Effectiveness of early-treatment interventions on self-reported long COVID: A multi-arm, multi-stage adaptive platform control trial

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Abstract

Approximately 20% of people infected with COVID-19 develop at least one persistent condition potentially attributable to their SARS-CoV-2 infection. We sought to determine the effectiveness of early COVID-19 treatment interventions on long COVID symptoms. We conducted a multi-arm multi-stage adaptive platform trial at 12 public health clinics in Brazil between June 2020 and July 2022. Participants were followed for 60. Patients received one of six interventions (doxazosin, fluvoxamine, fluvoxamine in combination with inhaled budesonide, interferon-lambda, ivermectin, or metformin) or matching placebo. The primary outcome was persistence of COVID-19 symptoms at 60 days after randomization. We analyzed data from 5,700 participants across study cohorts. Overall, approximately 22% of patients reported at least one ongoing symptom 60 days after randomization, regardless of the early treatment they received. At day 60, we did not find any statistical benefit of any intervention on recovery, cure fractions, or PROMIS scores (mental and physical).

Introduction

Since its emergence in 2019, over 530 million cases of SARS-CoV-2 (COVID-19) have been reported around the world, resulting in over 6 million reported deaths and widespread morbidity.[1] While outcomes vary widely among people infected with COVID-19,[2] even individuals that report relatively mild cases can experience debilitating symptoms in the longer-term in the form of “long COVID”, broadly defined as symptoms that persist for more than 28 days following initial SARS-CoV-2 infection.[3,4] Over 50 different symptoms have been associated with long COVID, most prominently including fatigue, headache, chest pain, and memory loss,[5–7] as well as more severe outcomes such as long-term tissue damage and disability.[7] Long COVID has been documented among patients of all ages and levels of disease severity.[7] In addition to the physical consequences associated with long COVID, patients report severe disruptions in their ability to work, concentrate, and perform daily tasks, resulting in substantial reductions in their reported quality of life. Recent estimates suggest that approximately 20% of people infected with COVID-19 go on to develop at least one persistent condition potentially attributable to their infection,[4] but prevalence estimates vary widely between studies due to conflicting definitions and methods of recording cases.[8] Rates of long COVID appear to be higher among females[7,9], older adults,[10] and those who experience more than five symptoms within the first week of infection.[7,10]

Despite the substantial number of patients who experience persistent symptoms, long COVID remains poorly understood, and no clear definition or test has yet been developed. In addition, there a major lack of research into cases of long COVID,[7,11] a gap that is increasingly concerning as symptoms persist. Greater understanding of potential risk factors and the possibility of increased long-term harm due to emergent variants could improve treatment and rehabilitation planning for those at greatest risk.[12] Some have postulated that early treatment interventions may prevent long COVID.[11] While several studies have been conducted that have evaluated the effectiveness of a variety of potential therapeutics in terms of their ability to alleviate acute symptoms of COVID-19, the majority have focused on early treatment of relatively mild cases, and none have indicated that therapeutic benefit that reduces the incidence of long COVID. In order to address this gap, we analyzed data from participants in the TOGETHER Trial, a multi-arm multi-stage adaptive platform randomized control trial among a cohort of COVID-19 outpatients in Brazil. Using patient data collected at Day 60 post-randomization from each of six treatment arms and a placebo group, we sought to determine whether any of these interventions used in early treatment of COVID-19 could prevent symptoms associated with long COVID.

Results

Participants

Across the six treatment and placebo arms, a total of 5,700 patients were included in our analysis. Of these, 3,290 were female (57.7%) and the majority were under the age of 50 (51.7%, median 49 years). The largest proportion of participants (96.8%) reported being of mixed-race ethnicity. Participant demographics can be found in Table 1 and the relative size of treatment arms are presented in Fig. 1.

Table 1
Participant Demographics

	Doxazosin (N = 123)	Fluvoxamine (N = 740)	Fluvoxamine-Budesonide (N = 743)	Interferon lambda (N = 916)	Ivermectin (N = 755)	Metformin (N = 217)	Placebo (N = 2206)	Total (N = 5700)
Sex n (%)								
Female	55 (44.7)	408 (55.1)	448 (60.3)	523 (57.1)	431 (57.1)	121 (55.8)	1304 (59.1)	**3290 (57.7)**
Male	68 (55.3)	332 (44.9)	294 (39.6)	393 (42.9)	324 (42.9)	96 (44.2)	901 (40.8)	**2408 (42.2)**
Race n (%)								
Mixed Race	120 (97.6)	724 (97.8)	713 (96.0)	875 (95.5)	737 (97.6)	210 (96.8)	2139 (97.0)	**5518 (96.8)**
White	2 (1.6)	4 (0.5)	15 (2.0)	22 (2.4)	11 (1.5)	4 (1.8)	40 (1.8)	**98 (1.7)**
Black or African American	-	6 (0.8)	13 (1.7)	17 (1.9)	6 (0.8)	1 (0.5)	19 (0.9)	**62 (1.1)**
Unknown	-	6 (0.8)	1 (0.1)	-	1 (0.1)	2 (0.9)	7 (0.3)	**17 (0.3)**
Other	1 (0)	-	-	2 (0.1)	-	-	-	**3 (0.0)**
Age n (%)								
≤50	70 (56.9)	355 (48.0%)	322 (43.3%)	576 (62.9%)	365 (48.3%)	82 (37.8%)	1176 (53.3%)	**2946 (51.7%)**
>50	53 (43.1%)	385 (52.0%)	417 (56.1%)	340 (37.1%)	390 (51.7%)	135 (62.2%)	1029 (46.6%)	**2749 (48.2%)**
Median [Min, Max]	47 [18, 75]	50 [18, 96]	51 [18, 102]	43 [18, 92]	50 [18, 95]	52 [18, 89]	47 [18, 102]	**49 [18, 102]**
Cardiovascular Disease n (%)								
Yes	1 (0.8)	20 (2.7)	29 (3.9)	19 (2.1)	16 (2.1)	9 (4.1)	63 (2.9)	**157 (2.8)**
Hypertension n (%)	41 (33.3)	304 (41.1)	333 (44.8)	259 (28.3)	323 (42.8)	103 (47.5)	819 (37.1)	**2182 (38.3)**
Lung Disease n (%)	3 (2.4)	19 (2.6)	12 (1.6)	25 (2.7)	17 (2.3)	2 (0.9)	59 (2.7)	**137 (2.4)**
Asthma n (%)	14 (11.4)	44 (5.9)	87 (11.7)	91 (9.9)	58 (7.7)	20 (9.2)	217 (9.8)	**531 (9.3)**
Type 1 Diabetes n (%)	1 (0.8%)	17 (2.3%)	14 (1.9%)	10 (1.1%)	4 (0.5%)	4 (1.8%)	34 (1.5%)	**84 (1.5%)**
Type 2 Diabetes n (%)	12 (9.8%)	82 (11.1%)	130 (17.5%)	87 (9.5%)	92 (12.2%)	34 (15.7%)	280 (12.7%)	**717 (12.6%)**

* Fewer than 1% of patients reported auto-immune diseases, HIV infection, neoplasm, chronic kidney disease, neurological disease, dementia, or malnutrition .In the interest of patient confidentiality, randomization assignments for these domains are not presented in the table above.

	Doxazosin (N = 123)	Fluvoxamine (N = 740)	Fluvoxamine-Budesonide (N = 743)	Interferon lambda (N = 916)	Ivermectin (N = 755)	Metformin (N = 217)	Placebo (N = 2206)	Total (N = 5700)
Obesity n (%)	50 (40.7%)	373 (50.4%)	277 (37.3%)	322 (35.2%)	373 (49.4%)	95 (43.8%)	921 (41.7%)	**2411 (42.3%)**
Cancer n (%)	4 (3.3%)	10 (1.4%)	16 (2.2%)	13 (1.4%)	10 (1.3%)	3 (1.4%)	39 (1.8%)	**95 (1.7%)**
Day 28 Data								
Day 60 Data								

* Fewer than 1% of patients reported auto-immune diseases, HIV infection, neoplasm, chronic kidney disease, neurological disease, dementia, or malnutrition .In the interest of patient confidentiality, randomization assignments for these domains are not presented in the table above.

PROMIS Survey

Of 5,693 patients who completed the PROMIS questionnaire at baseline, data were available at Day 28 for 5,485 patients, of whom 119 received doxazosin, 706 received fluvoxamine, 703 received fluvoxamine in combination with budesonide, 905 received interferon-lambda, 719 received ivermectin, and 208 received metformin. The remaining 2,125 patients received a placebo. The most commonly reported persistent symptoms were in the domain of Physical Health. By Day 28, 2,461 (45%) patients reported that their Physical Health remained poor or fair.

At Day 60, data were available for 5,359 patients, of whom 2,206 (41%) continued to report poor or fair Physical Health, indicating no important improvement from Day 28 in terms of overall rates of persistent physical symptoms. Pain also remained a major concern among participants. At Day 28, 463 participants (8%) reported pain at a level of 5 or worse. By Day 60, this had declined to 324 patients (6%).

In the physical domain, all treatments showed similar trends. The average increase in physical score was approximately 3.4 points, with no significant differences between treatment arms or compared to placebo. Similarly, the mental score saw average changes ranging from 2.2 to 2.7. Only doxazosin showed a significant reduction in symptoms relative to placebo ($p = 0.026$). The change from baseline to Day 60 for the mean composite Physical and Mental Health scores are summarized in Fig. 2 and parameter estimates are provided in **eTable 1**.

Self-Reported Recovery

A total of 3,398 participants completed the self-reported recovery assessment. By Day 28, the majority of participants across all groups (n = 2,718, 80%) reported that they had recovered from COVID-19. The largest proportion of patients who reported being recovered at Day 28 were in the Fluvoxamine-Budesonide group, with 87% of patients (n = 616) reporting recovery. By contrast, only 71% of patients who received fluvoxamine alone (n = 48) reported having recovered by Day 28.

At Day 60, 90% of participants across all groups (n = 2966) reported that they had recovered from COVID-19. The largest group of unrecovered patients was in the ivermectin group, with 15% (n = 12) reporting that they had not yet recovered. Self-reported lack of recovery by treatment group is presented in Fig. 3.

Using cure distribution models (Table 2), the proportion of un-recovered patients was consistently between 10% and 15%, with the exception of fluvoxamine-budesonide, which had a rate of 4% un-recovered. In no case did a treatment show a significant effect over matched concurrent placebo. Survival curves illustrating time to self-reported recovery by treatment arm are presented in Fig. 4.

Discussion

Across the treatment and control arms of our randomized controlled trial of patients with COVID-19, results from the PROMIS scale indicated that 22% of patients at high risk of progression to severe disease continued to experience symptoms in at least one domain 60 days after initial symptom onset. This is aligned with recent CDC estimates that report a similar rate of persistent symptoms among people previously infected with COVID-19.[4] This proportion was also consistent across treatment groups, reflecting the cohorts' uniformity due to the randomized trial design and bolstering the reliability of this rate.

Our study evaluated whether any of the six interventions evaluated in the TOGETHER Trial would prevent long COVID symptoms 60 days after randomization. The six interventions were chosen because of their hypothesized or purported roles for the prevention of severe COVID-19 when used early in the infection period (0–7 days after symptom onset). Of the six included interventions, three have indicated a beneficial role in the early treatment of COVID-19 that was not observed in long COVID (fluvoxamine, fluvoxamine plus inhaled budesonide, and peginterferon lambda).[13] This finding diminishes the expectation that early-treatment interventions may prevent long-COVID and suggests that the mechanism of disease onset differs between early disease symptoms and long COVID symptoms.[14] Interventions that may have a role for long COVID are likely to target other aspects of the disease than the initial viral infection period and initial immune responses.

Notably, our findings did not indicate any statistically significant differences between treatment groups in terms of the proportion of patients who went on to develop long COVID. This may be due to the fact that many evaluations of potential COVID-19 therapeutics have focused primarily on antiviral medications. However, long COVID and the mechanisms that underlie it remain poorly understood, and antivirals may be unlikely to prevent symptoms beyond the early stages of infection. Further research into other types of therapeutics is warranted, as the lack of antiviral treatment effect beyond the early stages of infection suggests the mechanisms underlying acute COVID-19 infection and long COVID are different. Specifically, many of the symptoms experienced by those with long COVID (e.g., chronic fatigue, hair loss) may be indicative of potential inflammatory or autoimmune responses.[15] Trials that evaluate anti-inflammatory medications, immune modulators, and other potential therapeutics specifically for long COVID should be conducted in order to elucidate this syndrome's underlying mechanisms. The duration and timing of therapy are also areas requiring investigation.

Conducting trials for interventions in long COVID are challenging as it is not yet known whether preventing initial disease progression has a role in preventing long COVID. A different and more targeted strategy for interventions aimed at long-COVID could be to include patients already reporting long COVID symptoms and randomizing them. This approach is complicated by the lack of clear case definition that would determine inclusion criteria for long COVID, as well as the absence of defined outcomes associated with long COVID that would be necessary determine whether an intervention is exhibiting a treatment effect in this population. For any trial, clear baseline phenotypes need to be defined an responses assessed by phenotype as any therapeutic is unlikely to be universal in effect. Addressing these gaps and funding large-scale platform trials that can follow participants over longer periods of time will be critical to advancing research into long COVID.[11]

The major strength of our analysis is its use of prospective data collected from multiple trial arms of a large platform trial. By drawing on data collected from this cohort, the internal validity of our analyses is enhanced. In addition, this cohort contains only patients with a confirmed diagnosis of COVID-19. Our study also benefits from its large sample size; the TOGETHER Trial is the largest placebo-controlled randomized control trial for the evaluation of COVID-19 outpatient therapeutics that has been conducted.

Major limitations to our study primarily concern its reliance on self-reported data. The PROMIS questionnaire allows patients to report on a variety of symptoms but does not account for underlying health issues among participants or for baseline rates of poor health in the general population. As a result, we cannot definitively conclude that the symptoms patient report after 60 days were directly caused by their previous COVID-19. Finally, given the constantly evolving nature of the COVID-19 pandemic during the study period, it is unclear what impact changing COVID-19 variants may have had on the rates and characteristics of long COVID among our cohort, nor how increased vaccination rates may have impacted the prevalence of long COVID in any of our trial arms.

Our study did not identify any early treatment that had a therapeutic effect on long COVID symptoms. The ongoing lack of understanding, diagnostic tests, and therapeutics for long COVID more than two years after its initial identification demonstrate

that current research and diagnostic approaches into this syndrome are inadequate. The large proportion of patients still suffering from COVID-19 symptoms 28 and 60 days after initial symptom onset illustrate the need for dedicated platform trials into the prevalence and clinical manifestation of long COVID in order to generate high-quality evidence that can help to address long COVID.

Methods

The TOGETHER Trial

The TOGETHER Trial is a randomized, adaptive platform trial designed for the evaluation of repurposed therapeutics for COVID-19 among patients at risk of progressing to severe disease. The trial has been described in detail elsewhere.[13,16] In brief, adult COVID-19 outpatients meeting at least one criterion for high risk of disease progression were randomized and equally allocated to one of several intervention groups or matching placebos. The primary outcome was to evaluate a variety of potential interventions to determine whether they reduced rates of disease progression due to COVID-19 within 28 days of randomization and followed up to 60 days post-randomization.[17] Participants were recruited from 12 primary care and emergency department outpatient clinics in Minas Gerais, Brazil. At baseline, data were collected on demographics, medical history, medications, comorbidities, and exposure to COVID-19. The World Health Organization (WHO) clinical progression scale,[18] the Patient-Reported Outcomes Measurement Information System (PROMIS) Global-10 health scale, both mental and physical,[19,20] were administered. Following randomization, participants were contacted on days 3, 7, 10, 14, 28, and 60. The TOGETHER Trial complies with the International Conference of Harmonization – Good Clinical Practices, as well as local regulatory requirements. It has been approved by local and regional ethics boards in Brazil (CONEP CAAE: 41174620.0.1001.5120, approval letter 5.501.284) and by the Hamilton Integrated Research Ethics Board in Canada (approval letter 13390). The trial is ongoing and is registered at ClinicalTrials.gov (NCT04727424).

Inclusion Criteria

We included patients aged 18 years or older, presenting to an outpatient facility with symptoms consistent with COVID-19 within 7 days of symptom onset. In order to be considered at high-risk for progression to severe COVID-19, participants had to meet at least one of: age > 50 years, diabetes mellitus, hypertension with medication use, cardiovascular disease, lung disease, smoking, obesity (i.e., body mass index > 30 kg/m^2), organ transplantation, chronic kidney disease (stage IV) or receipt of dialysis, immunosuppressive therapy (receipt of ≥ 10 mg of prednisone or equivalent daily), a diagnosis of cancer within the previous 6 months, or current chemotherapy for cancer. Those vaccinated for COVID-19 were eligible for inclusion after July 2021.

Randomization and Blinding

Sample size was calculated at 681 participants per treatment arm, with a power of 80% to demonstrate a statistical significance ratio of 0.8. Patients were equally allocated to a treatment arm or placebo using an automated web-based randomization system that used a pre-generated randomization list using blocks of 10. Patients and the research team were blinded to treatment randomization information. The biostatistician conducting the analysis was non-blinded. Treatments were concealed in hermetically sealed containers.

Interventions

For the purposes of this report, results are analyzed from six interventions for the early treatment of COVID-19:

- Doxazosin – 2mg tablets administered once per day for 10 days
- Fluvoxamine – 100mg tablets administered twice daily for 10 days
- Fluvoxamine-Budesonide – 100mg tables plus inhaled budesonide 800ug twice daily for 10 days
- Interferon-lambda – Subcutaneous injection of 180μg peginterferon lambda (0.45ml) single dose
- Ivermectin – 400 μg per kilogram of body weight once daily for 3 days
- Metformin – 750mg extended-release tablets administered twice daily for 10 days

- Placebo – placebos were matched to each active intervention

Data Collection

The US National Research Action Plan on Long COVID broadly defines long COVID as signs, symptoms, and conditions that continue or develop after initial COVID-19 or SARS-CoV-2 infection, as follows: 1) Are present 4 weeks or more after the initial phase of infection; 2) May be multisystemic; 3) May present with a relapsing-remitting pattern and progression or worsening over time, with the possibility of severe and life-threatening events even months or years after infection. The plan emphasizes that long COVID is not one single condition and represents various symptoms and possible pathologies with different biological risks, causes and outcomes.

Patient-Reported Outcomes Measurement Information System (PROMIS)

Patient-reported quality of life data were collected using the Patient-Reported Outcomes Measurement Information System (PROMIS) Global-10 Health Scale.[19] This survey captures data on physical and mental health symptoms, as well as health-related quality of life. Participants completed the survey prior to any other evaluations to avoid biasing their answers. The PROMIS scale was administered at baseline and on days 14, 28, and 60.

The PROMIS Global-10 short form consists of 10 items that assess general domains of health and functioning, including overall physical health, mental health, social health, pain, fatigue, and overall perceived quality of life. Responses for all domains except “pain” were scored on a scale from 1–5, with 1 representing “Poor” health and 5 representing “Excellent” health. Pain was scored on a scaled from 0–10, with 0 representing no pain and 10 representing “worst imaginable pain.”

Self-Reported Recovery

Patients provided self-reported assessment of recovery at Day 28 and Day 60, classified as either “Recovered” or “Not Recovered”.

Statistical Analysis

Data were collected between June 2020 and July 2022 from patients who were assigned to any of the six treatment arms or corresponding placebo group. Kaplan-Meier estimates of time to recovery were produced, and mixture cure models were fit to each of the active treatment arms and their concurrent placebos. Mixture cure models are survival models that can more accurately model survival curves that feature distinct plateaus after some time point.[21,22] These models are commonly used in studies where a treatment can lead to complete remission in a patient, which then leads to a certain proportion of the patient population never experiencing the endpoint (i.e., the “cure fraction”). We drew upon cure models for our analysis because the presence of long COVID indicates that there is a distinct plateau in our survival curve: patients who never experience the endpoint of recovery. Thus, in our analysis, the term “cure fraction” describes the fraction of patients in our cohorts who did not recover after their initial infection.

Cure fraction models were fit to the time of recovery data, assuming an underlying Weibull distribution and a term for treatment. The Weibull parameters characterize the underlying distribution, the treatment term gives the acceleration factor for treatment relative to placebo, and the cure fraction identifies the proportion of patients who do not recover. Our cure model is defined as $S(t) = \pi + (1 - \pi)S_u(t)$, where $S(t)$ is the observed survival function of the entire cohort, π is the proportion of patients who did not recover (the statistical “cure fraction”), and $S_u(t)$ is the survival function of the recovered patients. Mixture cure models were implemented with the R package flexsurvcure v1.3.0.

Descriptive statistics generated displayed the frequency and distribution of PROMIS scores across participants. The summarized PROMIS Scores (global physical health and global mental health) were summations of the values across four domains each. Global physical health included: overall physical health, ability to carry out physical activities, fatigue, and pain. Global mental health included overall mental health, satisfaction with social activities and relationships, ability to carry out social activities, and overall emotional health. A generalized linear model modeled the change in PROMIS score from baseline to day 60 across all treatments.

Declarations

Data Sharing Statement

The first and last authors had full access to all the trial data and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. Deidentified data for the TOGETHER Trial arms are available to investigators upon request and pending a review process at Vivli (https://search.vivli.org). The study protocol and statistical analysis plan are available in the supplementary materials.

Contribution Statement

Dieter Ayers, Edward Mills, and Gilmar Reis had full access to all of the data and take responsibility for the integrity of the data and the accuracy of the analysis. All authors have read and approved this manuscript.

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Declaration of Interests

The authors confirm they have no conflicts of interest to declare.

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Tables

Table 2 is not available with this version

Figures

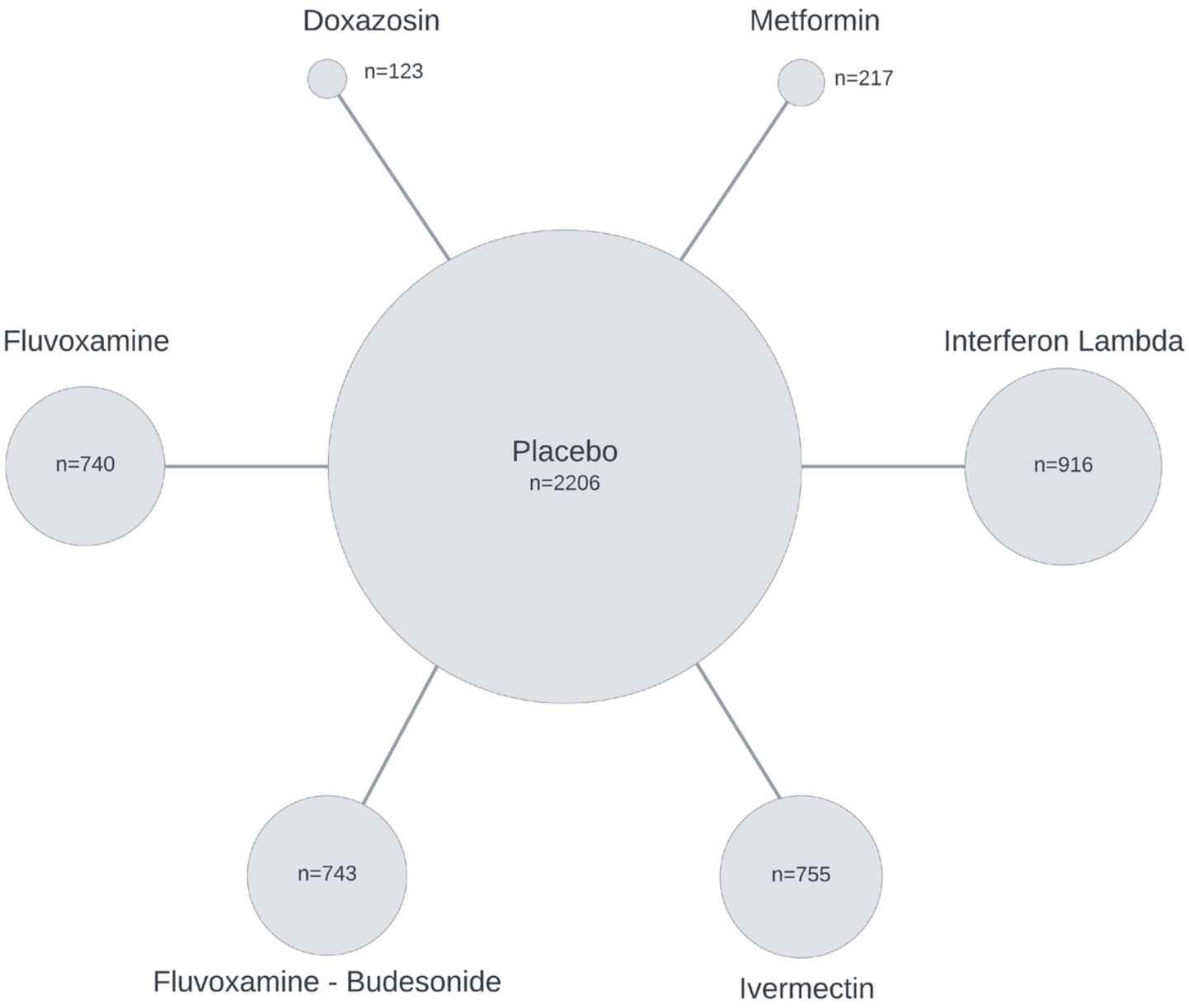

Figure 1

Participant allocation to treatment and placebo arms

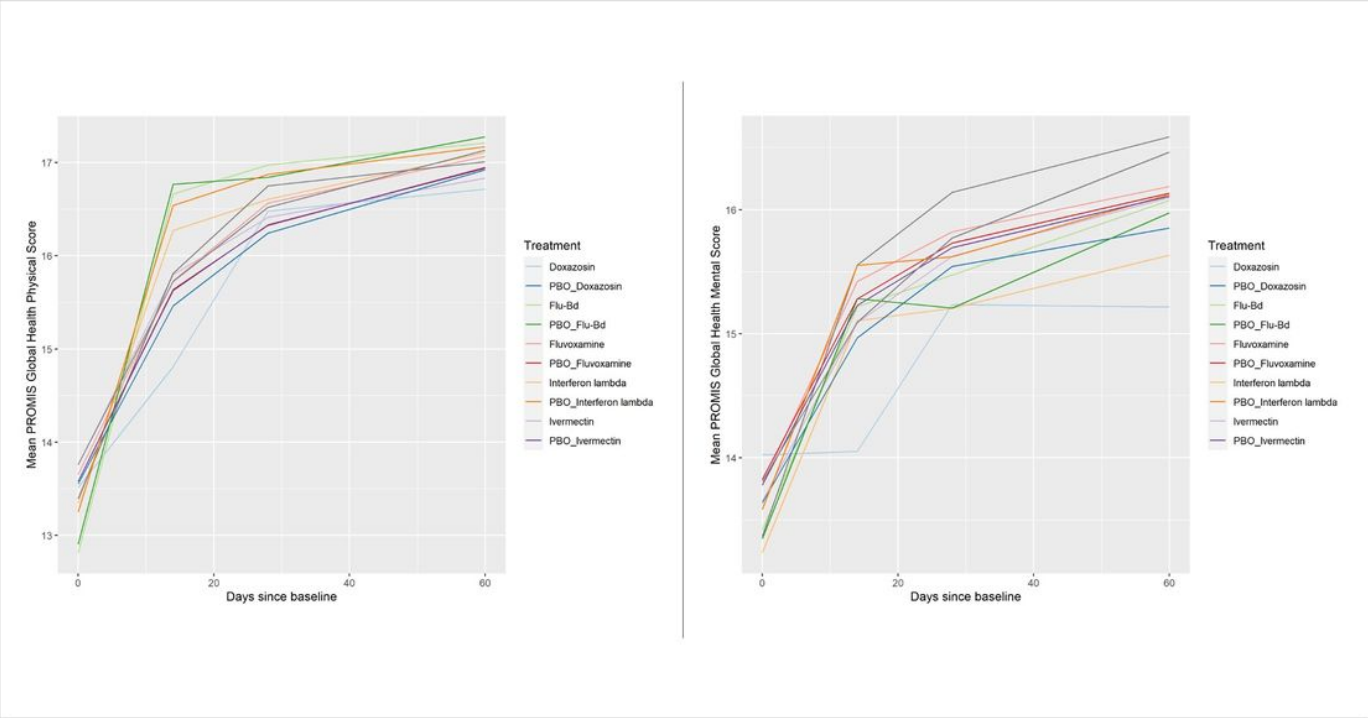

Figure 2

Change in mean composite physical and mental health score over time by treatment arm

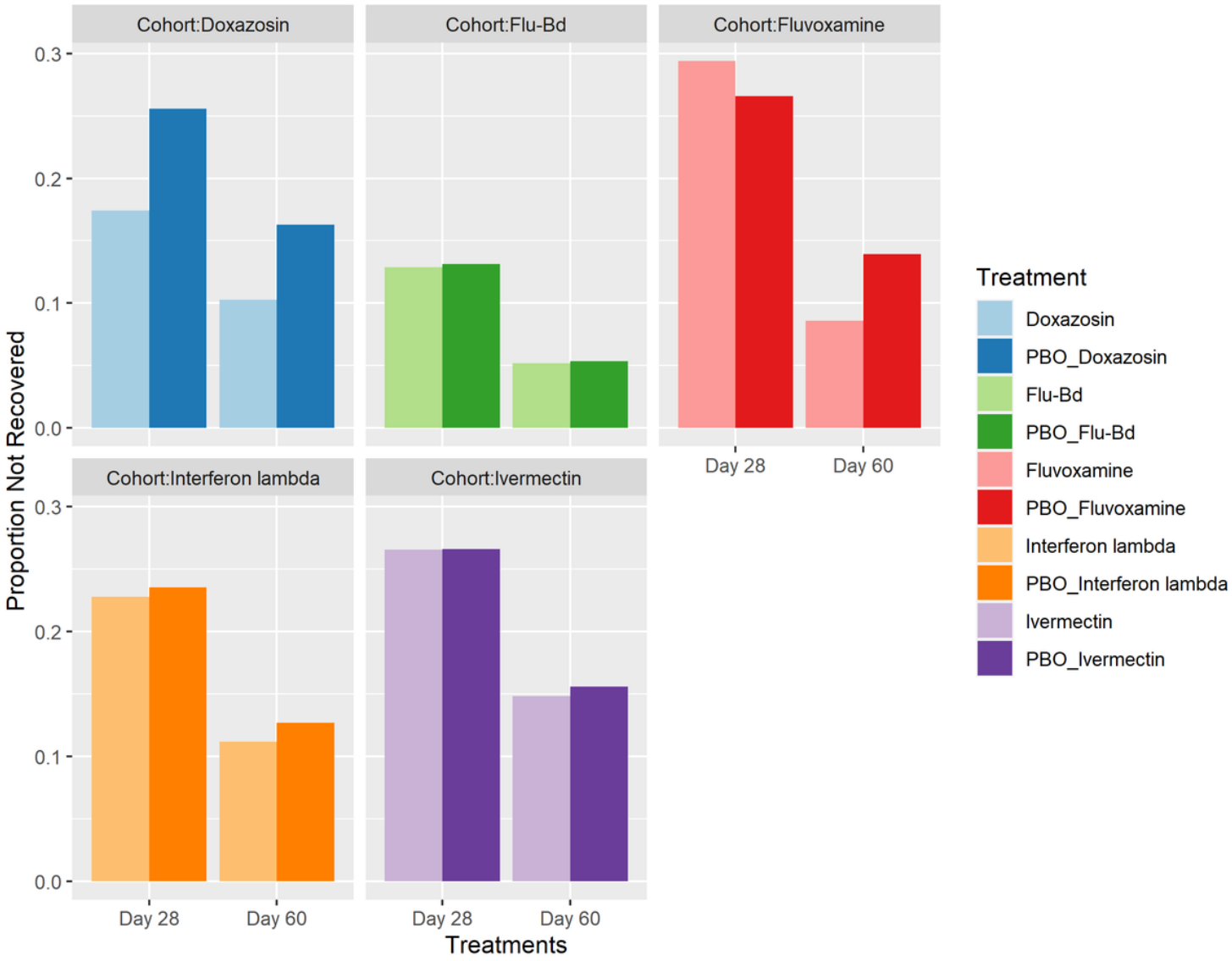

Figure 3

Proportion of Patients not Recovered at Day 28 and Day 60

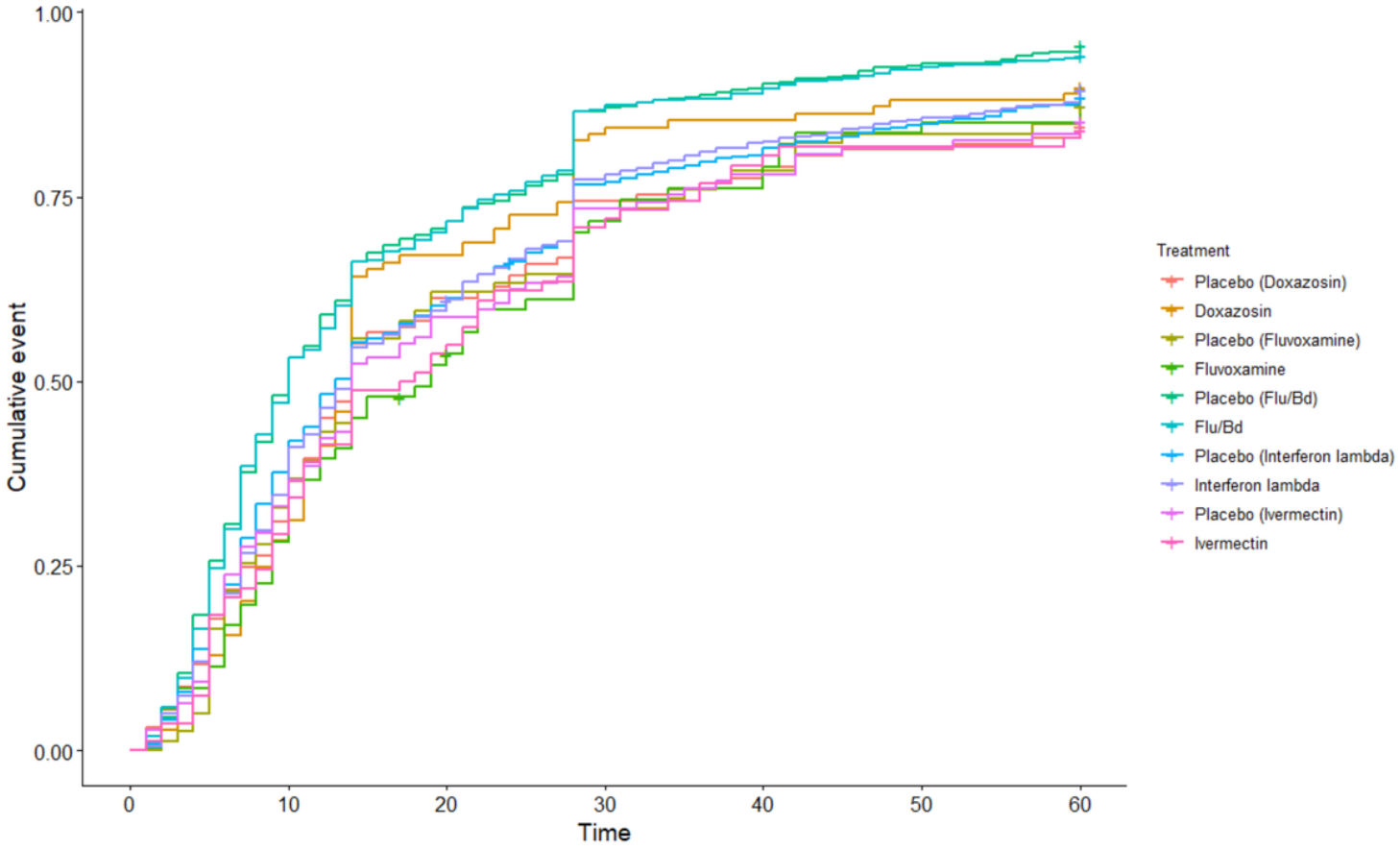

Figure 4

Time to self-reported symptom-free recovery by intervention

Supplementary Files

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