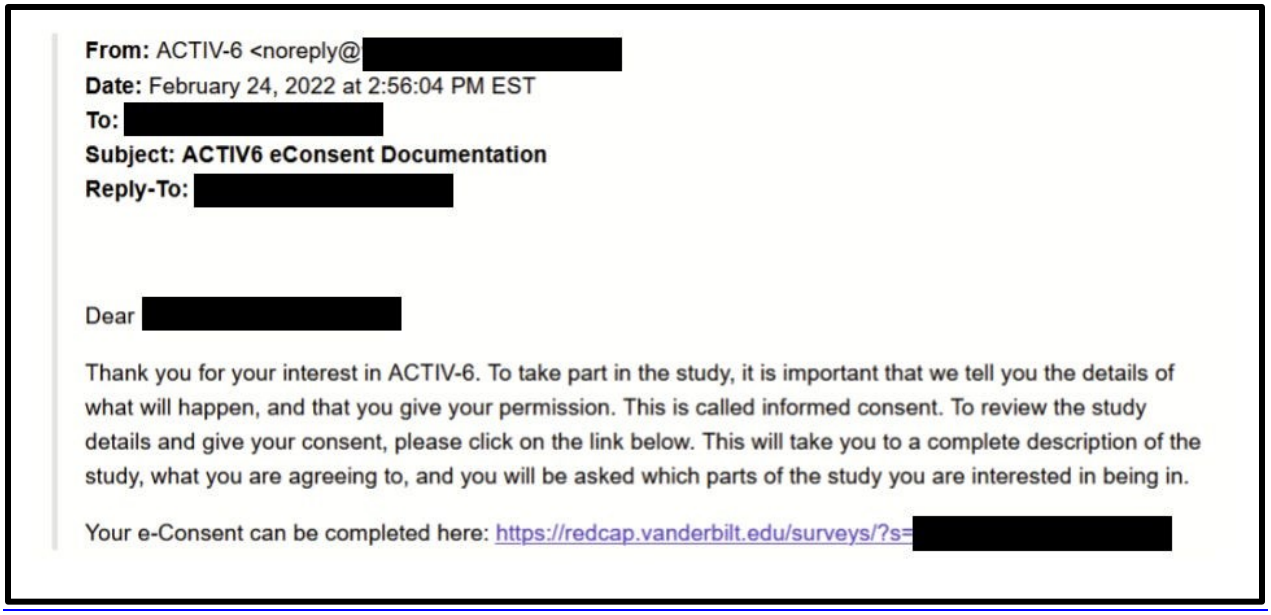
A $100 Amazon gift card was used as inducement to complete all the forms in the trial. (This was not advertised before signing up for the trial.)

The patient in this case participated in the ACTIV-6 600 arm[5]—whose recruitment is completed but results have not yet been published—and is part of the same overall trial as the recently published ACTIV-6 400 study.

I won't reveal the patient's name, as they have requested confidentiality, but they've provided proof that they were, in fact, part of the trial. This photo is of the trial instructions and the medicine bottle they received:

[5] This would be the research study cited by Dr. Simmer in his recommended readings showing IVM is not effective. DGL

They've also shared much of their communication from the trial—including the initial email linking to the consent form:



From: ACTIV-6 <noreply@[redacted]
Date: February 24, 2022 at 2:56:04 PM EST
To: [redacted]
Subject: ACTIV6 eConsent Documentation
Reply-To: [redacted]

Dear [redacted]

Thank you for your interest in ACTIV-6. To take part in the study, it is important that we tell you the details of what will happen, and that you give your permission. This is called informed consent. To review the study details and give your consent, please click on the link below. This will take you to a complete description of the study, what you are agreeing to, and you will be asked which parts of the study you are interested in being in.

Your e-Consent can be completed here: https://redcap.vanderbilt.edu/surveys/?s=[redacted]

Timeline

From the patient's descriptions, I have assembled the following timeline, which they have reviewed and confirmed as correct:

Feb 17, 2022 (Thursday) - Felt tired p.m.

Feb 18, 2022 (Friday) - Woke up feeling fine, by that afternoon had a cough and tickle in throat. (Later defined as first day of symptoms.)

Feb 19, 2022 (Saturday) - Woke up feeling worse than day prior. By dinner was in bed and feverish.

Feb 20, 2022 (Sunday) - Was the worst day. Bed ridden with fever and body aches.

Feb 21. 2022 (Monday) - Took a RAT [*ed: rapid antigen test*] out of curiosity. It indicated positive almost instantly. I think I actually just Googled "Ivermectin COVID-19 trials" when I tested positive.

Feb 22, 2022 (Tuesday) - Nothing.

Feb 23, 2022 (Wednesday) - Signed up online to be contacted. I specified IVM.

Feb 24, 2022 (Thursday) - Received consent documentation. I spoke with the trial people for screening. They asked if I had a preference between IVM and fluvoxamine, I said I preferred IVM. Was enrolled into that after answering some questions about basic health and any other medications I may be taking. Incidentally lost sense of smell on same day, but fever and aches were gone. Cough was improving.

Feb 25, 2022 (Friday) - Got enrollment questionnaire.

Feb 26, 2022 (Saturday) - Nothing.

Feb 27, 2022 (Sunday) - Nothing.

Feb 28, 2022 (Monday) - First daily check-in. Medicine filled & shipped.

Mar 1, 2022 (Tuesday) - Meds arrived. Daily check-in.

Mar 13, 2022 (Sunday) - Last daily check-in.

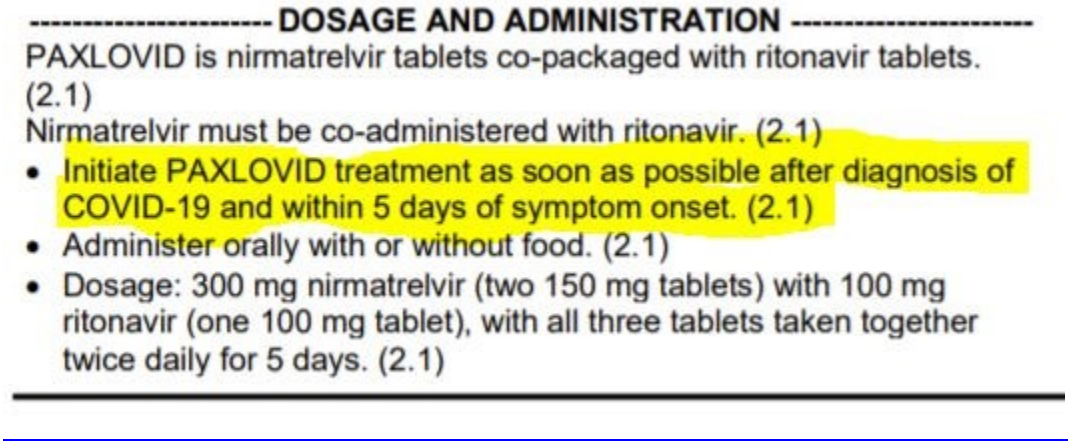
Mar 28, 2022 (Monday) - Last weekly check-in.

May 29, 2022 (Sunday) - Last long-term check-in.

Analysis

Timing

The patient first reached out to the trial on the 23rd of February. It took a whole six days to get the medication to them. It is well known and understood that antivirals must be given early in the course of treatment. For instance, this is what the package insert for Paxlovid says:



---------- DOSAGE AND ADMINISTRATION ----------

PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets. (2.1)

Nirmatrelvir must be co-administered with ritonavir. (2.1)

- Initiate PAXLOVID treatment as soon as possible after diagnosis of COVID-19 and within 5 days of symptom onset. (2.1)
- Administer orally with or without food. (2.1)
- Dosage: 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet), with all three tablets taken together twice daily for 5 days. (2.1)

We already know that 75% of the patients in the ACTIV-6 400 trial would not have qualified for the Paxlovid trial—given that they entered the trial after more than five days of symptoms.

What we learned from this testimony is that this was entirely avoidable had the organizers completed all the various enrollment steps within one day and made sure to have had staff working over the weekend, which I assume is the reason there was no progress over the Saturday and Sunday (Feb 26 & 27). The virus does not take days off.

Worse, the medications were shipped on day 1 of being admitted to the trial, meaning the results should be understood to include (at least) one day for shipping *after* day 1 of the trial. (And that's before we even consider possible delivery delays.)

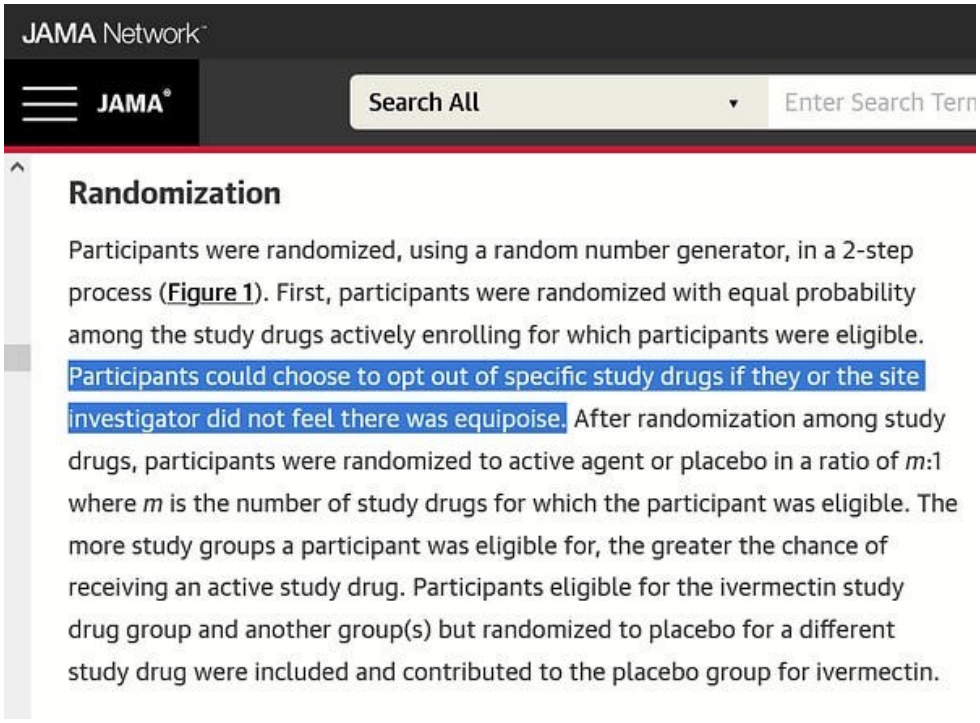
Delivery Issues

The authors report in the ACTIV-6 400 trial report that of the 1800 patients randomized, 209 did not receive their medication and were therefore excluded. Given that we now know these patients were randomized before the medicine was shipped, we should at least be shown their baseline characteristics to see if there was a systematic difference between included and excluded patients. (For instance, it could be that rural patients had more difficulties receiving their medication.) We also don't know if certain areas had more shipment delays. The patient reported that their medication was shipped from Arizona to North Carolina. What are the implications for patients in Hawaii or Alaska, or New York City, where package theft is common?

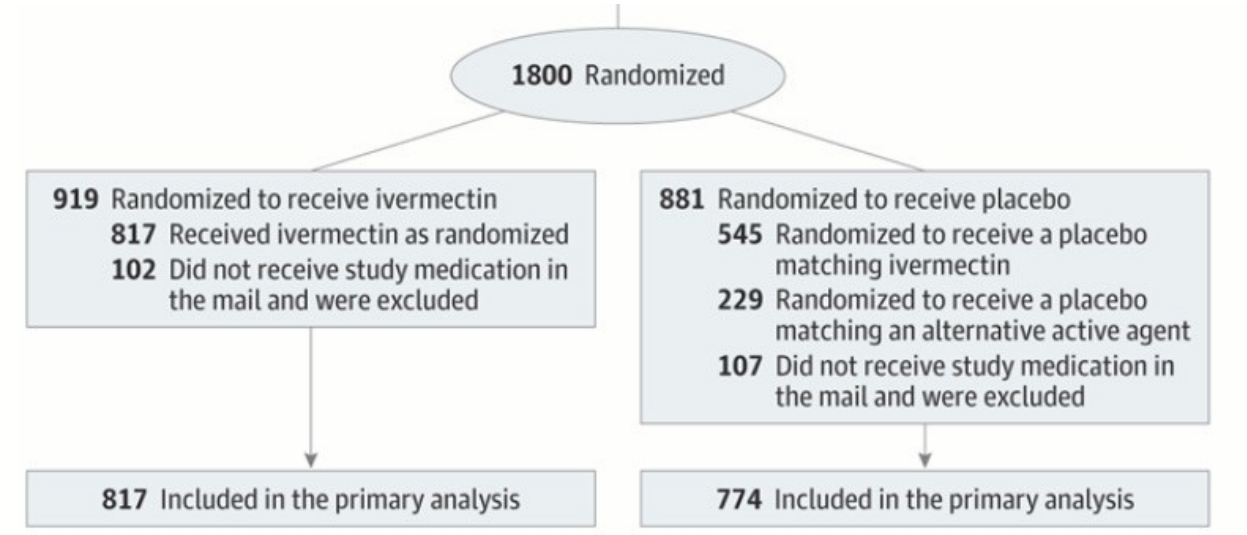
Randomization

When I first read the ACTIV-6 paper, learning that they'd given patients a choice of drug struck me as a surprising feature:

> Alexandros Marinos @alexandrosM
>
> ACTIV-6 ivermectin paper out... looking at the randomization section... WHAT?! Participants could opt out of a drug if they didn't FEEL it works. Or the site investigator could opt them out. "Here's our site menu, what drug would you like to randomize for?" This is not an RCT.



Let me explain what I meant, which this patient's testimony confirms. From the paper, we see that 229 of the 774 placebo patients were randomized to a placebo matching a different active agent:



This means that, besides the various issues related to taking different placebo regimens (e.g. fluticasone is given via an inhaler, not a pill), we have a systematic difference between placebo and treatment populations. If the patient's testimony is typical—and we have no reason to assume otherwise—the 817 treatment patients actively opted into ivermectin. However, when it comes to the placebo patients, it includes patients that either opted out of ivermectin or explicitly opted into another drug.

Ivermectin has been politicized in the US (due in no small part to the messaging coming out of high-profile NIH employees such as Dr. Anthony Fauci). This means we should expect the demographic differences between political groups to be reflected, in part, in the patients who opted in or out of ivermectin. This gives us a legitimate reason to be concerned about the quality of randomization in this trial: the groups are not drawn from identical patient populations.

Potential For Participation Fraud

While the $100 Amazon gift card tried to solve a real problem with patients in remote trials not completing their followup forms, it opens up an issue of participation fraud. Even though the perk was not advertised before signup, consider the following event sequence: Patient X takes part in the study and gets a $100 gift card. Patient X then tells Patient Y that they could sign up for the trial, pretend to be ill, fill in the various forms, and get a $100 gift card at the end. There exist people for whom this scam would be a worthwhile use of time. It would be good to know what—if anything—the trial organizers did to filter out such cases.

Conclusion

I empathize with the complexities of organizing a trial like this. However, the organizers simply cannot represent it as a well-run trial—whose results are informative as to the value of ivermectin and other repurposed drugs—without first understanding the various factors involved.

I have previously used the "FM radio receiver" metaphor to describe how I interpret clinical trial results. If a radio receiver is not precisely set to the right frequency—and the distance from the broadcast antenna is too far—there is all sorts of interference from other nearby radio stations. We can still hear the radio station we want to tune into—faintly—so this cannot be treated as evidence against the station's existence, but the signal cannot be called strong.

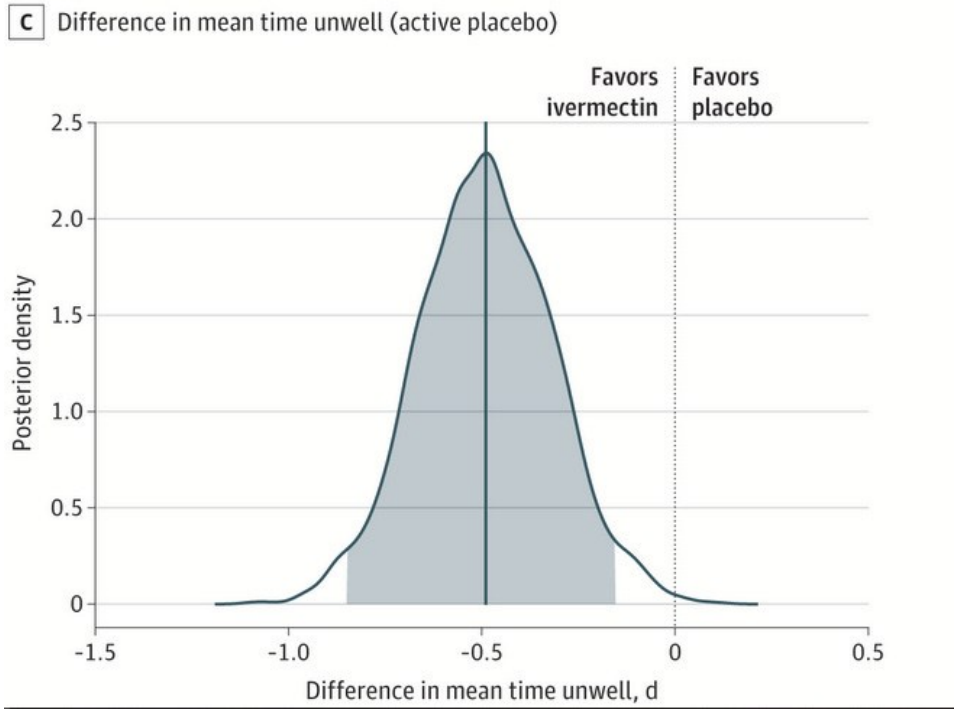
This is what I see in this trial. All sorts of things could have been done better. And yet, ivermectin showed a real signal, with some endpoints even meeting the authors' definition of "significance":

Secondary outcomes - Clinical progression scale

	OR (CrI)[a]	Posterior P(efficacy)
Day 7	0.76 (0.55, 1.00)	0.97
Day 14	0.73 (0.52, 0.98)	0.98
Day 28	0.90 (0.60, 1.21)	0.74

[a]OR<1 favors ivermectin

(source)



(source)

Still, different endpoints were selected to be emphasized. I hope the results of the ACTIV6-600 trial—which are yet to be reported—are approached with a more even hand.

This drug keeps failing to fail, and historians won't have a hard time putting two and two together.

I’d like to thank the source of this story for coming forward and giving us a unique look behind the scenes. This is the kind of information we’ve been missing so far, and these insights help us complete the puzzle of exactly what went on in these trials. If for nothing else, then at the very least for preservation in the historical record.