COVID-OUT Trial: Phase III Trial of Outpatient Treatment for Covid-19 with Metformin, Ivermectin, and Fluvoxamine

NIH Collaboratory Grand Rounds
July 8, 2022

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Overview

- Overview of current COVID-OUT Trial
- Brief Background
  - 3 distinct treatments
  - Design, Study population
- Statistical Considerations
  - DSMB Reviews and stopping criteria
  - Randomization
- Results
- A few lessons
- Limitations
  - Generalizability
  - Limitations of home oximeters

Disclosures

- Donations:
  - Apotex donated fluvoxamine placebo
  - Edenbridge donated ivermectin and ivermectin placebo

- Funding:
  - The trial was funded by the Parsemus Foundation, Rainwater Charitable Foundation, Fast Grants, and the UnitedHealth Group Foundation.
  - Dr. Bramante funded by National Institutes of Health's National Center for Advancing Translational Sciences, grants KL2TR002492 and UL1TR002494; and the National Institute of Digestive, Diabetes, and Kidney diseases K23 DK124654.

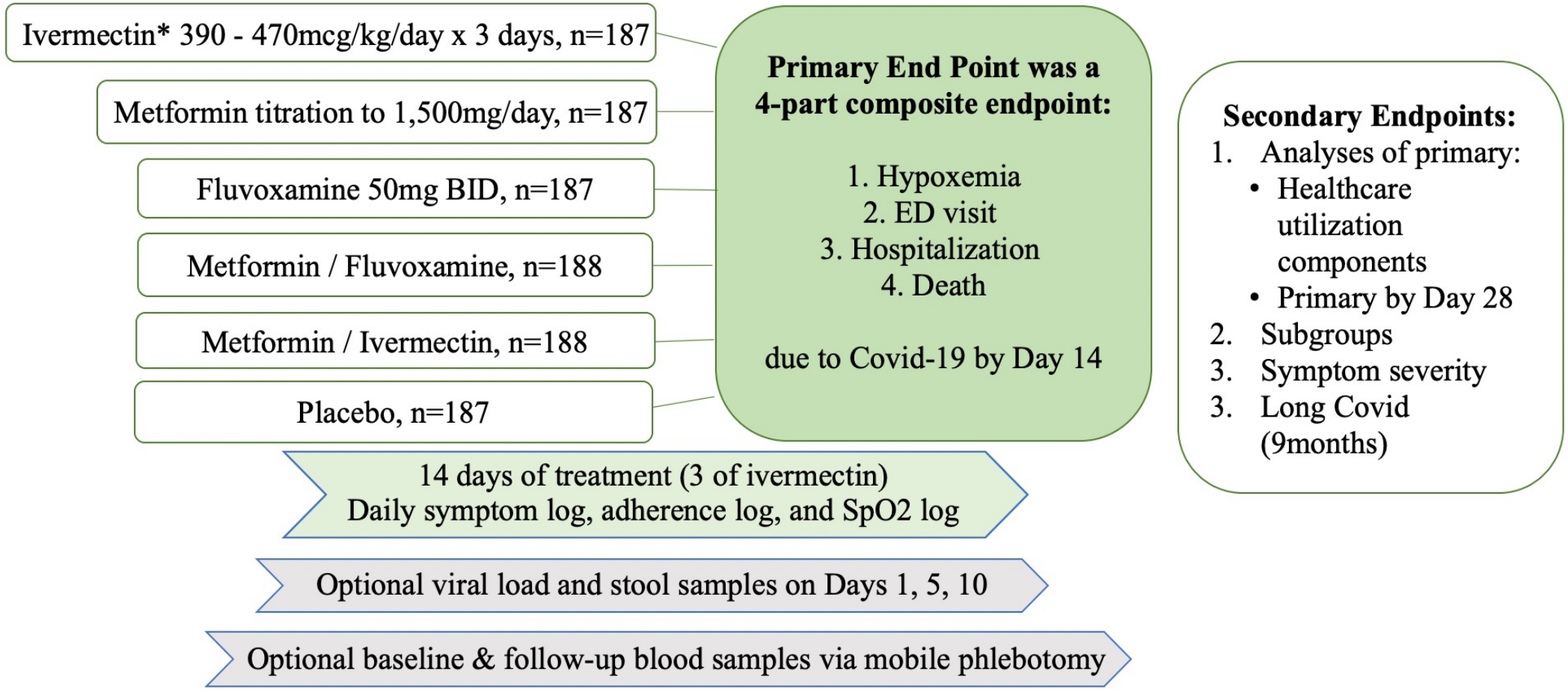
- No financial disclosures

- I will be discussing off-label use of metformin, ivermectin, and fluvoxamine

COVID-OUT Trial Overview

Early outpatient treatment to prevent severe COVID-19

- Remotely delivered, de-centralized trial at 6 participating institutions



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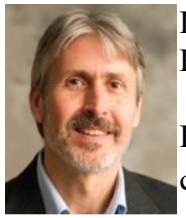
Metformin: started with in silico modeling, NLP identification



David Odde, PhD
Professor of Biomedical Engineering

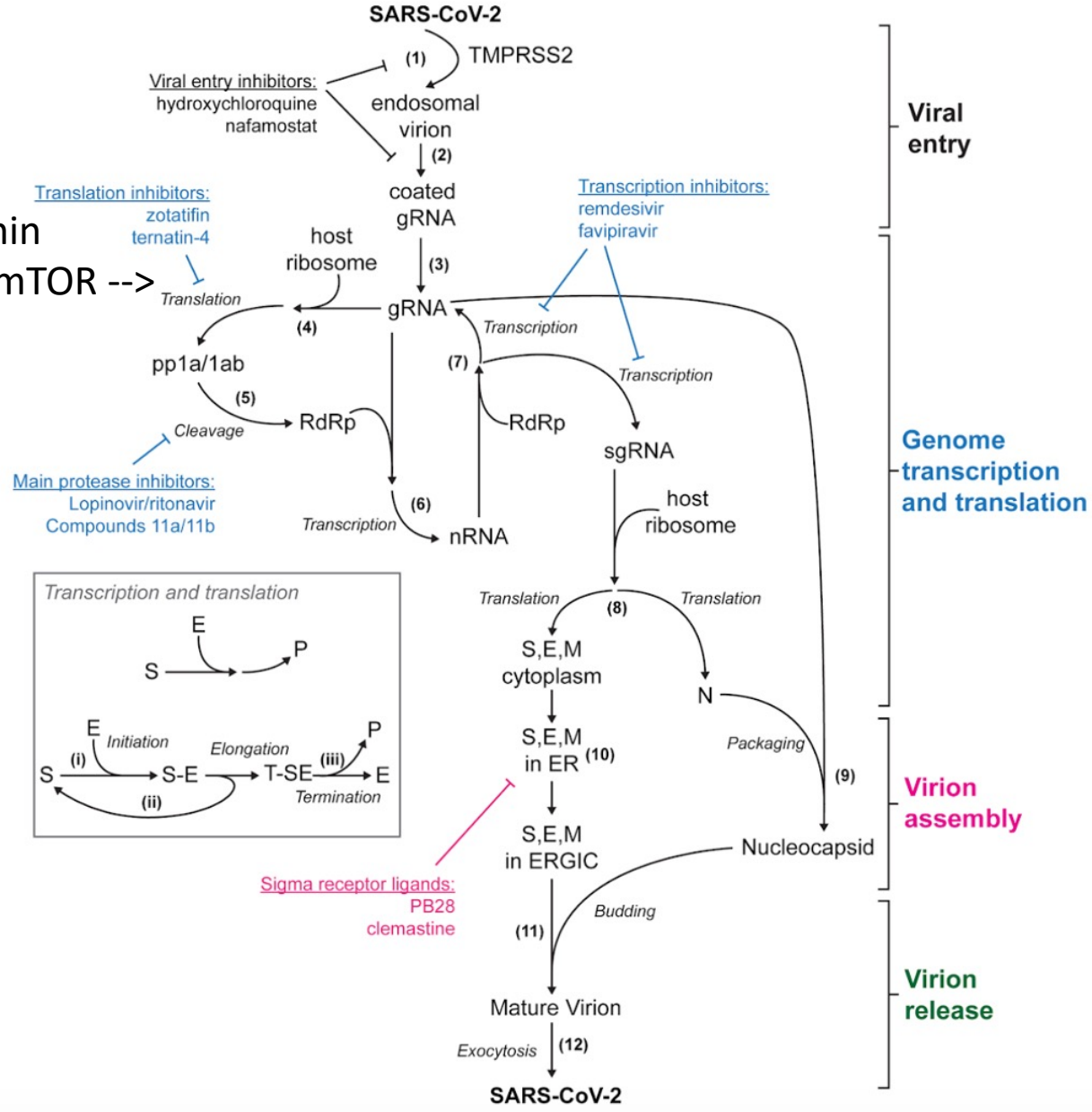
Early 2020 developed simulator on SARS-CoV-2 life cycle

Chris Tignanelli, MD MS
Department of Surgery, UMN

Natural language processing, Covid clinical trials
Learning Health System Scholar

Metformin
Inhibits mTOR -->

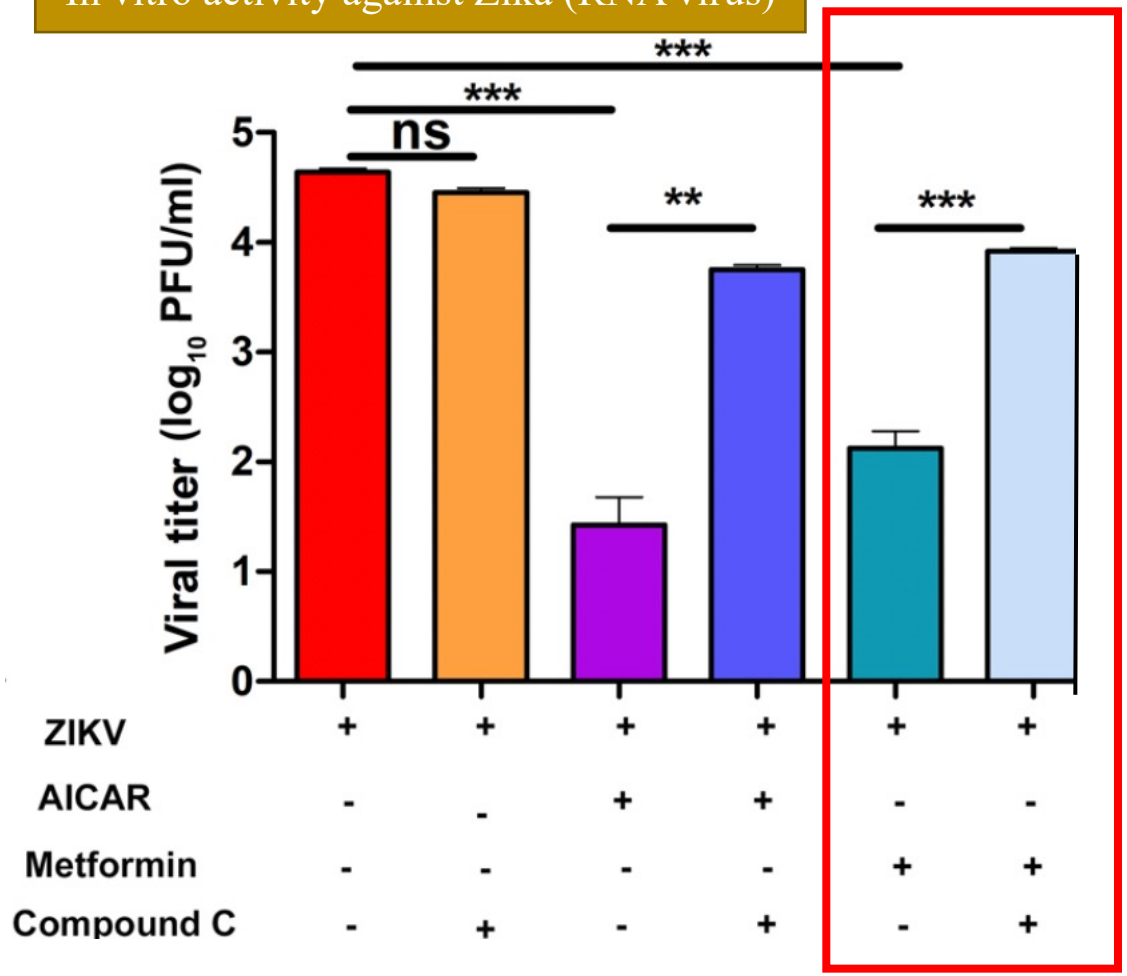
SARS-CoV-2 Antiviral Therapies	Model Prediction	NIH Panel Recommendations	Model Accuracy
Remdesivir	Effective	Recommended	Correct
Paxlovid	Effective	Recommended	Correct
Molnupiravir	Effective	Recommended	Correct
Hydroxychloroquine	Not Effective	Not Recommended	Correct
Chloroquine	Not Effective	Not Recommended	Correct
Lopinavir/Ritonavir	Not Effective	Not Recommended	Correct
Darunavir/Cobicistat	Not Effective	Not Recommended	Correct
Not addressed by our model: Interferons, Ivermectin, and Azithromycin			
Excluded due to unclear mechanism of action: Nitazoxanide			



Metformin: a history of potential antiviral properties

- Discovered in 1922
- 1950s, studied in influenza
  - associated with reduced incidence of H3N2 influenza (5.4 vs 24%, p<0.001)
  - Other biguanides had safety issues
- 1990s FDA approved for diabetes
- 2000s, growing interest in anti-cancer
- 2010 Interest as anti-infectious agent
  - Zika, hep C (autophagy, mTOR inhibition)
    - Was not prospectively assessed in Zika
- Current RCT's include: TB, dengue

In vitro activity against Zika (RNA virus)



1. Garcia EY (1950) Flumamine, J Philippine Med Assoc 26:287–293
2. Bailey C. Metformin: historical overview. Diabetologia (2017)
3. Boominathan L, Combinatorial Antiviral Therapy (CAT): Metformin, the widely used drug in the treatment of TIIDM, inhibits Hepatitis-B/C, Dengue, Zika, Ebola, HIV-1, 2017
4. Fan Cheng, et ai. *Journal of Virology* Jan 2018,
5. Yu J-W, Sun L-J, Zhao Y-H, Kang P, Yan B-Z. The effect of metformin on the efficacy of antiviral therapy in patients with genotype 1 chronic hepatitis C and insulin resistance. *Int J of Infec Dis.* 2012;16(6):e436-e441.
7. Singh S, et al. AMP-Activated Protein Kinase Restricts Zika Virus Replication in *The Journal of Immunology.* 2020
8. Babinski, 1971

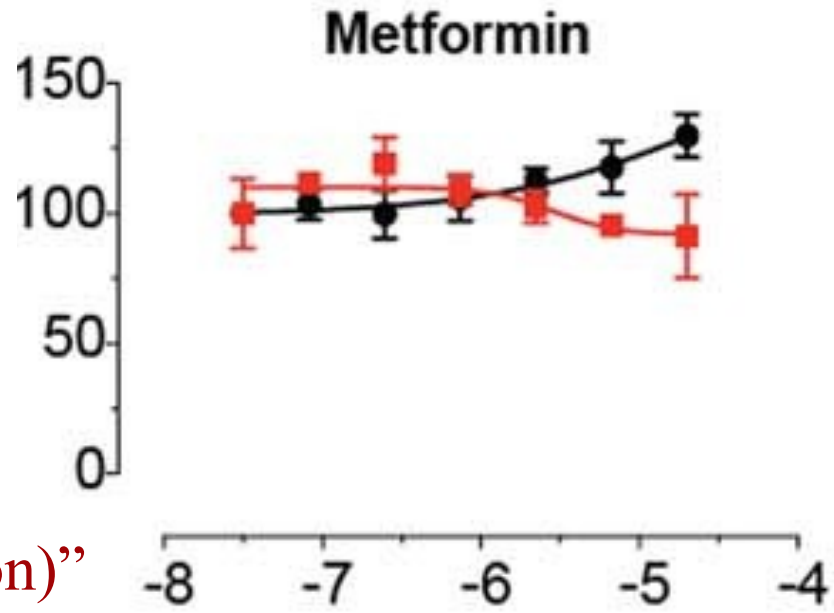
In-vitro activity against SARS-CoV-2

Article | Published: 30 April 2020

A SARS-CoV-2 protein interaction map reveals targets for drug repurposing

David E. Gordon, Gwendolyn M. Jang, ... Nevan J. Krogan + Show authors

Nature **583**, 459–468 (2020) | Cite this article



The Red line shows: "Decreased viral growth (percentage infection)"

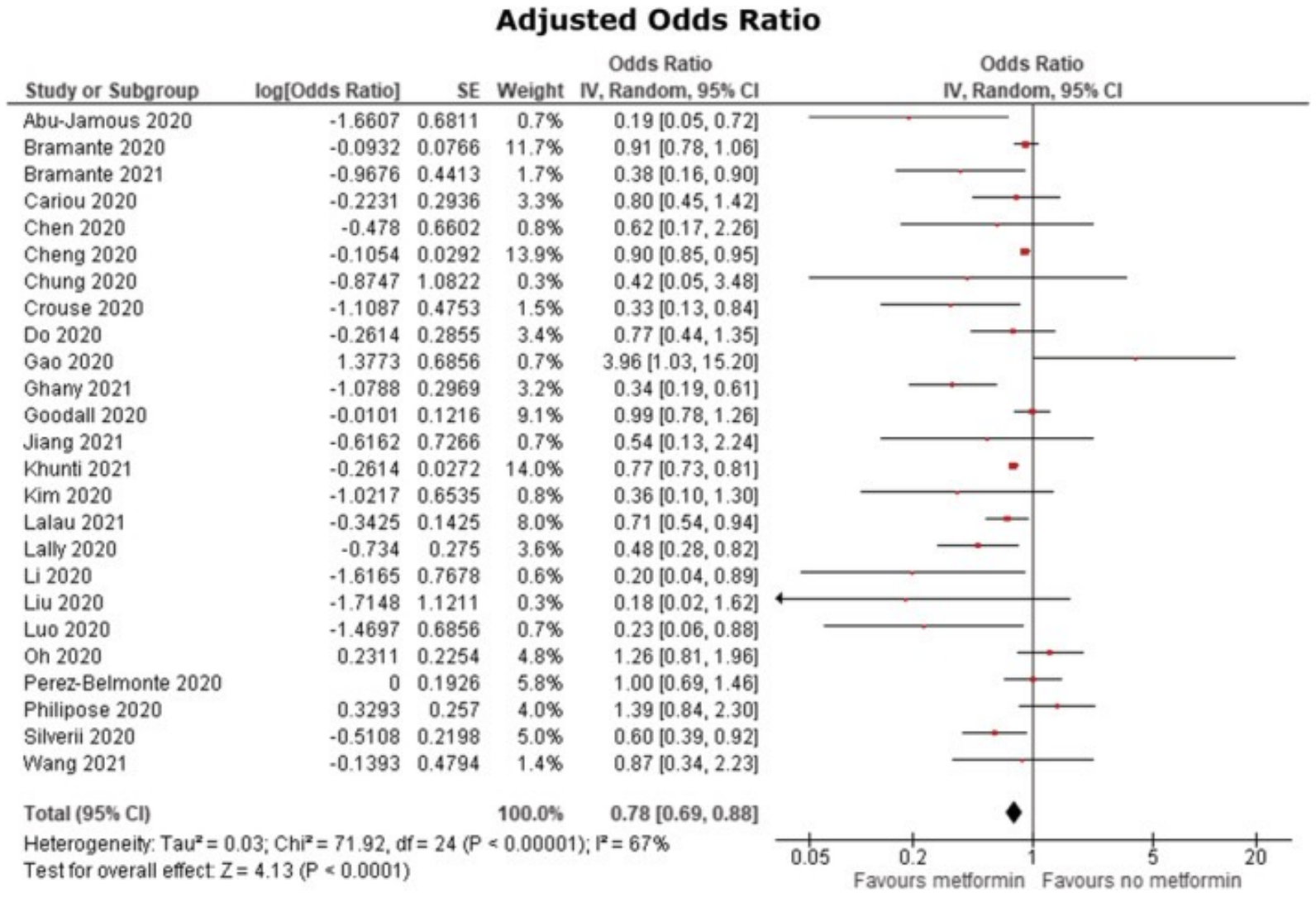
The Black line shows: "Decreased cytotoxicity, increased cell viability"

Extended Data Fig. 8: Viral growth and cytotoxicity for compounds tested in New York.

Observational analyses; potentially lower inflammation in Covid-19

Observational data in patients with Covid-19 showing favorable lab results

Chen et al. *Diabetes Care,* 2020	Cohort of adults with Type 2 DM	Metformin users had lower IL-6: 4.07 vs 11.1, p=0.02



Forest Plot: Heterogeneity: Tau = 0.03; Chi2 = 71.92, df=24 (p<0.00001); I2=67%
Test for overall effect: z=4.13 (p<0.0001)

Metformin is safe, inexpensive, and widely available

- <$4/month, available in probably all pharmacies
- Providers are familiar with prescribing it
- Few drug interactions
- Few contra-indications
- Safe in children and pregnancy
- No follow-up monitoring needed (for 12 months or more)
- Well tolerated in most people, especially at <2,000mg/day

So a clinical trial seemed warranted

(1) Alqudah A, McKinley MC, McNally R, et al. *Diabet Med*. 2018
(2) Kalafat E, Sukur YE, Abdi A, Thilaganathan B, Khalil A. *Ultrasound Obstet Gynecol*.

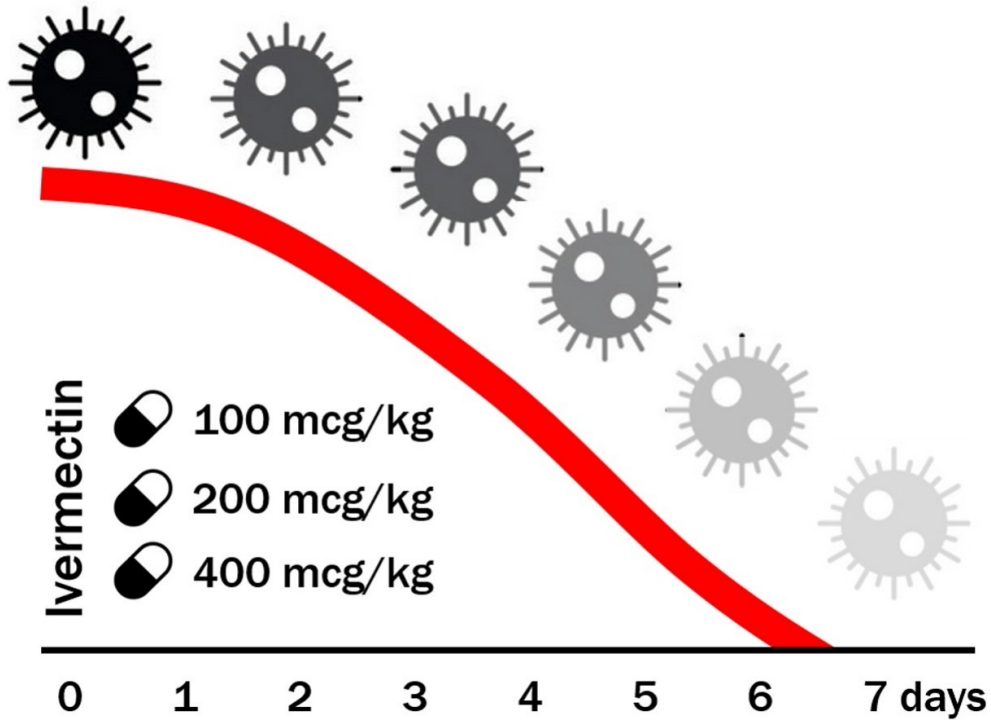
Initial Ivermectin data

Initial data suggested anti-viral activity of ivermectin, at high doses.

Combination treatment that included ivermectin suggested prevention of hospitalization.

A small double-blinded RCT suggested significant increased chance of viral clearance after a 5-day course of ivermectin.

Safe, orally administered, few contraindications, widely available.



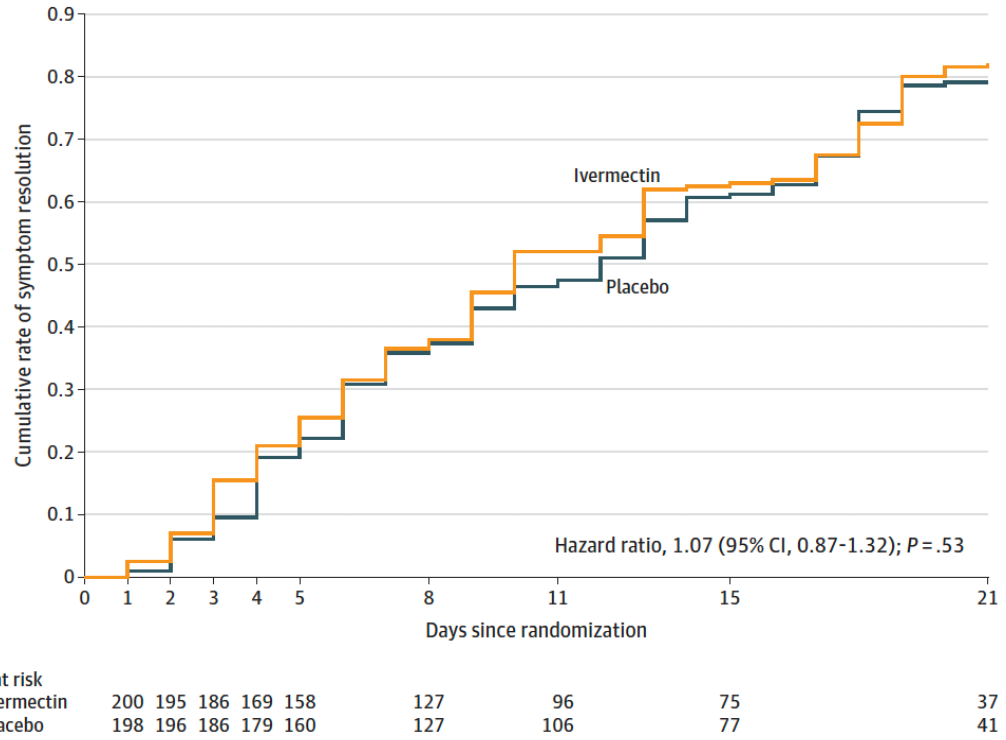
-Portmann-Baracco A, Bryce-Alberti M, Accinelli RA. Antiviral and Anti-Inflammatory Properties of Ivermectin and Its Potential Use in COVID-19. *Arch Bronconeumol.* 2020;56(12):831.
-Lima-Morales R, Méndez-Hernández P, Flores YN, et al. Effectiveness of a multidrug therapy consisting of ivermectin, azithromycin, montelukast and acetylsalicylic acid to prevent hospitalization and death among ambulatory COVID-19 cases in Tlaxcala, Mexico. *International Journal of Infectious Diseases.* 2021.
-Ahmed S, Karim MM, Ross AG, et al. A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. *International Journal of Infectious Diseases.* 2021;103:214-216.

Ivermectin initial data

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline and Medications Initiated Since Symptom Onset in the Primary Analysis Population

Characteristic	No. (%) Ivermectin (n = 200)	Placebo (n = 198)
Age, median (IQR), y	37 (29-47.7)	37 (28.7-49.2)
Age groups, y		
<40	119 (59.5)	112 (56.6)
40-64	73 (36.5)	70 (35.3)
≥65	8 (4.0)	16 (8.1)
Sex		
Male	78 (39)	89 (44.9)
Female	122 (61)	109 (55)
Race or ethnic group[a]		
Mixed race	178 (89)	179 (90.4)
Black or African American	16 (8.0)	16 (8.1)
Colombian native	6 (3.0)	3 (1.5)
Health insurance		
Private/semiprivate	177 (88.5)	174 (87.9)
Government subsidized	20 (10.0)	23 (11.6)
Uninsured	3 (1.5)	1 (0.5)
No. of persons in the same household, median (IQR)	4 (3-5)	3 (3-4)
Current smoker	3 (1.5)	8 (4.0)
BMI, median (IQR)	26.1 (23.1-28.8)	26.4 (22.7-29.0)

Figure 2. Time to Resolution of Symptoms in the Primary Analysis Population



The cumulative rate of symptom resolution is the percentage of patients who experienced their first day free of symptoms. All patients were followed up for 21 days.

300mcg/kg/day for 5 days

Lopez-Medina E, Lopez P, Hurtado IC, et al. Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19: A Randomized Clinical Trial. *Jama.* 2021.

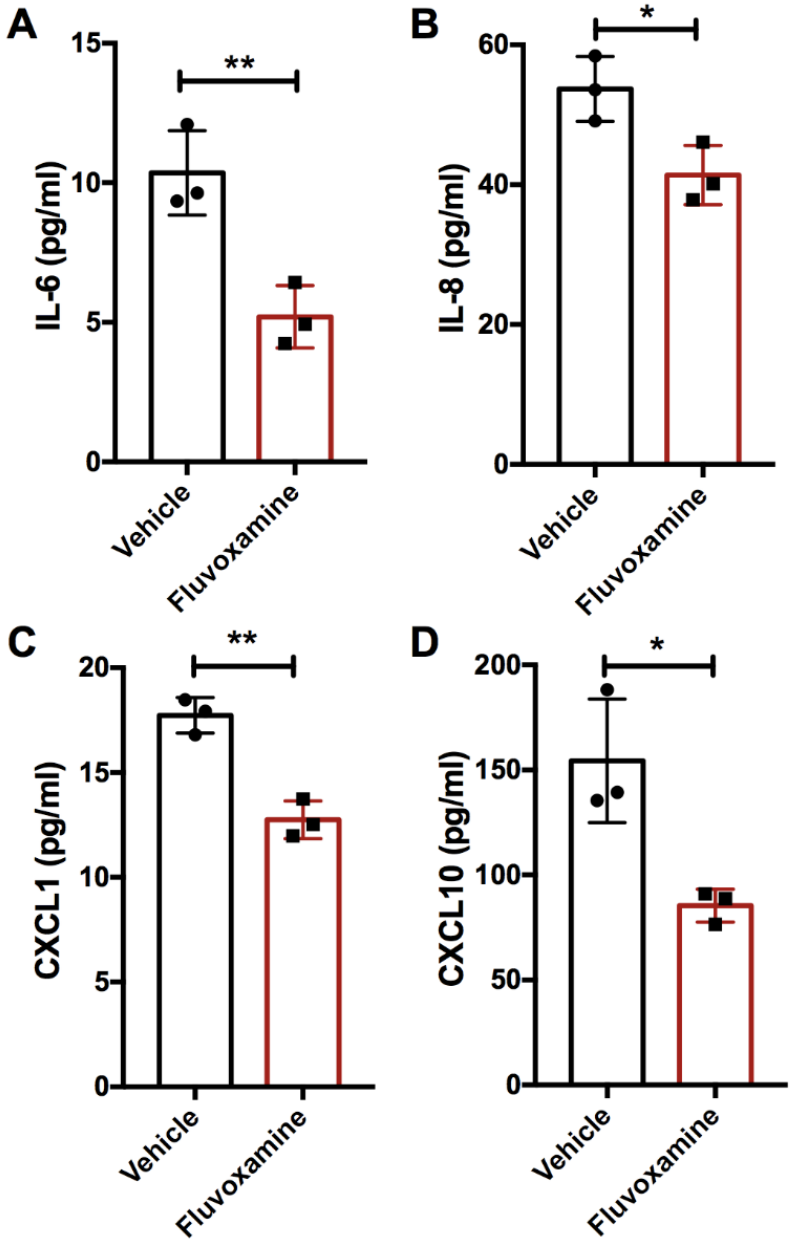
Fluvoxamine: In Vitro Anti-Inflammatory Action

CACO2 cells were infected with SARS-CoV-2 at **MOI of 0.01** in the **presence or absence of fluvoxamine.**

Fluvoxamine was able to block the production of a subset of cytokines/chemokines, including:

IL-6 IL-8 CXCL1 CXCL10

Possible Mechanism:
Activation of S1R with fluvoxamine may overcome Nsp6 inhibition of S1R to allow autophagy to clear SARS-CoV-2.



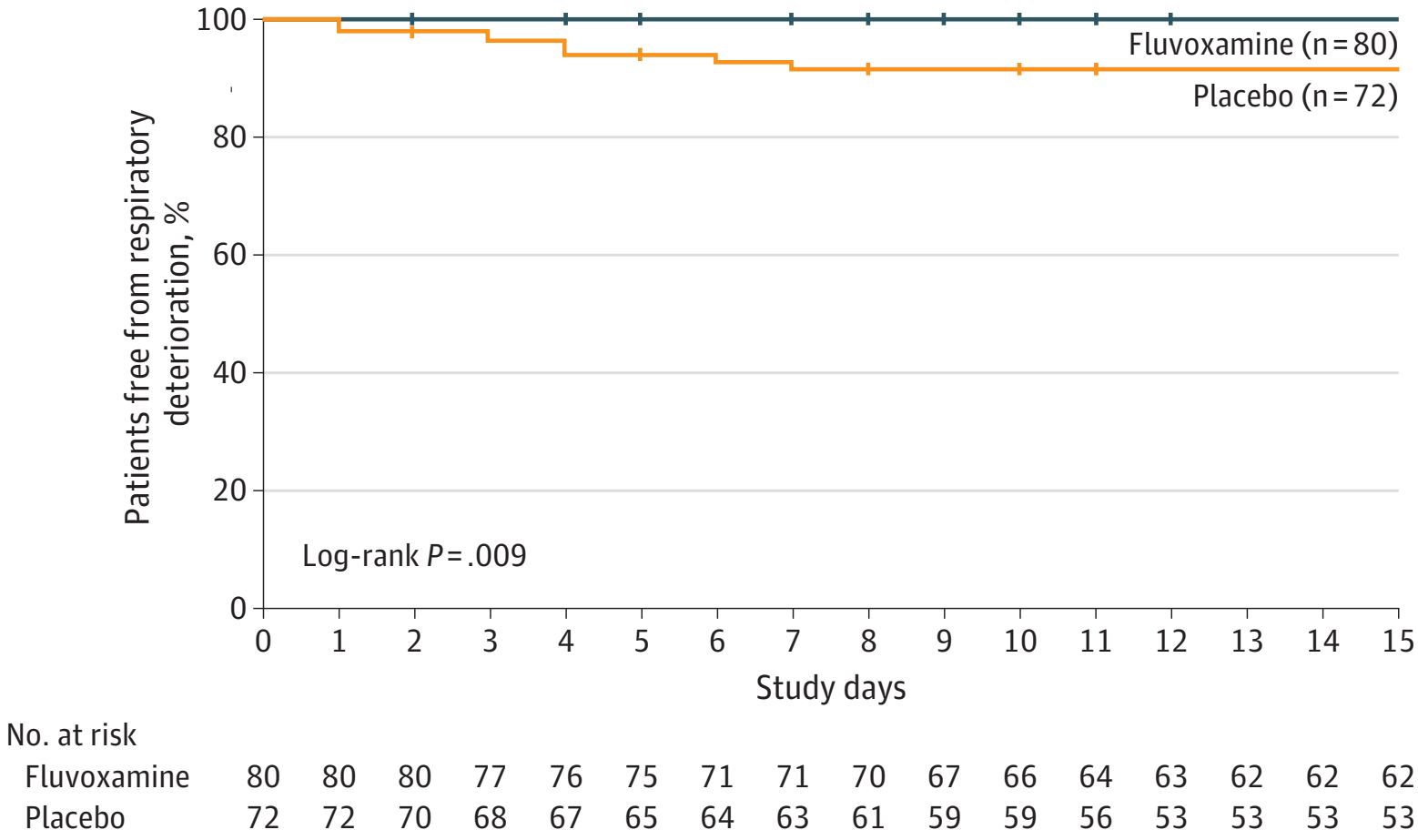
(Alban Gaultier, et al.)
Courtesy of Angela Reiersen, MD

Fluvoxamine RCT: 100mg TID prevented severe disease

Table 3. Adverse Events

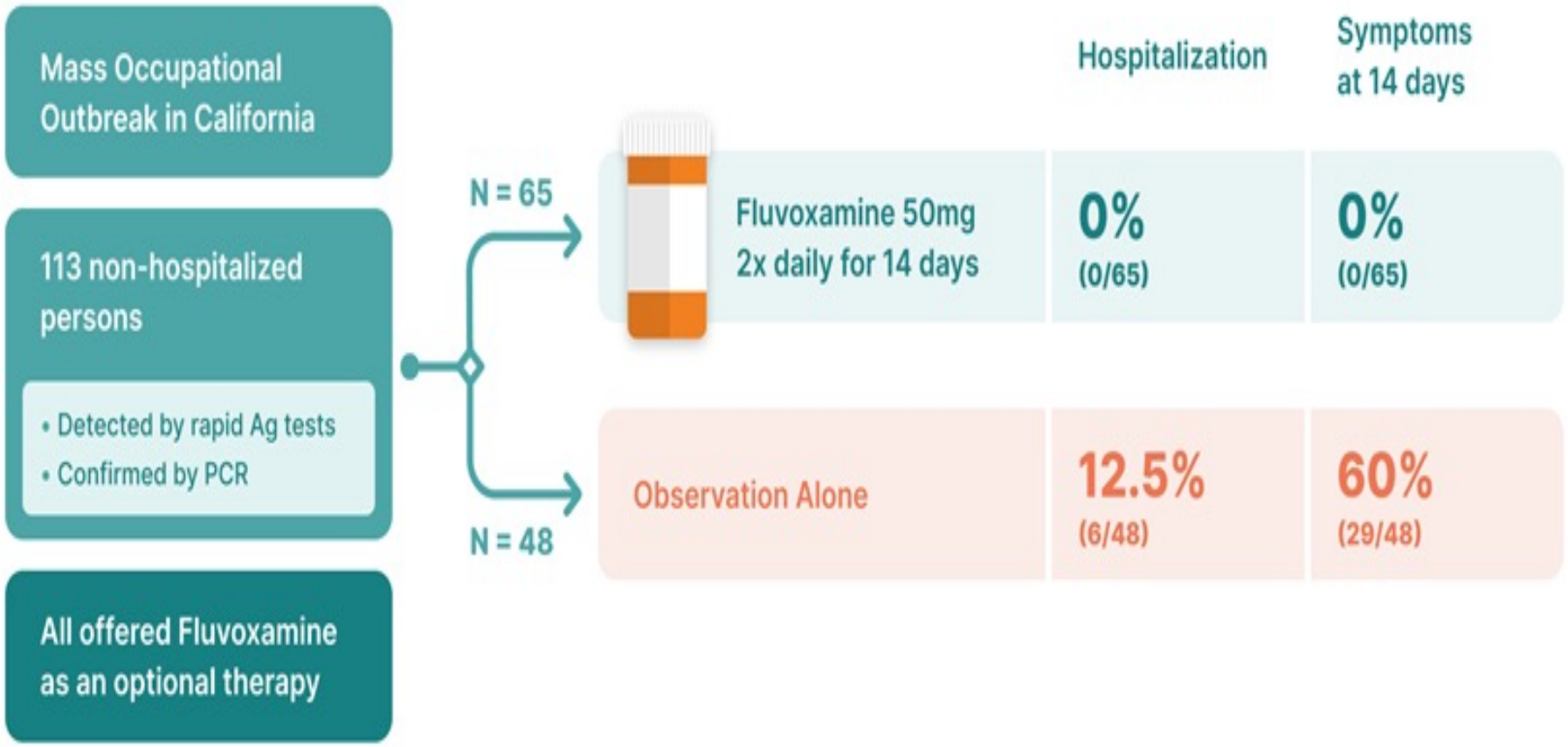
	No. of adverse events (%)[a]	
	Fluvoxamine (n = 80)	Placebo (n = 72)
Pneumonia	3 (3.8)	6 (8.3)
Shortness of breath	2 (2.5)	4 (5.6)
Headache or head pain	2 (2.5)	1 (1.4)
Gastroenteritis, nausea, or vomiting	1 (1.3)	5 (6.9)
Muscle aches	1 (1.3)	0
Bacterial infection	1 (1.3)	0
Vasovagal syncope	1 (1.3)	0
Teeth chattering	1 (1.3)	0
Dehydration	1 (1.3)	0
Low oxygen saturation or hypoxia	0	6 (8.3)
Chest pain or tightness	0	2 (2.8)
Fever	0	2 (2.8)
Acute respiratory failure	0	1 (1.4)
Hypercapnia	0	1 (1.4)
Flank pain	0	1 (1.4)
By No. of patients		
Serious adverse events[b]	1 (1.3)	5 (6.9)
Other adverse events[c]	11 (13.8)	6 (8.3)

Figure 2. Time to Clinical Deterioration in the Fluvoxamine and Placebo Groups



Lenze et al, *JAMA* 2021

Fluvoxamine prospective cohort: 50mg BID may work



100mg TID and BID can cause side effects and drug:drug interactions.

Seftel, Boulware, 2021.

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6-arm parallel group trial

- Ivermectin* 390 - 470mcg/kg/day x 3 days, n=187
- Metformin titration to 1,500mg/day, n=187
- Fluvoxamine 50mg BID, n=187
- Metformin / Fluvoxamine, n=188
- Metformin / Ivermectin, n=188
- Placebo, n=187

Primary End Point was a 4-part composite endpoint:

1. Hypoxemia
2. ED visit
3. Hospitalization
4. Death

due to Covid-19 by Day 14

Secondary Endpoints:

1. Analyses of primary:
   - Healthcare utilization components
   - Primary by Day 28
2. Subgroups
3. Symptom severity
3. Long Covid (9months)

14 days of treatment (3 of ivermectin)
Daily symptom log, adherence log, and SpO2 log

Optional viral load and stool samples on Days 1, 5, 10

Optional baseline & follow-up blood samples via mobile phlebotomy

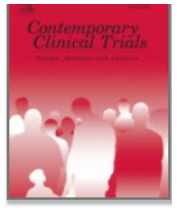
*6 weight categories.
Doses to minimize side effects

No adjustment for parallel treatments in the same trial

ELSEVIER

Contemporary Clinical Trials

Volume 113, February 2022, 106656



Short Communication

Multiplicity adjustments in parallel-group multi-arm trials sharing a control group: Clear guidance is needed

Síle F. Molloy [a] [1] ✉, Ian R. White [b, 1], Andrew J. Nunn [b], Richard Hayes [c], Duolao Wang [d], Thomas S. Harrison [a]

Recommends against adjusting for multiplicity of multiple treatments

CLINICAL TRIALS

Perspective

Non-adjustment for multiple testing in multi-arm trials of distinct treatments: Rationale and justification

Clinical Trials
2020, Vol. 17(5) 562–566

DOI: 10.1177/1740774520941419
journals.sagepub.com/home/ctj
SAGE

No adjustment for parallel treatments in the same trial

Effect of anti-interleukin drugs in patients with COVID-19 and signs of cytokine release syndrome (COV-AID): a factorial, randomised, controlled trial

Jozefien Declercq, Karel F A Van Damme*, Elisabeth De Leeuw*, Bastiaan Maes*, Cedric Bosteels*, Simon J Tavernier, Stefanie De Buyser, Roos Colman, Maya Hites, Gil Verschelden, Tom Fivez, Filip Moerman, Ingel K Demedts, Nicolas Dauby, Nicolas De Schryver, Elke Govaerts, Stefaan J Vandecasteele, Johan Van Laethem, Sebastien Anguille, Jeroen van der Hilst, Benoit Misset, Hans Slabbynck, Xavier Wittebole, Fabienne Liénart, Catherine Legrand, Marc Buyse, Dieter Stevens, Fre Bauters, Leen J M Seys, Helena Aegerter, Ursula Smole, Victor Bosteels, Levi Hoste, Leslie Naesens, Filomeen Haerynck, Linos Vandekerckhove, Pieter Depuydt, Eva van Braeckel, Sylvie Rottey, Isabelle Peene, Catherine Van Der Straeten, Frank Hulstaert, Bart N Lambrecht*

Esomeprazole and aspirin in Barrett's oesophagus (AspECT): a randomised factorial trial

*Janusz A Z Jankowski, John de Caestecker, Sharon B Love, Gavin Reilly, Peter Watson, Scott Sanders, Yeng Ang, Danielle Morris, Pradeep Bhandari, Claire Brooks, Stephen Attwood, Rebecca Harrison, Hugh Barr, Paul Moayyedi, the AspECT Trial Team**

Marine n–3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer

JoAnn E. Manson, M.D., Dr.P.H., Nancy R. Cook, Sc.D., I-Min Lee, M.B., B.S., Sc.D., William Christen, Sc.D., Shari S. Bassuk, Sc.D., Samia Mora, M.D., M.H.S., Heike Gibson, Ph.D., Christine M. Albert, M.D., M.P.H., David Gordon, M.A.T., Trisha Copeland, M.S., R.D., Denise D'Agostino, B.S., Georgina Friedenberg, M.P.H., et al., for the VITAL Research Group*

Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease

JoAnn E. Manson, M.D., Dr.P.H., Nancy R. Cook, Sc.D., I-Min Lee, M.B., B.S., Sc.D., William Christen, Sc.D., Shari S. Bassuk, Sc.D., Samia Mora, M.D., M.H.S., Heike Gibson, Ph.D., David Gordon, M.A.T., Trisha Copeland, M.S., R.D., Denise D'Agostino, B.S., Georgina Friedenberg, M.P.H., Claire Ridge, M.P.H., et al., for the VITAL Research Group*

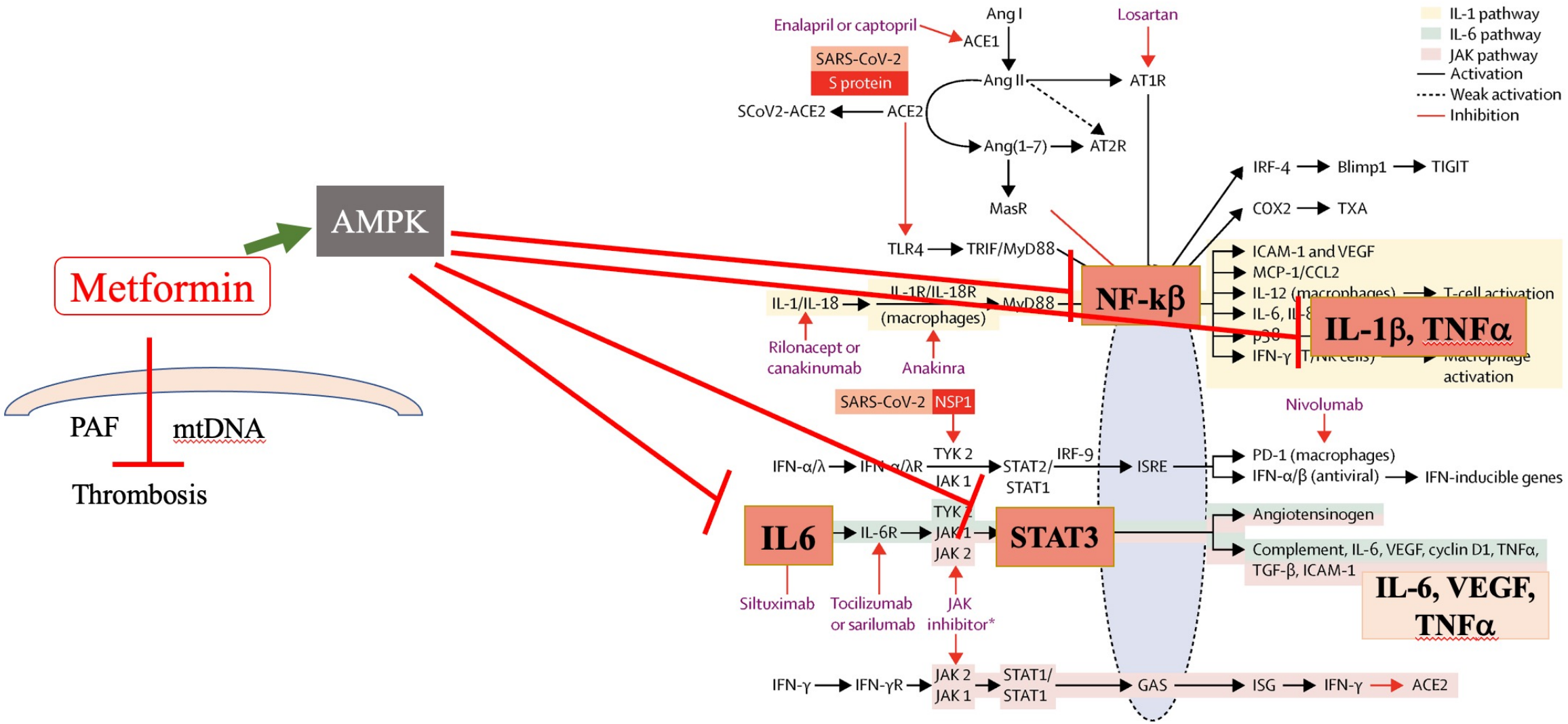
Polypill with or without Aspirin in Persons without Cardiovascular Disease

Salim Yusuf, D.Phil., Philip Joseph, M.D., Antonio Dans, M.D., Peggy Gao, M.Sc., Koon Teo, Ph.D., Denis Xavier, M.D., Patricio López-Jaramillo, Ph.D., Khalid Yusoff, M.B., B.S., Anwar Santoso, Ph.D., Habib Gamra, M.D., Shamim Talukder, M.B., B.S., Courtney Christou, B.Sc., et al., for the International Polycap Study 3 Investigators*

COVID-OUT: Study Population

- Adults age 30 - 85
- +SARS-CoV-2 within 3 days
- < 7 days of symptoms
- No known prior infection with SARS-CoV-2
- No severe kidney, liver, or heart failure
  - Tested GFR on persons > 75 or persons with a history of heart, liver, or kidney disease
- Not excluding or restricting to patients with diabetes or prediabetes
  - Excluding those on insulin or sulfonylurea
- Pregnancy not excluded
- With overweight or obesity

Metformin may inhibit SARS-CoV2 induced adipokine cascade



Ingraham N, …, Tignanelli CJ, Immunomodulation in COVID-19, Lancet Respiratory Medicine, 2020
Xin et al. 2016.

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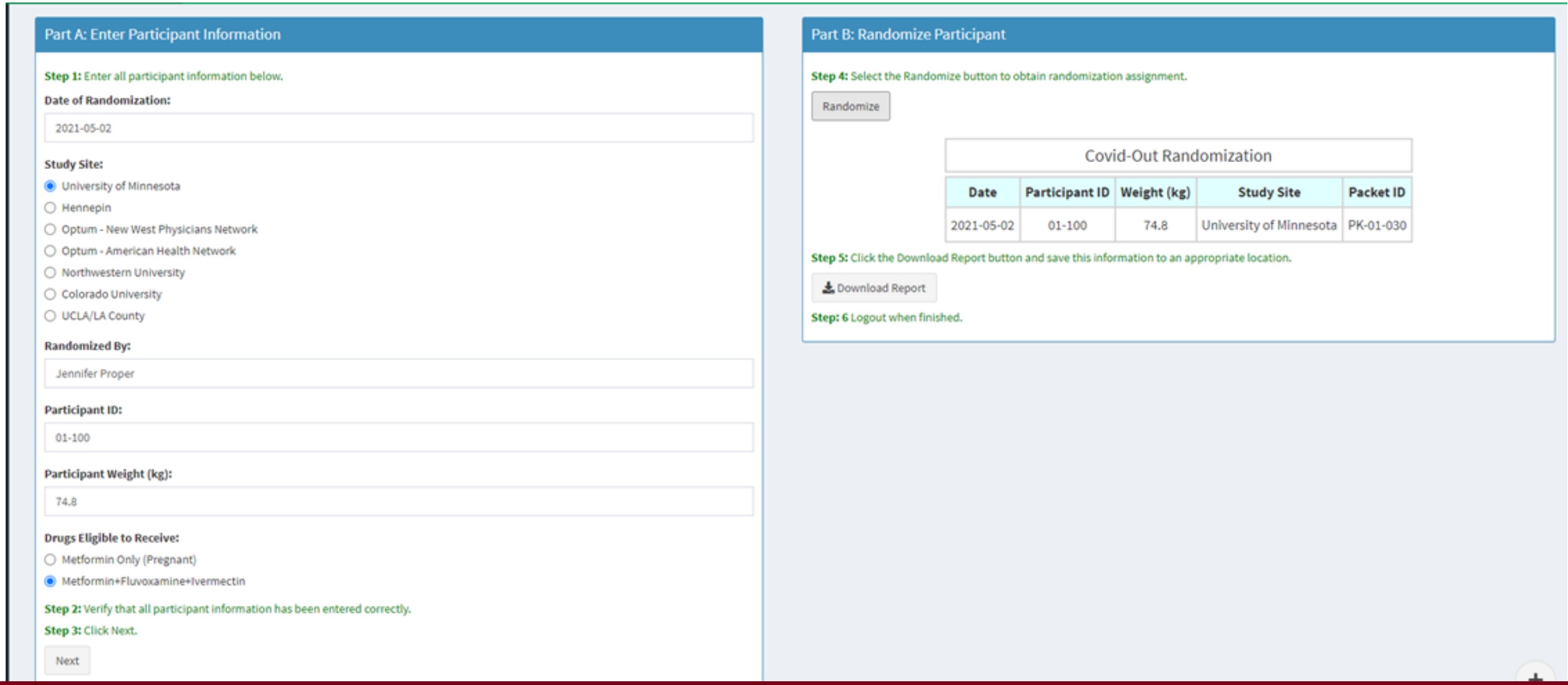
Randomization

- Equal allocation to open arms using pre-generated schedules
  - 1:1 to Metformin or Placebo -> 1:1:1:1:1:1 to 6 arms -> 1:1:1:1 to 4 arms w/o Flu

	Metformin	**Placebo**
Fluvoxamine	1: Met + Fluvoxamine	4: Placebo + Fluvoxamine
Ivermectin	2: Met + Ivermectin	5: Placebo + Ivermectin
Placebo	3: Met + Placebo	6: Placebo + Placebo

  - Stratification by study site pharmacy
- Weight-based dosing for ivermectin and ivermectin placebo
  - Shiny app to allocate pre-packed, individually labeled, blinded meds to each enrollee based on their weight and random assignment

Randomization via Shiny App



Statistical Considerations - Primary Analysis

- Clinical progression within 14 days
  - O_2 saturation ≤ 93% or supplemental O_2, ED visit, Hospitalization, Death
- mITT Analysis
  - Excluded those who did not receive or confirmed not taking study IP, and those who had a post-randomization eligibility disqualification
- Evaluate main effect of each agent using logistic regression (adjusted OR)
  - Active group received agent and control group were at risk of receiving agent but received control condition instead (i.e. concurrently randomized controls).
    - Metformin: 1+2+3 vs 4+5+6
    - Fluvoxamine: 1+4 vs 3+6
    - Ivermectin: 2+5 vs 3+6
  - Adjusted for vaccination + other study agents
  - Multiple imputation of missing outcomes

	Metformin	**Placebo**
Fluvoxamine	1: Met + Flu	4: Pla + Flu
Ivermectin	2: Met + Iver	5: Pla + Iver
Placebo	3: Met + Pla	6: Pla + Pla

Power Considerations

- 1,350 participants (~204 per arm)
  - Accounts for up to 10% withdrawal
- Metformin main effect (all participants)
  - 90% power for 35% relative risk reduction
    - (20% placebo, 11% mono-therapy, 6% combo-therapy)
    - If fluvoxamine and ivermectin don't work, power is higher
- Fluvoxamine / Ivermectin main effects (~2/3 participants)
  - 80% power for 35% relative risk reduction
- Final sample size due to power recalculation
  - new information from other trials
  - a high percent of vaccinated individuals enrolling
  - lower than expected drop out rate

Secondary Analyses

- Subgroup analyses
  - Assigned Sex at Birth, BMI, Age, Time from Symptom Onset, Vaccination Status
  - Adherence Analyses

- Secondary Endpoints
  - Removing least severe component of composite:
    - ED visit, Hospitalization, or Death
    - Hospitalization, or Death
  - Symptomatology
  - Labs
  - Post-acute sequelae of SARS-CoV-2 infection

- Drug-Drug Synergies/Interactions
  - Metformin + Ivermectin / Fluvoxamine

Data Monitoring

- Bi-weekly Safety Reports to DSMB
  - SAEs/AEs, Side Effects
- Three Full DSMB Reviews
  - May drop agent / arm(s) for efficacy, futility or harm
    - Conservative Efficacy Boundary (O'Brien-Fleming-like)
    - Haybittle-Peto Lower Harm Boundary
    - Non-binding Futility Boundary + Conditional Power
- At the last review DSMB recommended closing the fluvoxamine arms
  - The stopping guidelines was conditional power < 10%
  - Actual conditional power < 3 %

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- Results
  - **Sample Population**
    - Figure 1, Consort diagram
    - Table 1
  - Covid Severity Outcomes, primary analysis
    - Table 2
      - Complete Case Results
    - Supplemental Figure 1
    - Supplemental Figure 2
    - Supplemental Figure 7, 8
  - Covid Severity Outcomes, intention to treat
    - Overview of Intention to Treat versus Modified Intention to Treat
    - Table 1 of ITT versus mITT
    - Table 2 of ITT
  - Symptom Outcomes
    - Figure 2
    - Supplemental Figures 5
  - Study Drug Discontinuation
  - Other medication use

Figure 1.

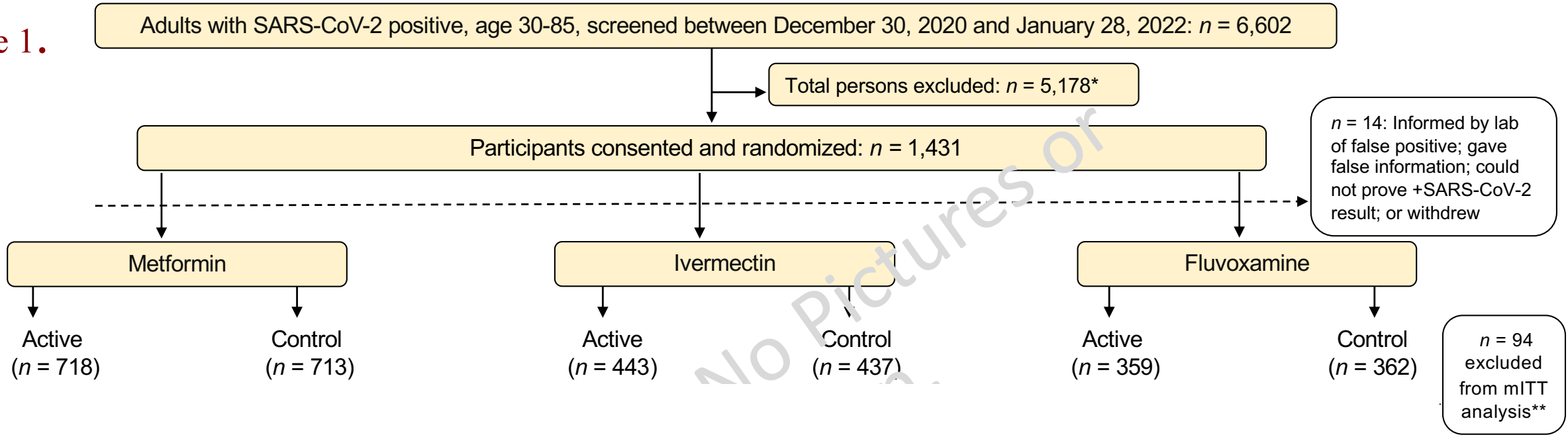
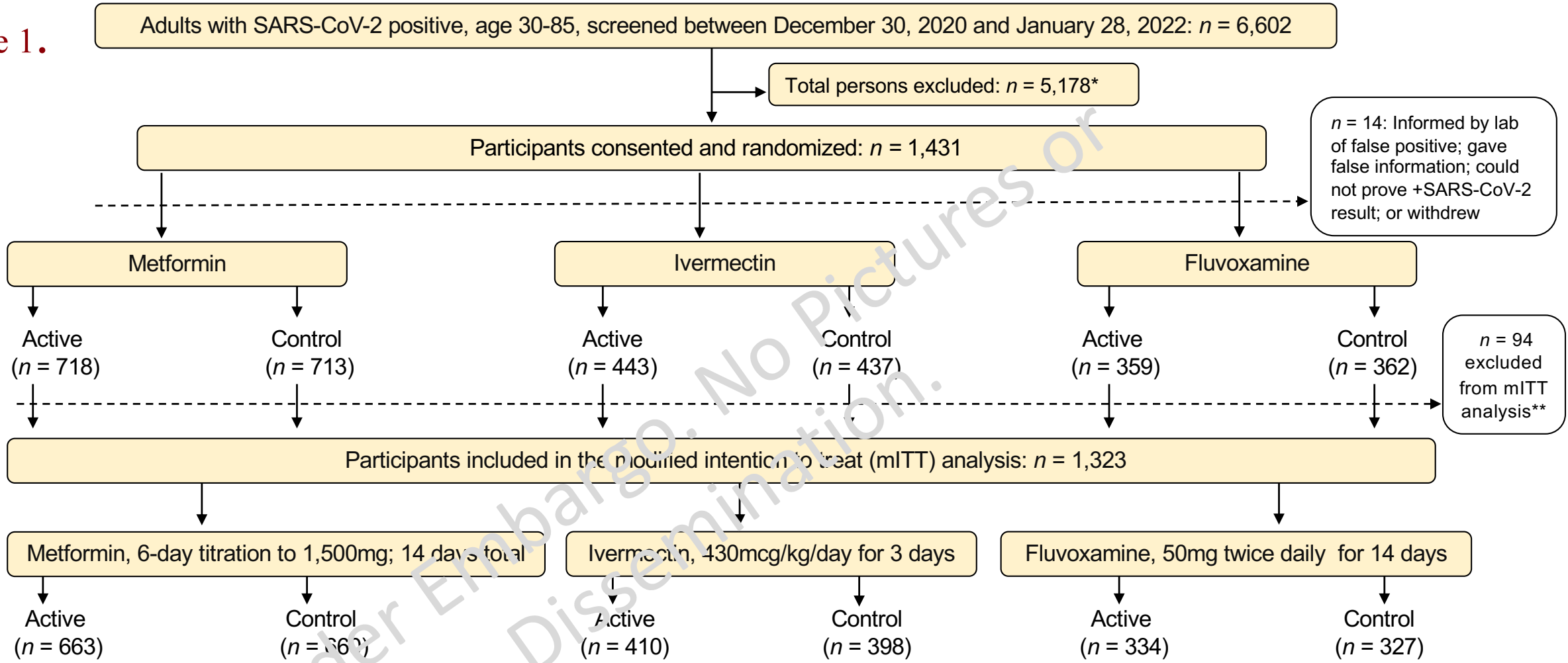

Adults with SARS-CoV-2 positive, age 30-85, screened between December 30, 2020 and January 28, 2022: n = 6,602
Total persons excluded: n = 5,178*
Participants consented and randomized: n = 1,431
n = 14: Informed by lab of false positive; gave false information; could not prove +SARS-CoV-2 result; or withdrew
Metformin
Ivermectin
Fluvoxamine
Active (n = 718)
Control (n = 713)
Active (n = 443)
Control (n = 437)
Active (n = 359)
Control (n = 362)
n = 94 excluded from mITT analysis**

Figure 1.



Factorial Design Groups.	Metformin = 1+2+3 vs 4+5+6	Placebo
Fluvoxamine = 1+4 vs 3+6	1: Metformin + Fluvoxamine	4: Placebo + Fluvoxamine
Ivermectin = 2+5 vs 3+6	2: Metformin + Ivermectin	5: Placebo + Ivermectin
Placebo	3: Metformin + Placebo	6: Placebo + Placebo

While groups 1 and 2 were the only groups with two active medications, all participants received two types of pills to maintain the blind and have a similar pill burden in each group.

*Detail on the number excluded for each reason are outlined in the Supplementary Appendix.

**Excluded from mITT analysis: did not receive kit (n=9); confirmed taking zero doses (n=77); hospitalized before received study medications (n=8). These 94 participants are included in the intention to treat analysis.

Reasons for Trial Exclusion

Not interested in research was the most common

- Total Persons excluded (*n* = 5,178)
- BMI <25 kg/m^2, or <23 kg/m^2 for those who identify as Asian or Latinx background (*n* = 769)
- Medication exclusion (*n* = 594)
- Symptoms started >7 days ago (*n* = 593)
- More than 3 days since positive SARS-CoV-2 test (*n* = 589)
- Currently admitted to hospital (*n* = 427)
- Previously tested positive for SARS-CoV-2 in prior illness (*n* = 413) study)

Table 1. Baseline characteristics of participants, overall and by each study medication with its concurrent randomized placebo control.

Baseline Characteristics		Overall n=1,323	Metformin		Ivermectin		Fluvoxamine†	
			Active n=663	Control n=660	Active n=410	Control n=398	Active n=336	Control n=327
Age, median (IQR)		46 (37, 55)	46 (38, 55)	45 (37, 55)	46 (39, 55)	45 (37, 56)	46 (38, 53)	43 (37,53)
Women, n (%), 6% of whom were pregnant		741 (56)	359 (54)	382 (58)	216 (53)	226 (57)	170 (51)	188 (57)
Race, n (%)								
Native American		27 (2.0)	10 (1.5)	17 (2.6)	7 (1.7)	9 (2.3)	8 (2.4)	9 (2.8)
Asian		51 (3.9)	25 (3.8)	26 (3.9)	19 (4.6)	18 (2.5)	9 (2.7)	12 (3.7)
Hawaiian, Pacific Islander		9 (0.7)	5 (0.8)	4 (0.6)	2 (0.5)	3 (0.8)	2 (0.6)	3 (0.9)
Black		100 (7.6)	55 (8.3)	45 (6.8)	30 (7.3)	29 (7.3)	28 (8.4)	23 (7.0)
White		1091 (82)	545 (82)	546 (83)	340 (83)	322 (81)	272 (81)	267 (82)
Other/Declined		80 (6.0)	43 (6.5)	37 (5.6)	24 (5.9)	29 (7.3)	21 (6.3)	23 (7.0)
Ethnicity, n (%) Latinx		160 (11)	76 (11)	84 (13)	41 (10)	57 (14)	42 (12)	46 (14)
Medical history, insurance status								
BMI, median (IQR)		30 (27, 34)	30 (27, 34)	30 (27, 34)	30 (27, 34)	30 (27, 34)	30 (27, 34)	30 (27, 34)
BMI ≥ 30 kg/m^2		646 (49)	316 (48)	330 (50)	194 (47)	189 (47)	155 (46)	157 (48)
Cardiovascular disease*		353 (27)	178 (27)	175 (27)	94 (23)	90 (23)	104 (31)	74 (23)
Diabetes		26 (2.0)	10 (1.5)	16 (2.4)	8 (2.0)	5 (1.3)	4 (1.2)	3 (0.9)
Vaccinated, primary series		690 (52)	359 (54)	331 (50)	222 (54)	227 (57)	55 (186)	187 (57)
Symptom duration, mean (±SD)		4.8 (±1.9)	4.8 (±1.9)	4.8 (±1.9)	4.6 (±1.9)	4.8 (±1.8)	5.0 (±2.2)	4.7 (±1.8)
Symptoms ≤4 days		603 (47)	298 (46)	305 (48)	199 (49)	174 (45)	147 (45)	147 (46)
Variant Period	Alpha (pre 6/19/21)	159 (12)	79 (12)	80 (12)	11 (2.7)	11 (2.8)	12 (3.6)	11 (3.4)
	Delta (6/19-12/12/21)	871 (66)	440 (66)	431 (65)	278 (68)	275 (69)	278 (83)	275 (84)
	Omicron (post 12/12/21)	293 (22)	144 (22)	149 (23)	121 (30)	112 (28)	46 (14) †	41 (13)†
Insurance Status	Medicaid	200 (15)	92(14)	108 (15)	70 (17)	60 (15)	43 (13)	42 (13)
	Medicare	100 (7.7)	52 (7.9)	48 (7.4)	27 (6.6)	31 (7.8)	27 (8.0)	21 (6.4)
	Private	823 (62)	410 (62)	413 (63)	257 (63)	230 (58)	206 (61)	197 (60)
	No insurance	178 (13)	97 (15)	81 (12)	52 (13)	67 (17)	55 (16)	58 (18)

- † Enrollment in the fluvoxamine arm was stopped on January 7, 2022 by the DSMB, for lack of conditional power.

COVID-OUT sample compared to US population and Covid Cases

Comparison of Background Information on race, ethnicity, age, sex of the broader population affected by SARS-CoV-2 based on CDC data.

	COVID-19 Cases		U.S. General Population
	U.S. CDC Data	Covid-Out Participants	
Female %	53%	54%	51%
Age, years (median)	36-41	46	38.1
Race (%)			
Native American	1.1%	2.2%	0.7%
Asian	3.8%	3.8%	5.6%
Hawaiian, Pacific Islander	0.3%	0.6%	0.2%
Black	12.3%	7.3%	12.5%
White	54%	82%	60.1%
Ethnicity (%)			
Latino	25%	11%	18.5%

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Table 2. Analysis of the primary outcome sequentially omitting the least severe component.

Metformin Outcomes	Metformin (n=663)	Control (n=660)	Adjusted Odds Ratio	95% CI
Overall Primary Composite	154/652 (11)	179/653 (7)	0.844	(0.655 - 1.086)
Hypoxemia ≤93% only	147/650 (13)	158/651 (9)	0.939	(0.724 - 1.218)
ER visit / Hospitalization / Death	27/652 (11)	48/655 (5)	0.577	(0.354 - 0.942)
Hospitalization / Death	8/652 (11)	18/655 (5)	0.474	(0.203 - 1.107)
Death	1/657 (6)	0/655 (5)		

- n with event / n with known outcome (n with unknown outcome)
- Adjusted Odds Ratio and 95% CI are based on a logistic regression model adjusted for baseline vaccination and other study drugs, and used multiple imputation using chained equations and predictive mean matching.
- Comparison of absolute event rates across groups is not valid due to differences in timing of enrollment (with differences in vaccination rates and SARS-CoV-2 variants).

Table 2. Analysis of the primary outcome sequentially omitting the least severe component.

Ivermectin Outcomes	Ivermectin (n=410)	Control (n=398)	Adjusted Odds Ratio	95% CI
Overall Primary Composite	105/407 (3)	96/391 (7)	1.048	(0.758 - 1.448)
Hypoxemia ≤93% only	96/406 (4)	88/390 (8)	1.041	(0.745 - 1.455)
ER visit / Hospitalization / Death	23/406 (4)	16/394 (4)	1.392	(0.720 - 2.693)
Hospitalization / Death	4/406 (4)	5/394 (4)	0.732	(0.193 - 2.769)
Death	1/408 (2)	0/396 (2)		

- n with event / n with known outcome (n with unknown outcome)
- Adjusted Odds Ratio and 95% CI are based on a logistic regression model adjusted for baseline vaccination and other study drugs, and used multiple imputation using chained equations and predictive mean matching.
- Comparison of absolute event rates across groups is not valid due to differences in timing of enrollment (with differences in vaccination rates and SARS-CoV-2 variants).

Table 2. Analysis of the primary outcome sequentially omitting the least severe component.

Fluvoxamine Outcomes	Fluvoxamine (n=336)	Control (n=327)	Adjusted Odds Ratio	95% CI
Overall Primary Composite	79/329 (5)	30/321 (6)	0.943	(0.657 - 1.355)
Hypoxemia ≤93% only	71/328 (6)	73/320 (7)	0.929	(0.639 - 1.350)
ER visit / Hospitalization / Death	18/329 (5)	15/324 (3)	1.167	(0.569 - 2.395)
Hospitalization / Death	6/329 (5)	5/324 (3)	1.113	(0.329 - 3.763)
Death	0/330 (4)	0/325 (2)		

- n with event / n with known outcome (n with unknown outcome)
- Adjusted Odds Ratio and 95% CI are based on a logistic regression model adjusted for baseline vaccination and other study drugs, and used multiple imputation using chained equations and predictive mean matching.
- Comparison of absolute event rates across groups is not valid due to differences in timing of enrollment (with differences in vaccination rates and SARS-CoV-2 variants).

Analysis of the primary outcome sequentially omitting the least severe component – complete case analysis (no imputation)

Outcome	Metformin (n=663)	Control (n=660)	Adjusted Odds Ratio	95% CI
Primary Composite	154/650 (13)	179/651 (9)	0.841	(0.653 - 1.082)
Hypoxemia ≤93% only	147/648 (15)	158/649 (11)	0.940	(0.725 - 1.218)
ER Visit, Hospitalization, Death †	27/650 (13)	48/653 (7)	0.570	(0.35 - 0.929)
Hospitalization or Death†	8/649 (14)	18/653 (7)	0.463	(0.199 - 1.078)
Death	1/654 (9)	0/653 (7)		

- Figures reflect the # with event / # with complete data in the modified intention to treat cohort.
- The number with incomplete data reflects the number of people with a missing outcome or unknown vaccination status (n=5).
- Results are consistent when not excluding the participants with a missing vaccination status and treating them as unvaccinated (data not shown).

Analysis of the primary outcome sequentially omitting the least severe component – complete case analysis (no imputation)

Outcome	Ivermectin (n=410)	Control (n=398)	Adjusted Odds Ratio	95% CI
Primary Composite	105/406 (4)	96/390 (8)	1.051	(0.761 - 1.452)
Hypoxemia ≤93% only	96/405 (5)	88/389 (9)	1.044	(0.748 - 1.457)
ER Visit, Hospitalization, Death †	23/405 (5)	16/393 (5)	1.382	(0.715 - 2.673)
Hospitalization or Death†	4/405 (5)	5/393 (5)	0.737	(0.195 - 2.784)
Death	1/407 (3)	0/395 (3)		

- Figures reflect the # with event / # with complete data in the modified intention to treat cohort.
- The number with incomplete data reflects the number of people with a missing outcome or unknown vaccination status (n=5).
- Results are consistent when not excluding the participants with a missing vaccination status and treating them as unvaccinated (data not shown).

Analysis of the primary outcome sequentially omitting the least severe component – complete case analysis (no imputation)

Outcome	Fluvoxamine (n=334)	Control (n=327)	Adjusted Odds Ratio	95% CI
Primary Composite	79/327 (7)	80/320 (7)	0.949	(0.661 - 1.363)
Hypoxemia ≤93% only	71/326 (8)	73/319 (8)	0.930	(0.64 - 1.351)
ER Visit, Hospitalization, Death †	18/327 (7)	15/323 (4)	1.169	(0.571 - 2.394)
Hospitalization or Death†	6/327 (7)	5/323 (4)	1.12	(0.332 - 3.778)
Death	0/328 (6)	0/324 (3)		

- Figures reflect the # with event / # with complete data in the modified intention to treat cohort.
- The number with incomplete data reflects the number of people with a missing outcome or unknown vaccination status (n=5).
- Results are consistent when not excluding the participants with a missing vaccination status and treating them as unvaccinated (data not shown).

Oxygen data had the highest amount of missingness

Descriptive statistics regarding the incomplete aspects of the primary endpoint.

	Overall	Metformin		Ivermectin		Fluvoxamine	
		Active	Control	Active	Control	Active	Control
Missing Participant -Reported Component	18/1323 (1%)	11/663 (2%)	7/660 (1%)	3/410 (1%)	7/398 (2%)	5/334 (1%)	6/327 (2%)
Hypoxia / Supplemental O2	18/1323 (1%)	11/663 (2%)	7/660 (1%)	3/410 (1%)	7/398 (2%)	5/334 (1%)	6/327 (2%)
ED Visit	15/1323 (1%)	10/663 (2%)	5/660 (1%)	3/410 (1%)	4/398 (1%)	5/334 (1%)	3/327 (1%)
Hospitalization	14/1323 (1%)	9/663 (1%)	5/660 (1%)	3/410 (1%)	4/398 (1%)	5/334 (1%)	3/327 (1%)
Death	10/1323 (1%)	5/663 (1%)	5/660 (1%)	2/410 (0%)	2/398 (1%)	0/334 (0%)	0/327 (0%)
Incomplete or missing SpO2 Daily Log Data (<14 Days)	371/1323 (28%)	199/663 (30%)	172/660 (26%)	100/410 (24%)	111/398 (28%)	99/334 (30%)	89/327 (27%)
0 Days with Data	250/1323 (19%)	134/663 (20%)	116/660 (18%)	69/410 (17%)	77/398 (19%)	68/334 (20%)	63/327 (19%)
1 - 7 Days with Data	29/1323 (2%)	14/663 (2%)	15/660 (2%)	5/410 (1%)	13/398 (3%)	6/334 (2%)	7/327 (2%)
8 - 13 Days with Data	92/1323 (7%)	51/663 (8%)	41/660 (6%)	26/410 (6%)	21/398 (5%)	25/334 (7%)	19/327 (6%)

Many sources of bias and error for the oxygen values

1. **Inherent error in the device:** In Feb, 2021, the FDA issued a safety communication with concerns expressed over the accuracy of home pulse oximeters.[7]
   - For prescription oximeters, 66% of readings will fall within 2-3% of the gold standard (arterial blood gas)

2. **Recall bias:** ED visit, hospitalization are more memorable, and are verifiable in the EHR

3. **Measurement error:** i.e. having cold hands; or having the oximeter on a finger with the thickest skin.
   - Additionally, the devices may not fit all individuals' fingers the same, causing measurement error in some.

4. **Misclassification bias:** Transient state of lower oxygen saturation that does not represent true hypoxemia (i.e. atelectasis because they had not coughed, stood up, or walked in some time).

5. **Selection bias:** The protocol did not specify a certain number of times that each person had to measure their oxygen each day, with specified spacing and movement between measurements.
   - Nor did the protocol specify that participants should record their highest value for the day.
   - Some individuals may have entered their lowest number, and some may have entered their highest number.
   - Some may have entered many readings per day, while others entered only 1 or none.

Figure S2A.

Metformin vs. control for healthcare utilization, overall and by subgroups.

Subgroup	Metformin	Control	Adjusted Odds Ratio (95% CI) for ER Visit, Hospitalization, Death
	n events /	n (n missing)	
All Participants	27/652 (11)	48/655 (5)	0.58 (0.35 to 0.94)
Sex			
Female	17/351 (8)	29/378 (4)	0.62 (0.34 to 1.16)
Male	10/301 (3)	19/277 (1)	0.52 (0.23 to 1.16)
Body Mass Index (BMI)			
< 30 kg/m^2	9/343 (4)	15/327 (3)	0.65 (0.28 to 1.51)
≥ 30 kg/m^2	18/309 (7)	33/328 (2)	0.55 (0.30 to 1.01)
Symptom onset to drug initiation			
< 4 days	11/290 (6)	26/299 (4)	0.45 (0.22 to 0.93)
≥ 4 days	16/352 (5)	21/338 (1)	0.75 (0.38 to 1.47)
Unknown	0/10 (0)	1/18 (0)	
Age			
< 45 years	11/303 (5)	24/309 (4)	0.50 (0.24 to 1.05)
≥ 45 years	16/349 (6)	24/346 (1)	0.65 (0.34 to 1.25)
Covid−19 Variant Time Period			
Alpha	10/77 (2)	12/80 (0)	0.84 (0.33 to 2.10)
Delta	16/435 (5)	29/427 (4)	0.55 (0.29 to 1.03)
Omicron	1/140 (4)	7/148 (1)	0.16 (0.02 to 1.32)
Vaccinated, primary series			
No	22/292 (9)	34/323 (4)	0.70 (0.40 to 1.23)
Yes	5/358 (1)	14/330 (1)	0.31 (0.11 to 0.88)
Unknown	0/2 (1)	0/2 (0)	
Preganant			
Not Pregnant	27/630 (10)	45/632 (4)	0.62 (0.38 to 1.01)
Pregnant	0/22 (1)	3/23 (1)	0.00 (0.00 to Inf)

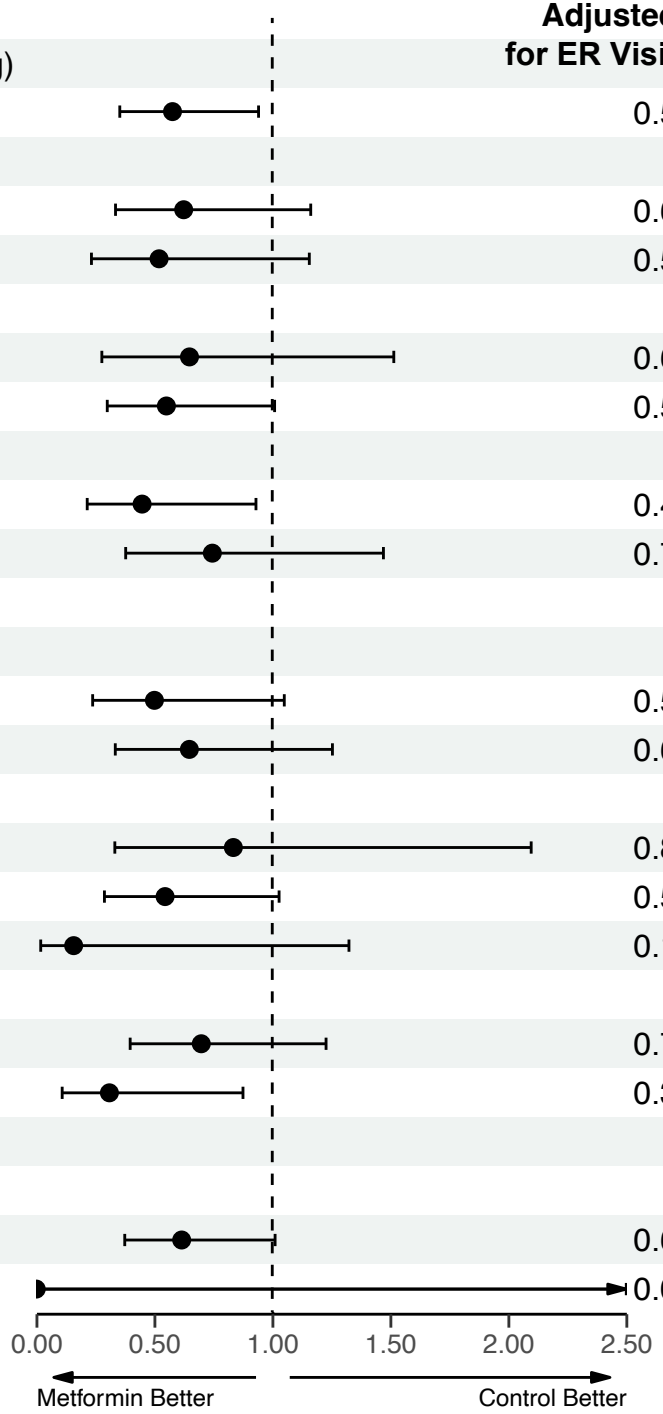
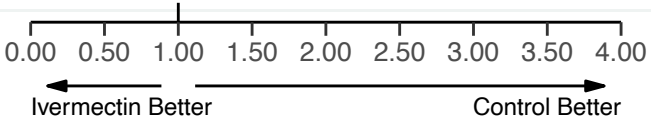


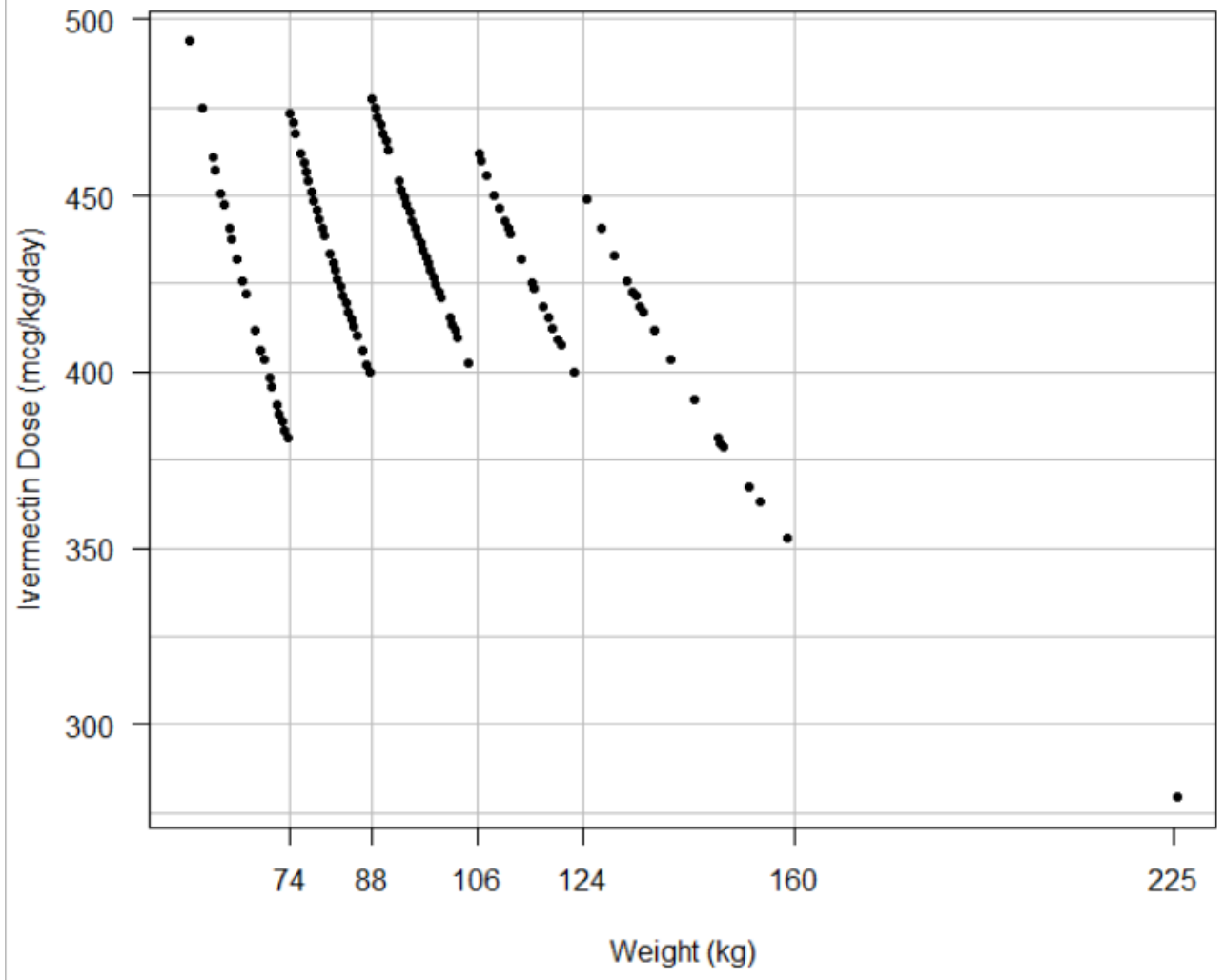
Figure S2B.

Ivermectin vs. control for healthcare utilization, overall and by subgroups.

Subgroup	Ivermectin	Control	Adjusted Odds Ratio (95% CI)
	n events /	n (n missing)	for ER Visit, Hospitalization, Death
All Patients	23/406 (4)	16/394 (4)	1.39 (0.72 to 2.69)
Sex			
Female	14/213 (3)	10/224 (2)	1.50 (0.65 to 3.47)
Male	9/193 (1)	6/170 (2)	1.27 (0.43 to 3.74)
BMI			
<30kg/m2	6/214 (2)	5/207 (3)	1.17 (0.35 to 3.94)
>=30kg/m2	17/192 (2)	11/187 (1)	1.50 (0.68 to 3.34)
Symptom onset to drug initiation			
< 4 days	11/197 (3)	10/184 (2)	0.99 (0.40 to 2.40)
>= 4 days	12/205 (1)	6/203 (2)	2.07 (0.75 to 5.69)
Unknown	0/4 (0)	0/7 (0)	
Age			
<45 years	10/175 (3)	12/188 (1)	0.91 (0.38 to 2.20)
>=45 years	13/231 (1)	4/206 (3)	2.78 (0.88 to 8.73)
Covid−19 Variant			
<=2021−06−19	2/10 (1)	2/11 (0)	1.10 (0.09 to 13.12)
2021−06−19 – 2021−12−20	16/276 (2)	12/272 (3)	1.29 (0.59 to 2.82)
>2021−12−20	5/120 (1)	2/111 (1)	2.51 (0.47 to 13.56)
Vaccinated			
No	15/183 (4)	12/167 (3)	1.16 (0.52 to 2.56)
Yes	8/222 (0)	4/226 (1)	2.10 (0.62 to 7.12)
Unknown	0/1 (0)	0/1 (0)	
Dose (mcg/kg)			
<= 430 mcg/kg	9/201 (2)	16/394 (4)	1.09 (0.47 to 2.54)
> 430 mcg/kg	14/205 (2)	16/394 (4)	1.73 (0.81 to 3.66)



Ivermectin mcg/kg/day

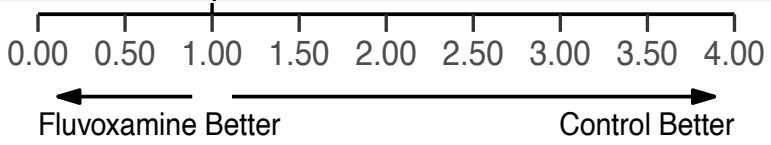


Weight	Mg dose of Ivermectin
<74kg	28mg (2x14mg)
74 to < 88kg	35mg (2 x 14mg + 7mg)
88 to < 106kg	42mg (3 x 14)
106 to < 124kg	49mg (3 x 14mg + 7mg)
124kg to < 160kg	56mg (4 x 14mg)
≥ 160 kg	63mg (4 x 14mg + 7mg)

Figure S2C.

Fluvoxamine vs. control for healthcare utilization, overall and by subgroups.

Subgroup	Fluvoxamine n events / n (n missing)	Control n events / n (n missing)	Adjusted Odds Ratio (95% CI) for ER Visit, Hospitalization, Death
All Patients	18/329 (5)	15/324 (3)	1.17 (0.57 to 2.40)
Sex			
Female	12/166 (4)	9/187 (1)	1.48 (0.60 to 3.66)
Male	6/163 (1)	6/137 (2)	0.85 (0.26 to 2.79)
BMI			
<30kg/m2	6/179 (1)	4/168 (2)	1.36 (0.37 to 5.02)
>=30kg/m2	12/150 (4)	11/156 (1)	1.13 (0.47 to 2.73)
Symptom onset to drug initiation			
< 4 days	10/145 (4)	9/152 (1)	1.02 (0.39 to 2.68)
>= 4 days	8/180 (1)	6/167 (2)	1.35 (0.45 to 4.07)
Unknown	0/4 (0)	0/5 (0)	
Age			
<45 years	7/150 (3)	11/171 (1)	0.73 (0.26 to 1.99)
>=45 years	11/179 (2)	4/153 (2)	2.30 (0.71 to 7.53)
Covid−19 Variant			
<=2021−06−19	3/12 (0)	2/11 (0)	1.60 (0.15 to 16.86)
2021−06−19 – 2021−12−20	14/274 (3)	12/272 (3)	1.13 (0.50 to 2.52)
>2021−12−20	1/43 (2)	1/41 (0)	1.13 (0.06 to 20.75)
Vaccinated			
No	12/143 (4)	12/136 (3)	0.90 (0.38 to 2.11)
Yes	6/184 (1)	3/187 (0)	2.38 (0.58 to 9.84)
Unknown	0/2 (0)	0/1 (0)	



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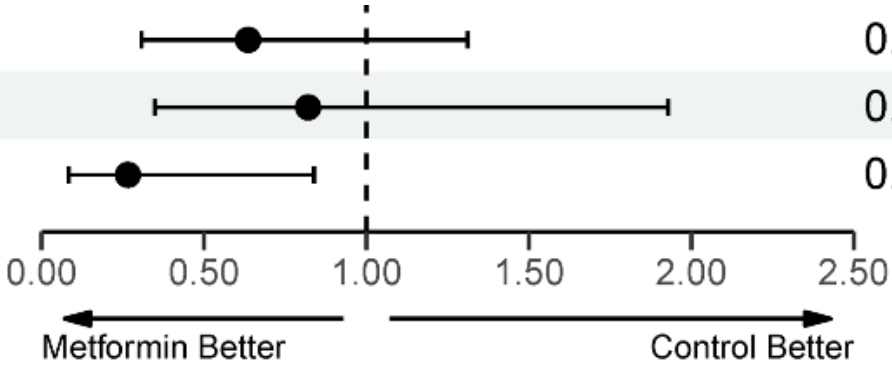
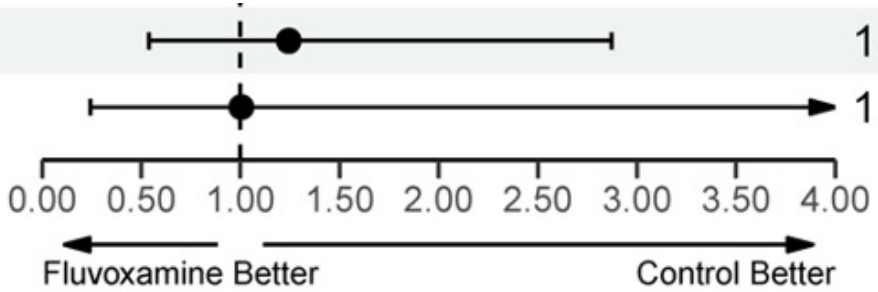
Combination Subgroups are underpowered

Metformin only vs. Placebo	13/279 (5)	21/293 (2)	0.64 (0.31 to 1.31)
Met+Ivermectin vs. Ivermectin	10/200 (4)	13/206 (0)	0.82 (0.35 to 1.93)
Met+Fluvoxamine vs. Fluvox	4/173 (2)	14/156 (3)	0.27 (0.08 to 0.84)

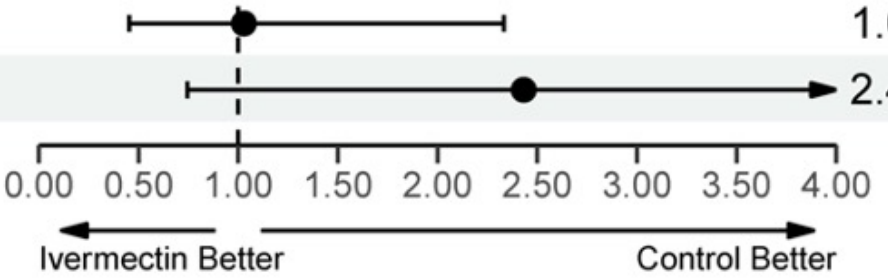


Fluvoxamine only vs. Placebo	14/156 (3)	11/165 (1)	1.24 (0.54 to 2.87)
Met+Fluvoxamine vs. Metformin	4/173 (2)	4/159 (2)	1.00 (0.24 to 4.14)

- Adding fluvoxamine does not move the point estimate left of 1.0



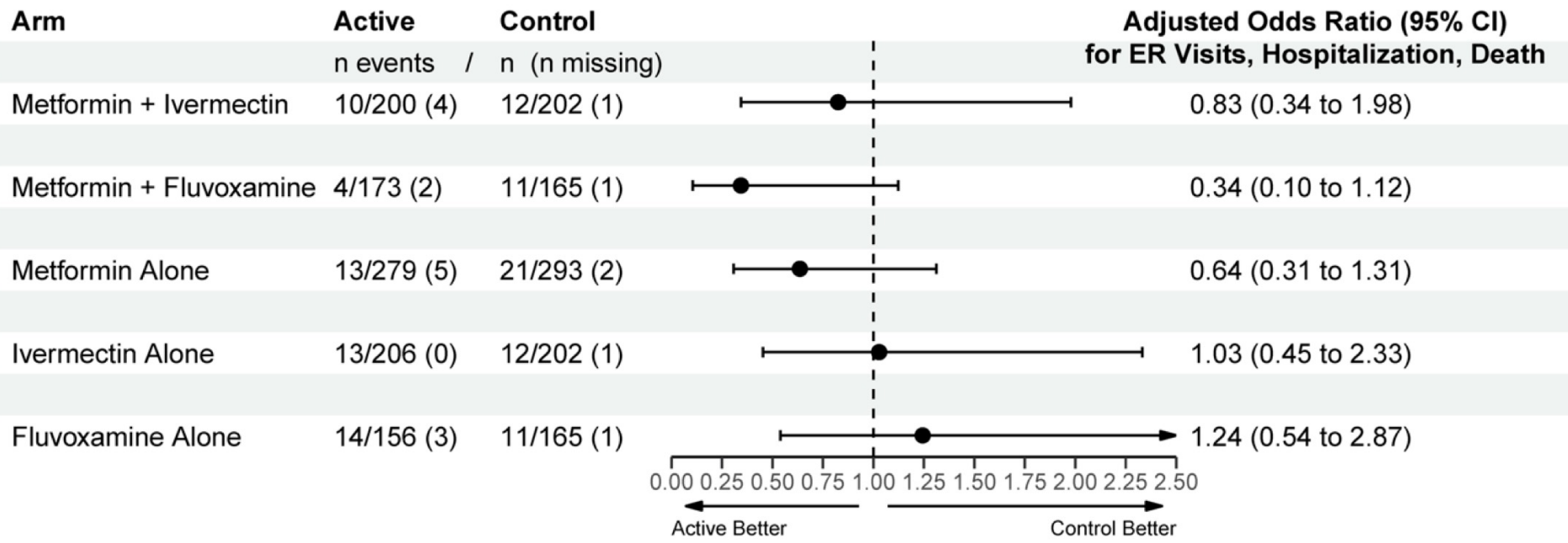
Ivermectin only vs. Placebo	13/206 (0)	12/202 (1)	1.03 (0.45 to 2.33)
Met+Ivermectin vs. Metformin	10/200 (4)	4/192 (3)	2.43 (0.75 to 7.93)



The trial was not powered for these comparisons.

Comparisons across treatments are not against concurrently enrolled participants

Vertical comparisons of these rows are not valid →



Enrollment in the treatment arms was through different variant periods of the pandemic

(From Table 1) n(%)

		Overall	Met	Met Control	Iver	Iver Control	Fluvox	Fluvox Control
Variant Period	Alpha (pre 6/19/21)	159 (12)	79 (12)	80 (12)	11 (2.7)	11 (2.8)	12 (3.6)	11 (3.4)
	Delta (6/19-12/12/21)	871 (66)	440 (66)	431 (65)	278 (68)	275 (69)	278 (83)	275 (84)
	Omicron (post 12/12/21)	293 (22)	144 (22)	149 (23)	121 (30)	112 (28)	46 (14)	41 (13)

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Our definition of modified intention to treat (mITT)

Participants eligible, consented, randomized

Intention to Treat (n = 1,431)

1. Did not receive medication (n=9)

2. Hospitalized when medication was delivered (n=8)

3. Told us they did not take any medication (n=77)
- They felt better
- They didn't like the medication/placebo
  - exact matching placebo, but could identify which 2 of the 3 meds or placebo they received

Modified Intention to Treat (n=1,323)

Includes those for whom we don't know whether or not they took study drug

A. Properties of conducting a remote trial	B. Properties of natural disease progression	C. Properties of the medication
X		
X	X	
	X	X

(and n=14 ineligible after randomization)

Baseline characteristics of participants who were randomized but not included in the modified intention to treat analysis

Baseline Characteristics	Overall n=1,323	ITT and not MITT N=94	Metformin		Ivermectin		Fluvoxamine	
			Active n=48	Control n=46	Active n=28	Control n=36	Active n=23	Control n=32
Age, median (IQR)	46 (37, 55)	46 (37, 55)	45 (37, 55)	48 (40, 56)	44 (38, 55)	50 (37, 56)	46 (38, 54)	48 (36, 55)
Female, % (n)	56% (741)	47% (44)	42% (20)	52% (24)	57% (16)	42% (15)	48% (11)	41% (13)
Race, % (n)								
Native American	2.0% (27)	5.3% (5)	6.2% (3)	4.3% (2)	0% (0)	5.6% (2)	13% (3)	6.2% (2)
Asian	3.9% (51)	2.1% (2)	2.1% (1)	2.2% (1)	0% (0)	2.8% (1)	4.3% (1)	3.1% (1)
Hawaiian/Pacific Isl.	0.7% (9)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)
Black	7.6% (100)	8.5% (8)	10% (5)	6.5% (3)	3.6% (1)	5.6% (2)	13% (3)	6.2% (2)
White	82%(1,091)	70% (66)	67%(32)	74%(34)	89%(25)	67%(24)	57% (13)	62% (20)
Other / Declined	6.1% (80)	16.5%(15)	16.2%(6)	15.2%(7)	7.2% (2)	19.3% (7)	21.3%(5)	21.5%(7)
Ethnicity, n (%) Latinx	12% (160)	12% (11)	8.2% (4)	15% (7)	7.1% (2)	14% (5)	13% (3)	12% (4)
Medical history, insurance status								
BMI, median (IQR)	29.8 (27, 34)	30.2 (27, 34)	28.2 (27, 32)	31.0 (28, 35)	30.1 (27, 34)	29.6 (28, 37)	30.4 (26, 33)	29.6 (28, 37)
BMI $\geq$ 30 kg/m^2	49% (646)	53% (50)	44% (21)	63% (29)	54% (15)	50% (18)	57% (13)	50% (16)
Cardiovascular disease*	27% (353)	28% (26)	33% (16)	22% (10)	25% (7)	22% (8)	30% (7)	19% (6)
Diabetes	2.0% (26)	2.1% (2)	2.1% (1)	2.2% (1)	3.6% (1)	0% (0)	4.3% (1)	0% (0)
Vaccinated, primary series	52% (690)	46% (43)	48% (23)	43% (20)	36% (10)	61% (22)	35% (8)	59% (19)
Symptom Days, mean ($\pm$SD)	4.8 (4.9)	4.9 (1.8)	4.4 (1.8)	5.3 (1.8)	4.3 (1.5)	4.9 (1.9)	5.4 (2.1)	5.0 (2.0)
Symptoms $\leq$4 days	47% (603)	42% (36)	53% (24)	29% (12)	54% (14)	40% (14)	29% (6)	35% (11)
Variant Period: Alpha	12% (159)	11% (10)	8.3% (4)	13% (6)	7.1% (2)	5.6% (2)	4.3% (1)	6.2% (2)
Variant Period: Delta	66% (871)	65% (61)	67% (32)	63% (29)	54% (15)	72% (26)	83% (19)	81% (26)
Variant Period: Omicron	22% (293)	24% (23)	25% (12)	24% (11)	39% (11)	22% (8)	13% (3)	12% (4)
Medicaid	15% (200)	16% (15)	21% (10)	11% (5)	14% (4)	14% (5)	17% (4)	16% (5)
Medicare	7.6% (100)	9.6% (9)	6.2% (3)	13% (6)	11% (3)	5.6% (2)	13% (3)	6.2% (2)
Private	62% (823)	51% (48)	52% (25)	50% (23)	57% (16)	61% (22)	30% (7)	59% (19)
No insurance	13% (178)	22% (21)	21% (10)	24% (11)	18% (5)	17% (6)	39% (9)	16% (5)

Values are n (%), median (interquartile range), or mean ($\pm$SD).

Abbreviations: BMI = body mass index; IQR=inter-quartile range; SD = standard deviation. * Cardiovascular disease defined as: hypertension, hyperlipidemia, coronary artery disease, past myocardial infarction, congestive heart failure, pacemaker, arrhythmias, or pulmonary hypertension.

Analysis of the primary outcome sequentially omitting the least severe component – Intention to Treat sample (with imputation)

Metformin Outcomes	Active (n=711)	Control (n=706)	Adj. Odds Ratio	(95% CI)
Overall Primary Composite	161/673 (38)	188/674 (32)	0.838	(0.655 - 1.073)
Hypoxemia ≤93% only	153/670 (41)	162/667 (39)	0.930	(0.721 - 1.200)
ER visit / Hospitalization / Death	31/73 (33)	54/682 (24)	0.586	(0.372 - 0.925)
Hospitalization / Death	11/678 (33)	24/682 (24)	0.479	(0.231 - 0.993)
Death	1/686 (25)	0/679 (27)		

- † Outcome reflects outcome defined as the corresponding component or worse.
- Numbers reflect: # with event / # with known outcome (# with unknown outcome) in ITT cohort.
- Adjusted Odds Ratio and 95% CI are based on a logistic regression model adjusted for baseline vaccination and other study drugs.
- Missing outcomes are multiply imputed.

Analysis of the primary outcome sequentially omitting the least severe component – Intention to Treat sample (with imputation)

Ivermectin Outcomes	Active (n=438)	Control (n=434)	Adj. Odds Ratio	(95% CI)
Overall Primary Composite	109/416 (22)	101/410 (24)	1.049	(0.763 - 1.443)
Hypoxemia ≤93% only	99/414 (24)	90/406 (28)	1.047	(0.753 - 1.457)
ER visit / Hospitalization / Death	27/420 (18)	20/417 (17)	1.287	(0.705 - 2.350)
Hospitalization / Death	8/420 (18)	8/417 (17)	0.897	(0.326 - 2.470)
Death	1/422 (16)	0/419 (15)		

- † Outcome reflects outcome defined as the corresponding component or worse.
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- Adjusted Odds Ratio and 95% CI are based on a logistic regression model adjusted for baseline vaccination and other study drugs.
- Missing outcomes are multiply imputed.

Analysis of the primary outcome sequentially omitting the least severe component – Intention to Treat sample (with imputation)

Fluvoxamine Outcomes	Active (n=357)	Control (n=359)	Adj. Odds Ratio	(95% CI)
Overall Primary Composite	86/342 (15)	83/337 (22)	1.007	(0.709 - 1.429)
Hypoxemia ≤93% only	76/339 (18)	74/334 (25)	0.994	(0.693 - 1.427)
ER visit / Hospitalization / Death	20/342 (15)	18/343 (16)	1.048	(0.537 - 2.048)
Hospitalization / Death	8/342 (15)	8/343 (16)	0.898	(0.327 - 2.467)
Death	0/342 (15)	0/344 (15)		

- † Outcome reflects outcome defined as the corresponding component or worse.
- Numbers reflect: # with event / # with known outcome (# with unknown outcome) in ITT cohort.
- Adjusted Odds Ratio and 95% CI are based on a logistic regression model adjusted for baseline vaccination and other study drugs.
- Missing outcomes are multiply imputed.

Analysis of the primary outcome sequentially omitting the least severe component – Intention to Treat sample (complete case)

Metformin Outcomes	Active (n=711)	Control (n=706)	Adj. Odds Ratio	(95% CI)
Overall Primary Composite	161/671 (40)	188/672 (34)	0.838	(0.654 - 1.073)
Hypoxemia ≤93% only	153/668 (43)	162/665 (41)	0.953	(0.737 - 1.231)
ER visit / Hospitalization / Death	31/676 (35)	54/680 (26)	0.586	(0.37 - 0.928)
Hospitalization / Death	11/675 (36)	24/680 (26)	0.482	(0.233 - 0.998)
Death	1/682 (29)	0/677 (29)		

- † Outcome reflects outcome defined as the corresponding component or worse.
- Numbers reflect: # with event / # with known outcome (# with unknown outcome) in ITT cohort.
- Adjusted Odds Ratio and 95% CI are based on a logistic regression model adjusted for baseline vaccination and other study drugs.
- Missing outcomes are multiply imputed.

Analysis of the primary outcome sequentially omitting the least severe component – Intention to Treat sample (complete case)

Ivermectin Outcomes	Active (n=438)	Control (n=434)	Adj. Odds Ratio	(95% CI)
Overall Primary Composite	109/415 (23)	101/409 (25)	1.061	(0.773 - 1.457)
Hypoxemia ≤93% only	99/413 (25)	90/405 (29)	1.079	(0.776 - 1.499)
ER visit / Hospitalization / Death	27/419 (19)	20/416 (18)	1.305	(0.716 - 2.380)
Hospitalization / Death	8/419 (19)	8/416 (18)	0.923	(0.34 - 2.503)
Death	1/421 (17)	0/417 (17)		

- † Outcome reflects outcome defined as the corresponding component or worse.
- Numbers reflect: # with event / # with known outcome (# with unknown outcome) in ITT cohort.
- Adjusted Odds Ratio and 95% CI are based on a logistic regression model adjusted for baseline vaccination and other study drugs.
- Missing outcomes are multiply imputed.

Analysis of the primary outcome sequentially omitting the least severe component – Intention to Treat sample (complete case)

Fluvoxamine Outcomes	Active (n=357)	Control (n=359)	Adj. Odds Ratio	(95% CI)
Overall Primary Composite	86/340 (17)	83/336 (23)	1.013	(0.712 - 1.442)
Hypoxemia ≤93% only	76/337 (20)	74/333 (26)	1.001	(0.694 - 1.445)
ER visit / Hospitalization / Death	20/340 (17)	18/342 (17)	1.062	(0.543 - 2.078)
Hospitalization / Death	8/340 (17)	8/342 (17)	0.912	(0.332 - 2.51)
Death	0/340 (17)	0/342 (17)		

- † Outcome reflects outcome defined as the corresponding component or worse.
- Numbers reflect: # with event / # with known outcome (# with unknown outcome) in ITT cohort.
- Adjusted Odds Ratio and 95% CI are based on a logistic regression model adjusted for baseline vaccination and other study drugs.
- Missing outcomes are multiply imputed.

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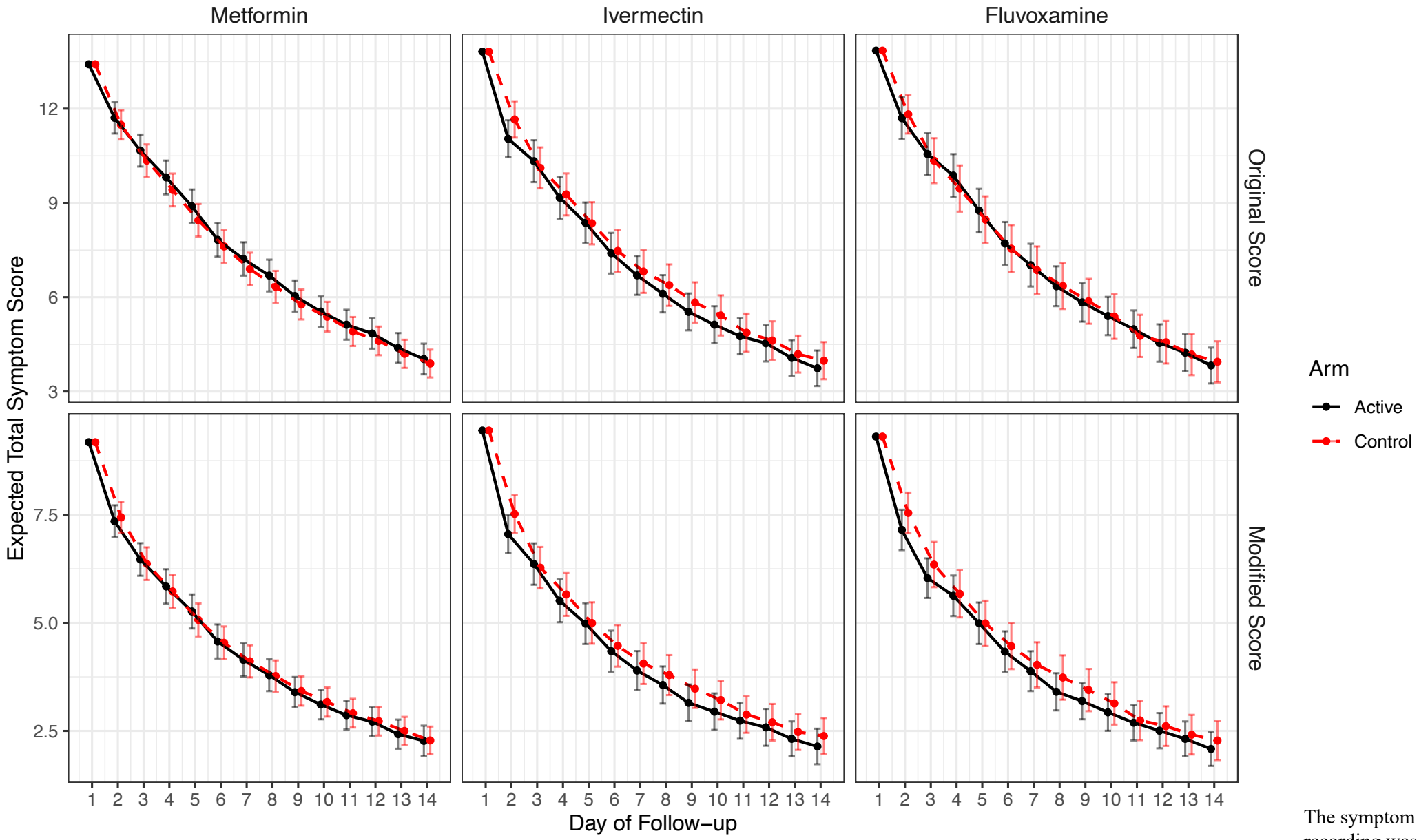
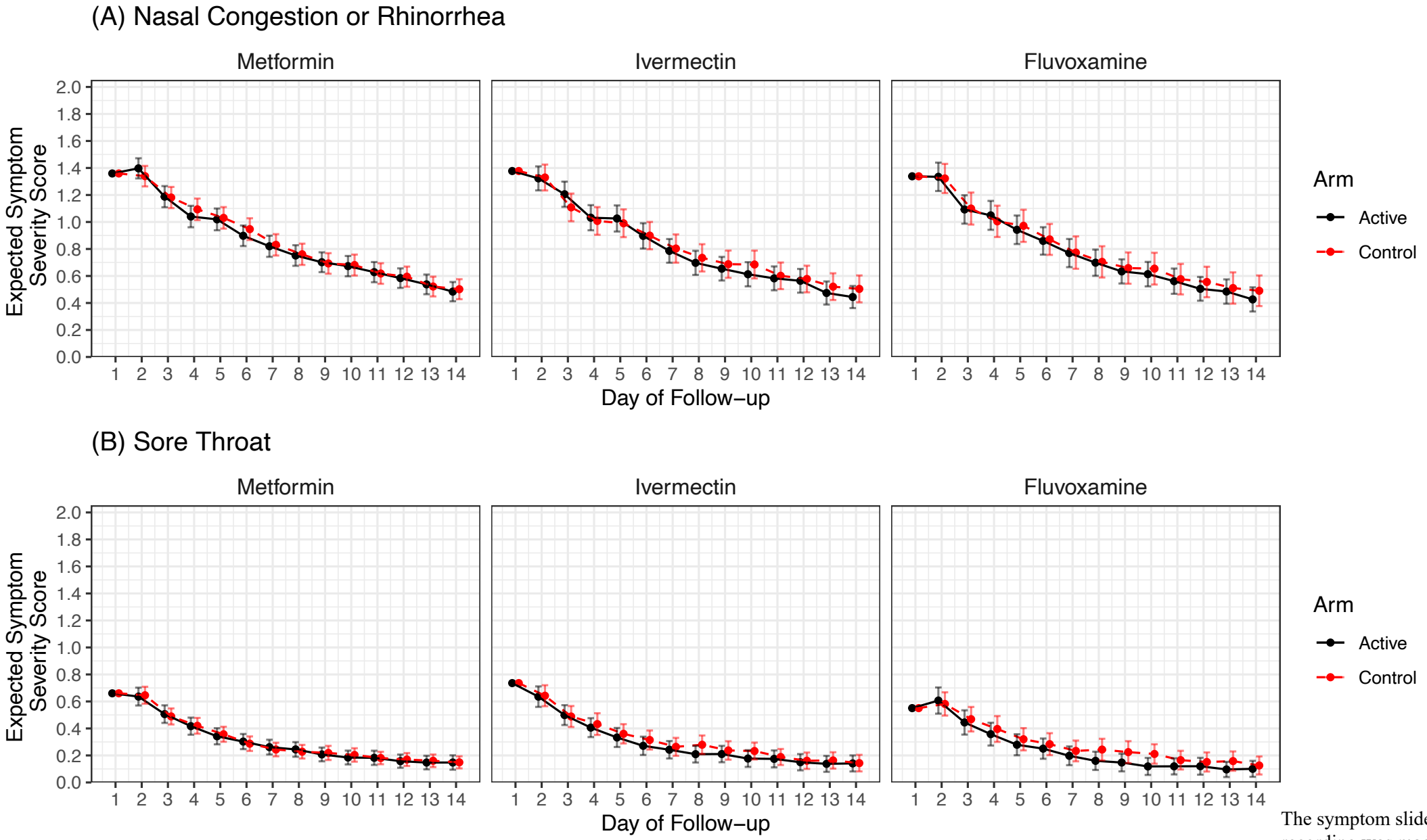
Symptom Outcomes – FDA symptom score



The symptom slides have been updated after the live recording was made. No other slides were updated.

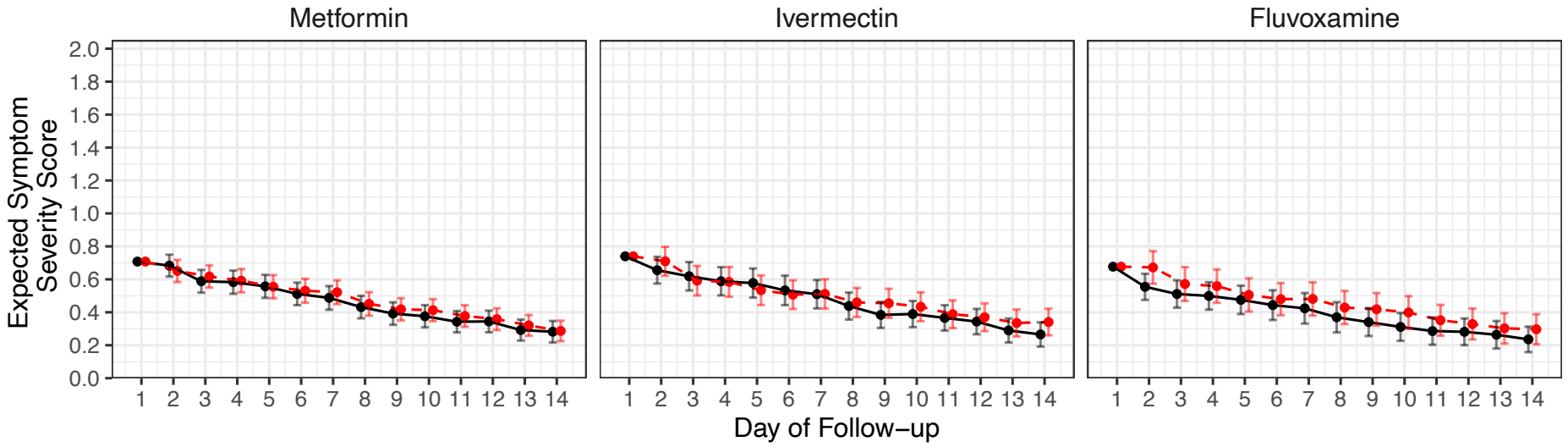
Individual Symptoms



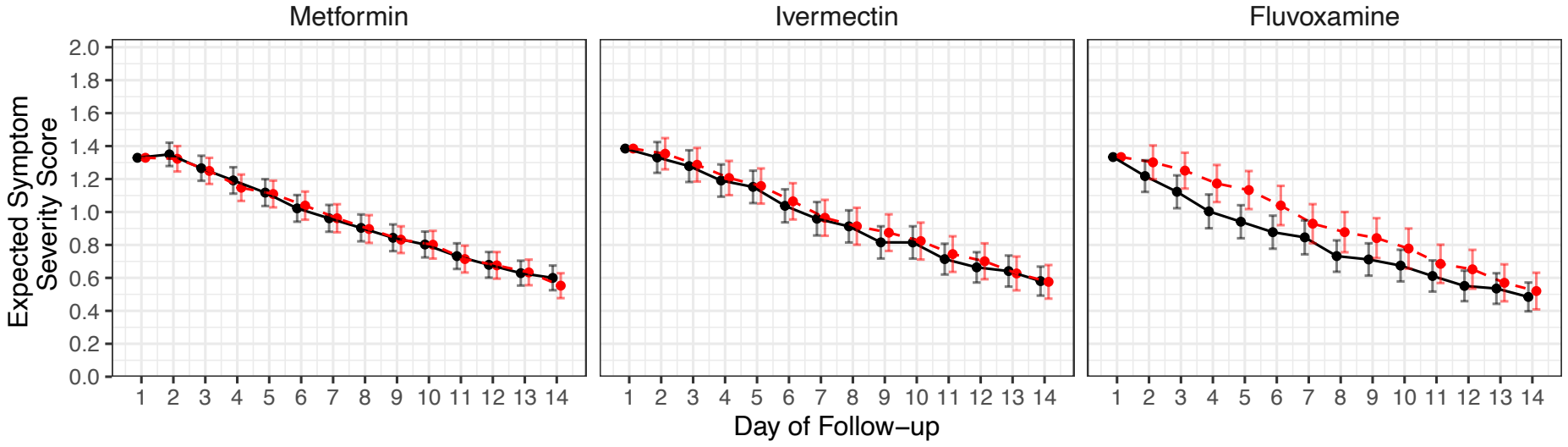
The symptom slides have been updated after the live recording was made. No other slides were updated.

Individual Symptoms

(C) Shortness of Breath or Difficulty Breathing



(D) Cough



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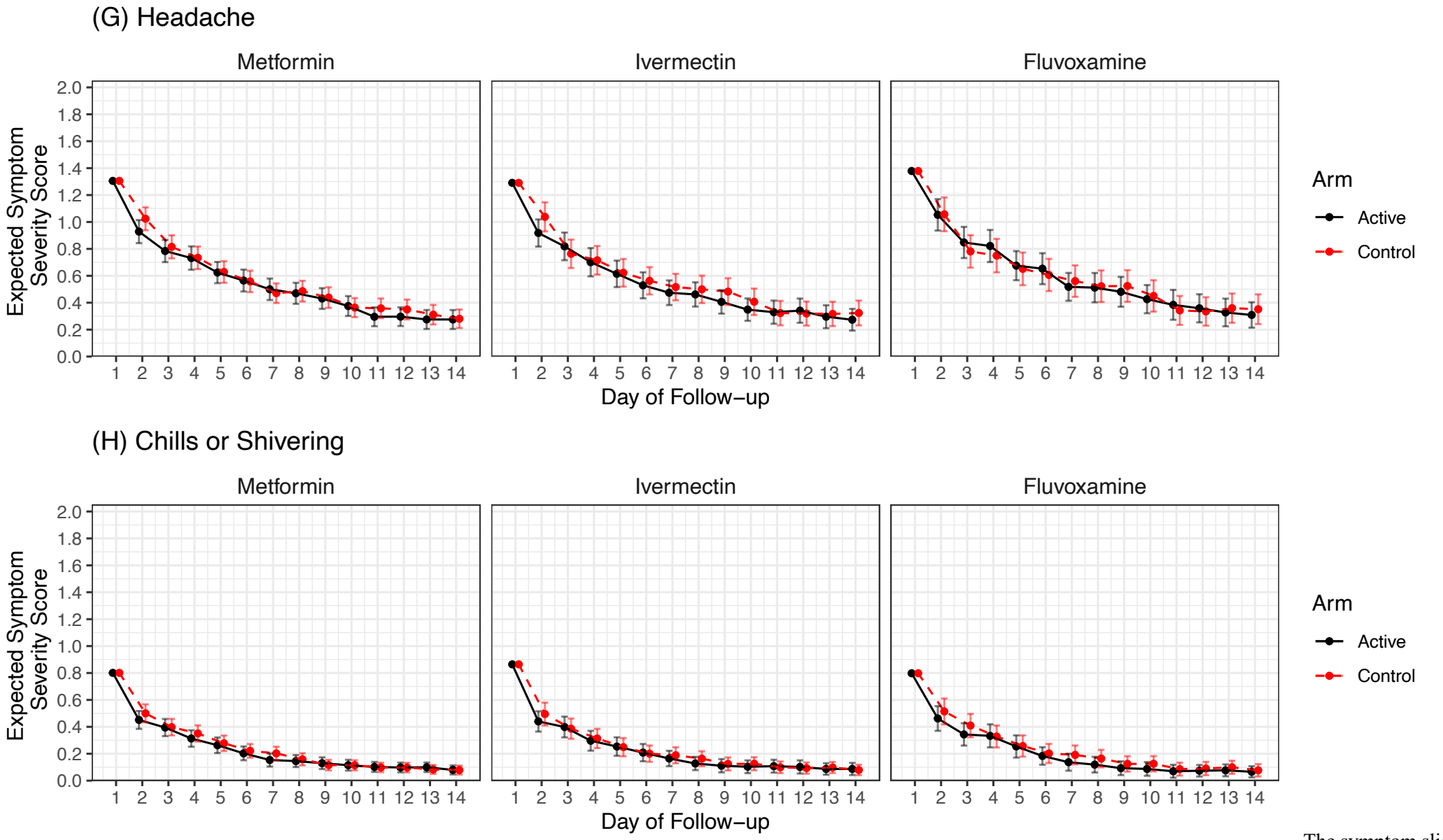
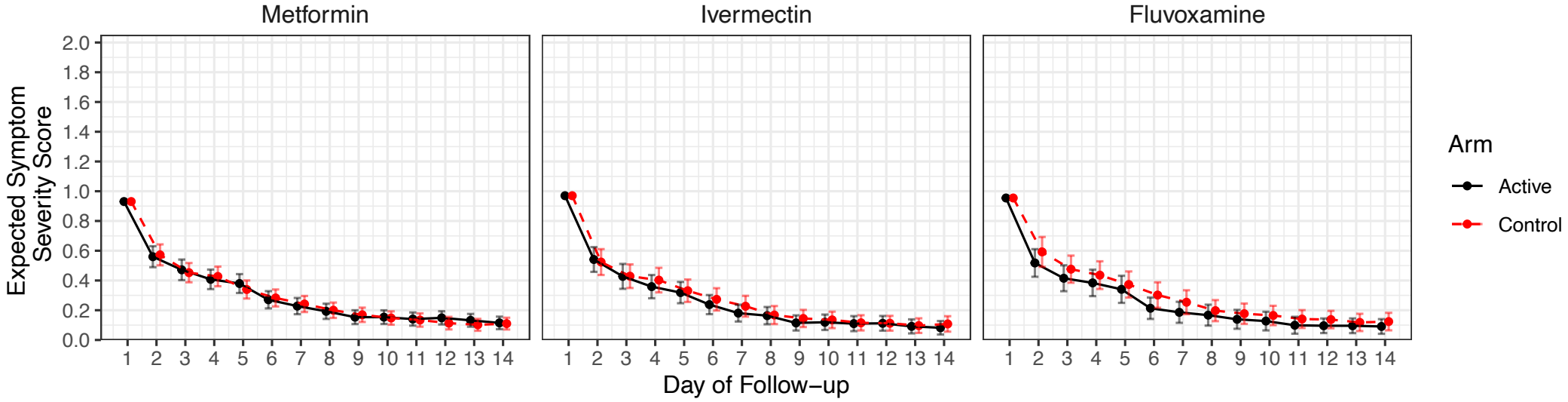
Individual Symptoms



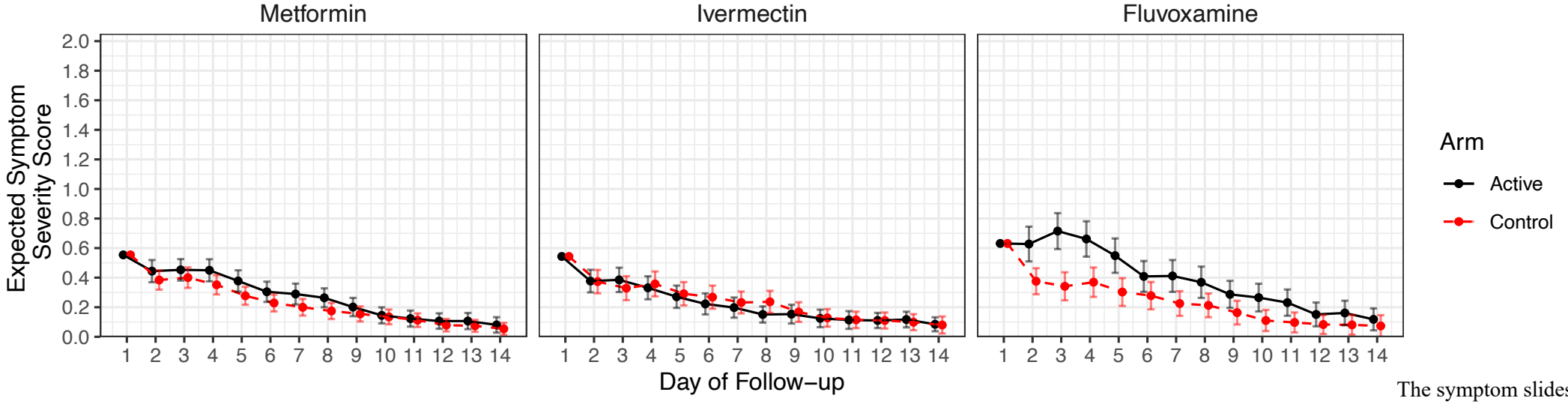
The symptom slides have been updated after the live recording was made. No other slides were updated.

Individual Symptoms

(I) Subjective Fever



(J) Nausea



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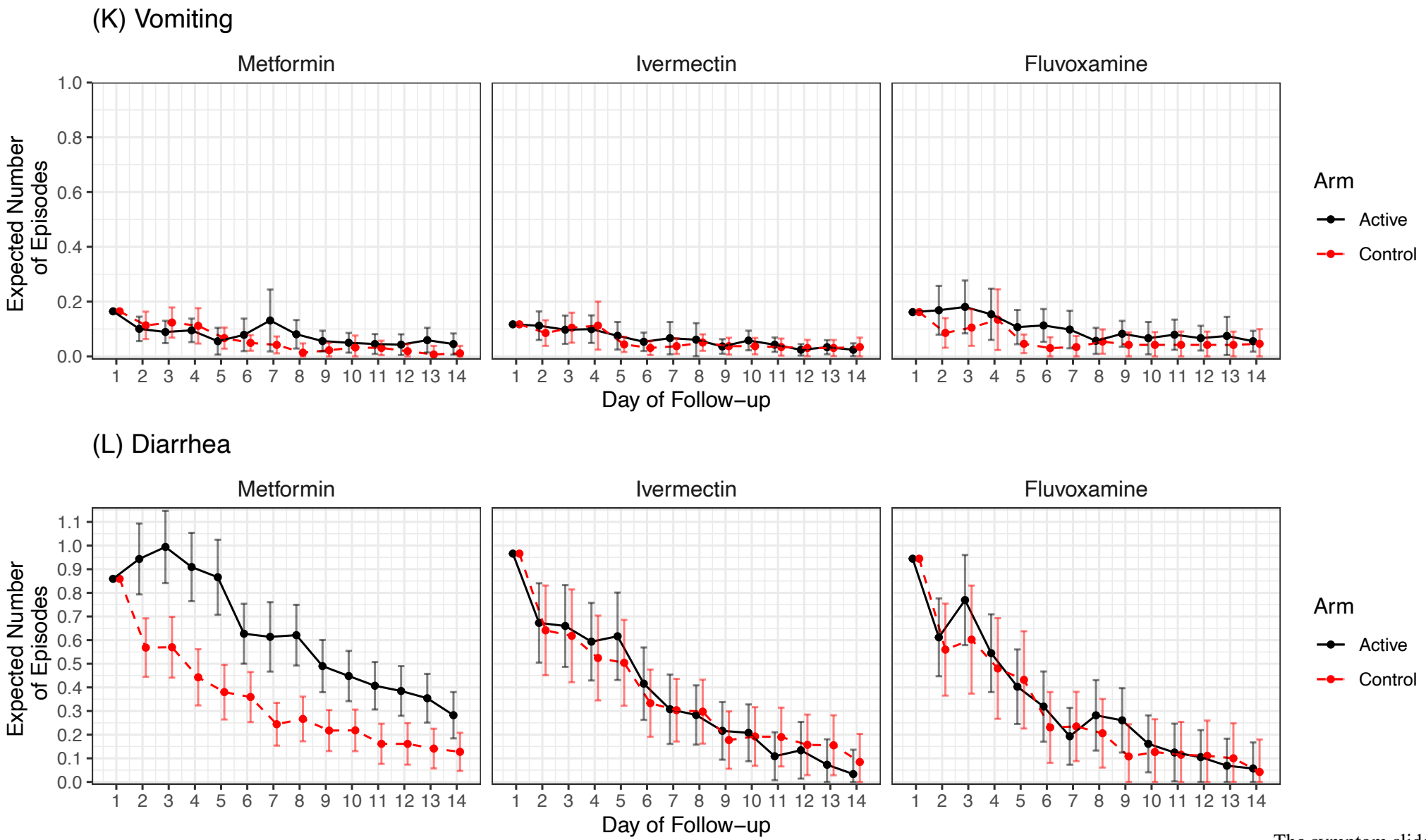
Individual Symptoms



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Individual Symptoms

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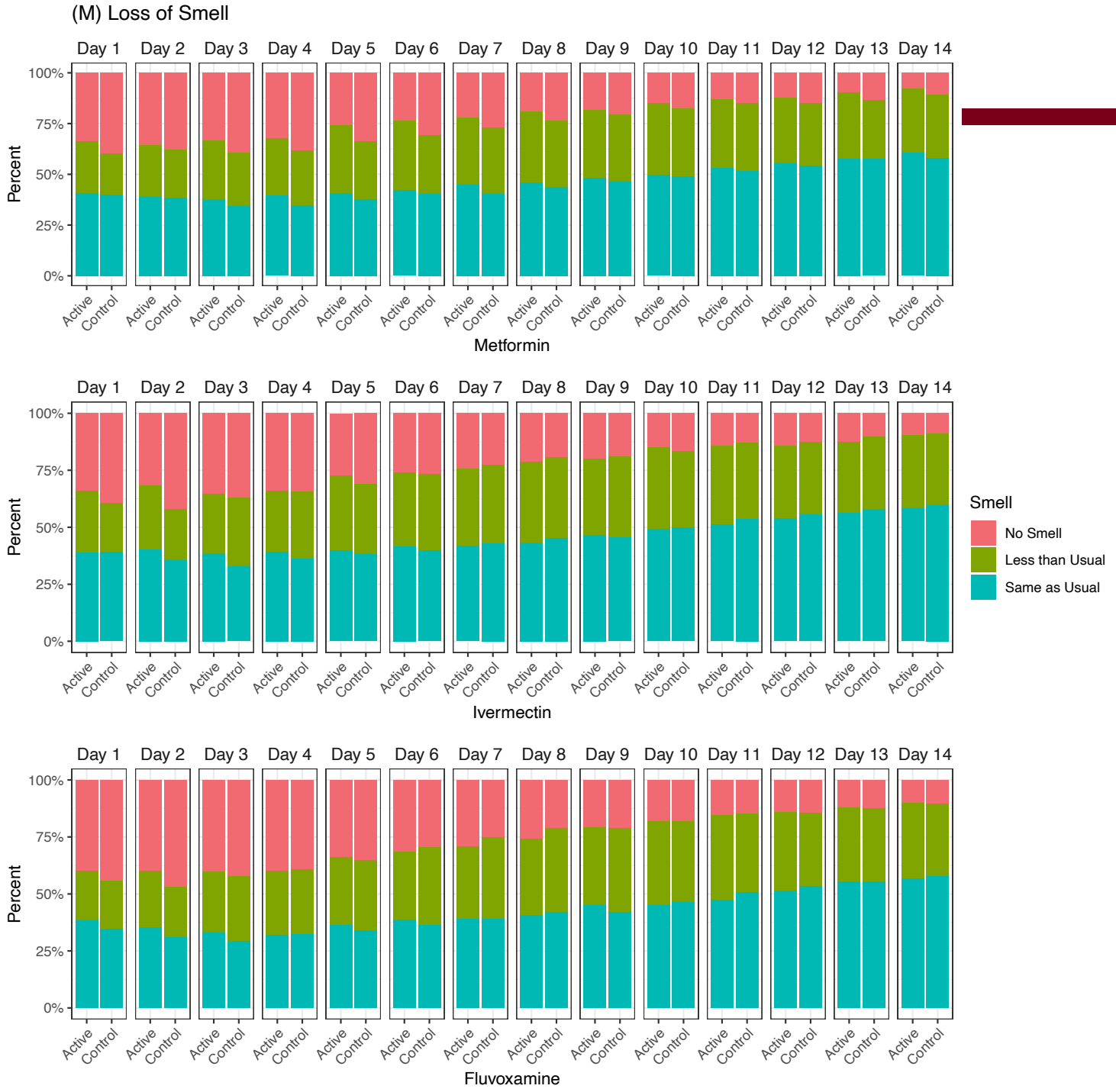

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Study Medication Adherence

Adherence	Overall N = 1,323	Metformin N = 284	Metformin+ Ivermectin N = 204	Metformin+ Fluvoxamine N = 175	Ivermectin N = 206	Fluvoxamine N = 159	Placebo N = 295
70-100%	1,015 (77)	208 (73)	165 (81)	116 (66)	175 (85)	121 (76)	230 (78)
35-70%	102 (7.7)	20 (7.0)	20 (9.8)	17 (9.7)	11 (5.3)	16 (10)	18 (6.1)
0-35%	139 (11)	36 (13)	9 (4.4)	33 (19)	14 (6.8)	16 (10)	31 (11)
Missing Adherence	67 (5.1)	20 (7.0)	10 (4.9)	9 (5.1)	6 (2.9)	6 (3.8)	16 (5.4)

Values are n (%)

Additional Open-label Therapeutics Used after Randomization

n(%)	Overall, mITT n = 1,323	Metformin n = 284	Metformin+ Ivermectin n = 204	Metformin+ Fluvoxamine n = 175	Ivermectin n = 206	Fluvoxamine n = 159	Placebo n = 295
Monoclonal Antibody	55 (4.2)	13 (4.6)	9 (4.4)	8 (4.6)	6 (2.9)	7 (4.4)	12 (4.1)
Ivermectin	8 (0.6)	3 (1.1)	1 (0.5)	0 (0)	2 (1.0)	0 (0)	2 (0.7)
Inhaler	30 (2.3)	8 (2.8)	4 (2.0)	3 (1.7)	2 (1.0)	2 (1.3)	11 (3.7)
Anti-coagulants	19 (1.4)	7 (2.5)	1 (0.5)	1 (0.6)	1 (0.5)	4 (2.5)	5 (1.7)
Outpatient Steroids	20 (1.5)	3 (1.1)	5 (2.5)	2 (1.1)	2 (1.0)	5 (3.1)	3 (1.0)
Other*	165 (12)	36 (13)	31 (15)	11 (6.3)	27 (13)	20 (13)	40 (14)
Sertraline †	35 (2.6)	12 (4.2)	2 (1.0)	3 (1.7)	5 (2.4)	2 (1.3)	11 (3.7)

* Other includes a wide variety of non-FDA EUA therapies.
† Sertraline is an antagonist to sigma-1 receptors, whereas fluvoxamine is an agonist.

Time constraints of Clinical Trials

Potential real-world use of these meds:

Step	Approximate Days
Symptoms	0
Positive test	0 to 3
Call Doctor	0 to 1
Get outpatient med (generic, available)	0 to 1
Start outpatient med (generic, available)	0 to 5 from symptom onset

Affected by:

Access to test	
Access to resources	
Patient bandwidth	Research team bandwidth
Patient bandwidth	
Research team bandwidth + Patient bandwidth	
Properties of remote trials: - pharmacy hours, supply - weather, distance, delivery	

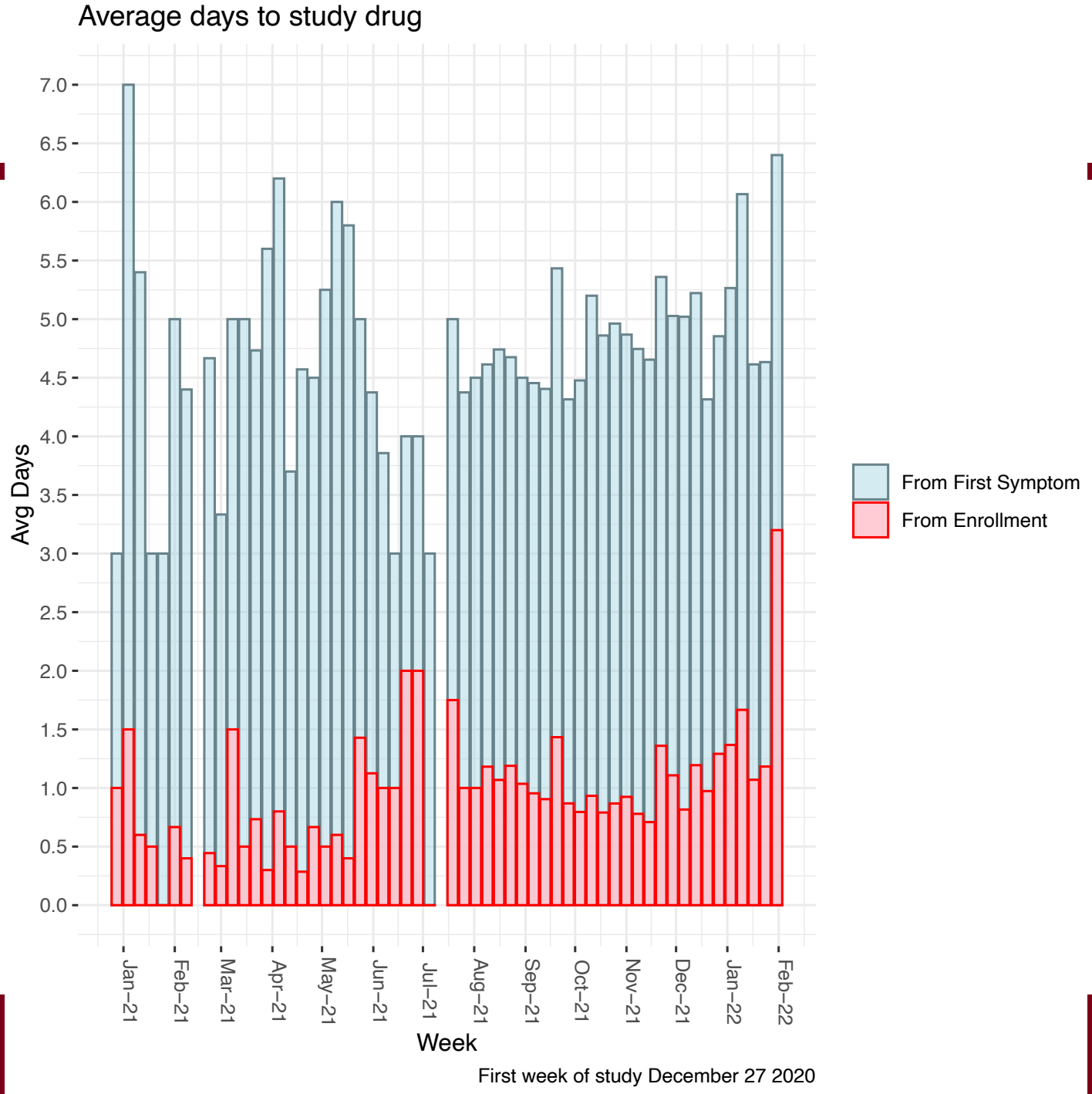
Constraints within a remote clinical trial

Step	Approximate Days
Symptoms	0
Positive test	0 to 3
Find patient / Find study	0 to 1
Reach out to patient	0 to 1
Get response from patient	0 to 1
Consent conversation	0 to 1
Dispense, then Ship to patient	0 to 4
Start study medication	0 to 11 from symptom onset

Delivered medication within 1 day of consenting

This trial was focused on *preventing* severe Covid-19, not treatment of Covid or of symptoms.

So early study drug initiation seemed to be **key** to increase the chances of differentiating between active med and placebo



Pre-packing allows faster delivery of IP

Primary outcome was prevention of severe disease, starting study drug ASAP was a major goal.

- The pharmacy needed all enrollments by 3:30pm to dispense same-day

- Study team distributed to courier or FedEx
  - 8:15pm on weekdays

  - FedEx same-day shipping on weekends
    - Courier delivers the box to a commercial airline flight with a courier to pick it up at destination
  - This is a new, increased cost of trial

Pre-packing was challenging with weight categories

Daily Drug Supply

	<162.8 lbs	162.8 - 193.5 lbs	193.6 - 233.1 lbs	233.2 - 272.7 lbs	272.8 - 352.6 lbs	352.7+ lbs	Pregnant
University of Minnesota	18	19	19	19	19	19	34
Optum - New West Physicians Network	10	18	18	18	18	10	8
Optum - American Health Network	13	32	32	32	32	13	15
Northwestern University	34	34	19	21	33	9	16
Colorado University	12	35	35	35	35	12	15
UCLA/ LA County	11	35	35	35	35	11	16

Overview

- Overview of current COVID-OUT Trial
- Brief Background
  - 3 distinct treatments
  - Design, Study population
- Statistical Considerations
  - DSMB Reviews and stopping criteria
  - Randomization
- Results
- Limitations
- Future Directions

Limitations

- Primary outcome
  - The protocol could have potentially mitigated some of the sources of bias with home oximeter use
- Generalizability
- Time to study drug initiation still longer than real life
- Definition of intention to treat

Potential Future Directions

1. Funding for lab assays:
    - Analyze the Day 1, 5, and 10 viral samples
        - Human virome
    - Ongoing shedding of virus in stool samples reduced by meds
2. Long Covid surveys
    - New onset diabetes
    - Incidence of re-infection
        - (metformin associated with improved T cell immunity)
3. Pediatric trial
4. Repeat COVID-OUT trial powered for ED visit/hospitalization/death as primary outcome?

Negative Clinical Trials

REVIEW ARTICLE THE CHANGING FACE OF CLINICAL TRIALS

The Primary Outcome Fails — What Next?

Stuart J. Pocock, Ph.D., and Gregg W. Stone, M.D.

Table 1. Questions to Ask When the Primary Outcome Fails.

Is there some indication of potential benefit?
Was the trial underpowered? ★
Was the primary outcome appropriate (or accurately defined)? ★
Was the population appropriate?
Was the treatment regimen appropriate?
Were there deficiencies in trial conduct?
Is a claim of noninferiority of value?
Do subgroup findings elicit positive signals? ★
Do secondary outcomes reveal positive findings? ★
Can alternative analyses help?
Does more positive external evidence exist?
Is there a strong biologic rationale that favors the treatment? ★

- "An unreasonable yet widespread practice is the labeling of all randomized trials as either positive or negative on the basis of whether the P value for the primary outcome is less than 0.05. This view is overly simplistic..
- Moreover, the interpretation of any trial should depend on the totality of the evidence (i.e., the primary, secondary, and safety outcomes), not just a single end point."

https://www.nejm.org/doi/full/10.1056/NEJMra1510064?query=featured_clinical-trials

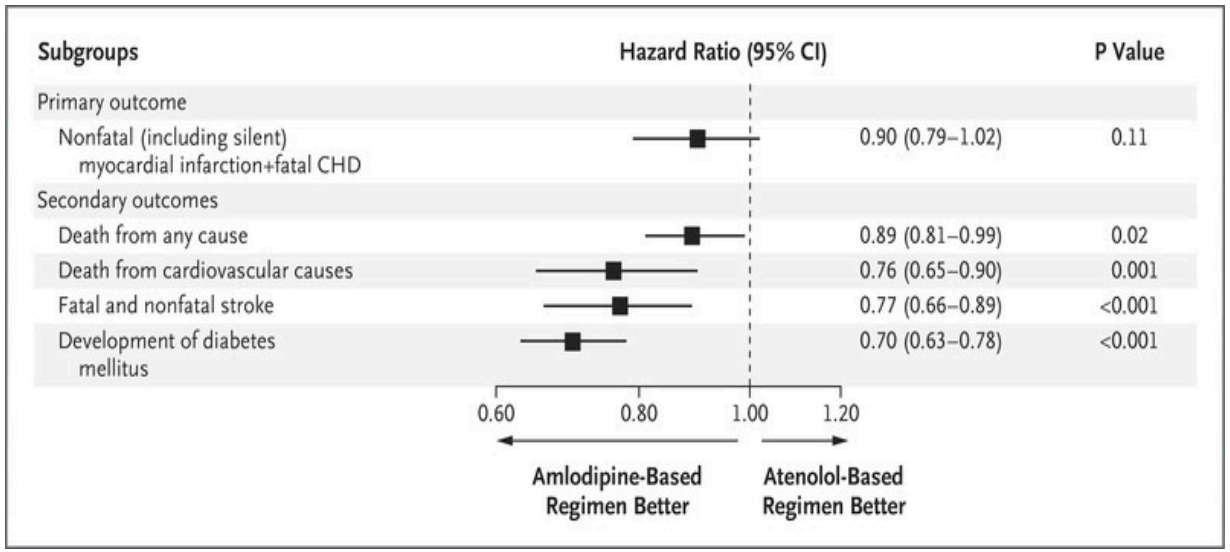
Negative Clinical Trials

REVIEW ARTICLE THE CHANGING FACE OF CLINICAL TRIALS

The Primary Outcome Fails — What Next?

Stuart J. Pocock, Ph.D., and Gregg W. Stone, M.D.

- "If the primary outcome is negative, positive findings for secondary outcomes are usually considered to be hypothesis-generating.
- Certainly, regulatory approval of a new drug is unlikely to follow.
- However, in some instances, secondary findings are compelling enough to affect guidelines and practice."



https://www.nejm.org/doi/full/10.1056/NEJMra1510064?query=featured_clinical-trials

Summary

- This is a negative trial
- Some aspects were a success
  - We delivered study medication nation-wide within 1 day of consent
- A pre-specified secondary analysis of the primary outcome indicates a substantial reduction in ED visits, hospitalizations, death from Covid-19 with metformin
- Metformin has a history of anti-viral properties
  - Is being studied in TB, Dengue, and other infectious disease studies
- Metformin has a history of anti-inflammatory properties
  - Sabizabulin is an oral, novel microtubule disruptor that has dual antiviral and anti-inflammatory activities in preclinical models
- Metformin is safe, has few contra-indications or interactions, and requires no monitoring for >12 months

Thank you

- Many people contributed to making this trial possible

Many helped with the study design, approach, search for funding

Chris Tignanelli, MD MS

Natural language processing,
Covid clinical trials
Learning Health System Scholar

Michelle Biros, MD

Clinical trials

David Odde, PhD

Biophysical modeling

David Boulware, MD

Infectious disease

Nancy Sherwood, PhD

Epidemiology

Michael Puskarich, MD MS

Covid Clinical trials

Nichole Klatt, PhD

Microbiome

Thomas Murray, PhD

Clinical trial design and analysis

John Buse, UNC

Diabetes pharmacotherapy,
clinical trials

Patient Advisory Board helped design the protocol

I formed patient advisory board as part of my Learning Health System training

- To guide research around obesity

They discussed this trial with me from the beginning

They reviewed every aspect of patient-facing material, consent, protocol

- Gave important feedback on recruitment and consent approach

Collaborative input from many on protocol for IND

PI	Expertise	Site
Leonardo Tamariz, MD, MPH	General Internal Medicine (GIM)	Univ of Miami, Chen Senior Medical Ctr clinic network, TAME PI
Ana Palacio, MD, MPH	GIM, Cardiovascular outcomes	University of Miami VA, Miami (TAME Site PI)
Jeanne Clark, MD, MPH	GIM, Obesity and Diabetes	Division Director and Look AHEAD PI, Johns Hopkins
Nia Mitchell, MD	GIM, Obesity research	Duke University Medical School
Jacinda Nicklas, MD, MSPH	GIM, Obesity research	University of Colorado, Denver
Eric Anderson, MD	Emergency Medicine	Alameda Cty Medical Center, Oakland, CA, UCSF Medical School
David Liebovitz, MD	GIM, Outpatient research	Northwestern Medicine, Chicago, IL
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Ildiko Lingvay, MD	Endocrinology, Diabetes pharmacotherapy	UT Southwestern
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Carlos Chaccour, MD

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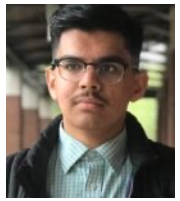
UCLA Olive View / LA County, Hrishikesh Belani, MD

University of Colorado, Denver, Jacinda Nicklas, MD

Vanderbilt (Pregnant women only),
Jennifer Thompson, MD and Anup Challa



Emory, Blake Anderson, MD

HEALTH FAIRVIEW

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CPOM: Cameron Naughton, Juanita Jenson, Lucas Simmons

GIM: Kate Brekke, Jill Charles, HR

CTSI: Casey Dahl, Study Monitor

SPA: contracts

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Spencer Erickson
Nandini Avula
Carissa Dock

Undergrad Students:

Hanna Saveraide
Faith Fairborn

Volunteers:

Folding boxes
Taping boxes

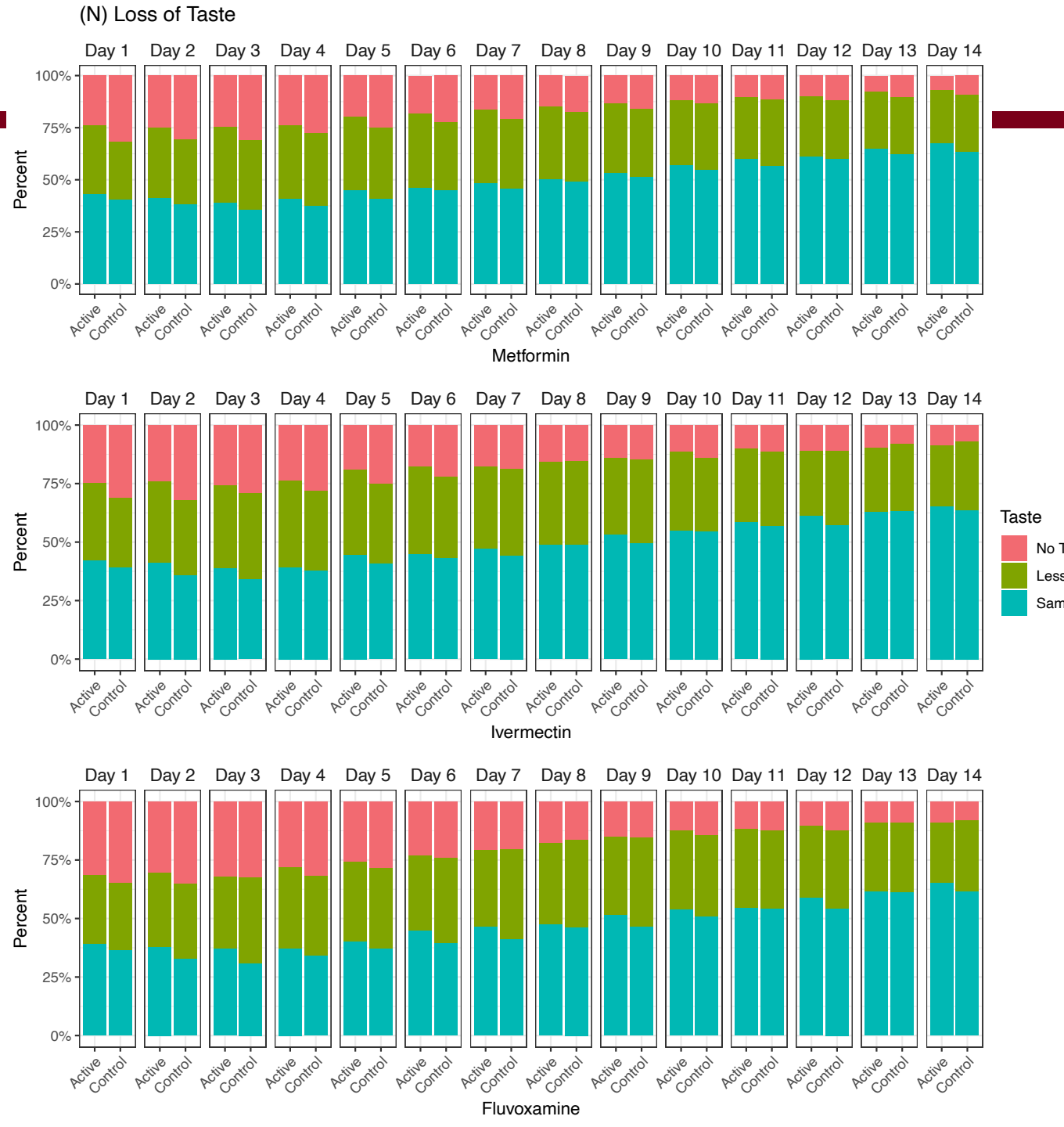
Thank you

- Appreciate any questions, discussion

Extra slides

Individual Symptoms

The symptom slides have been updated after the live recording was made. No other slides were updated.



Metformin data

Pre-specified analyses all in one visual:

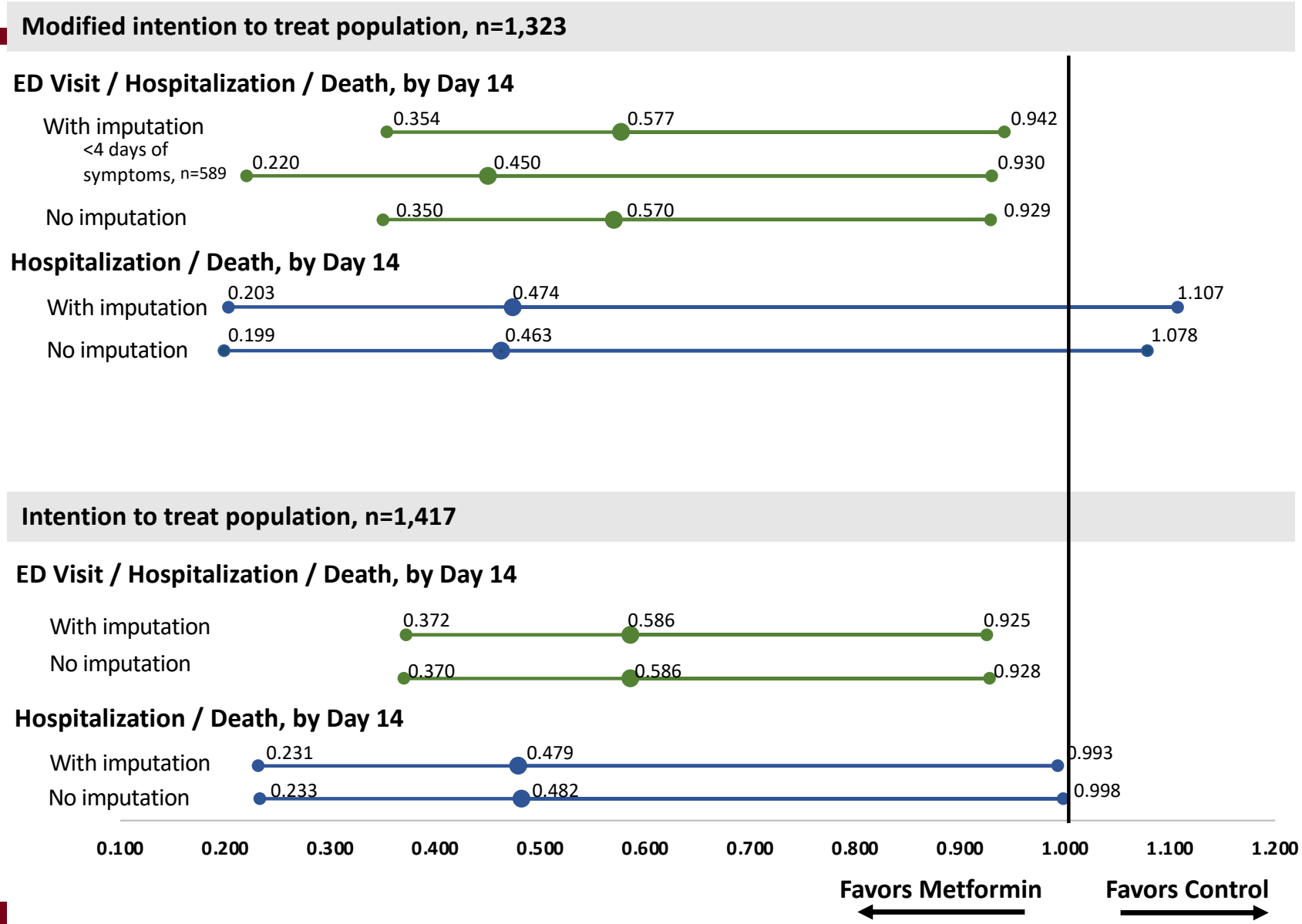


Figure S1A.

Effect of metformin vs. control for the primary outcome, overall and by subgroups.

Subgroup	Metformin	Control	Adjusted Odds Ratio (95% CI)
	n events / n (n missing)		
All Participants	154/652 (11)	179/653 (7)	0.84 (0.66 to 1.09)
Sex			
Female	78/352 (7)	107/378 (4)	0.73 (0.52 to 1.02)
Male	76/300 (4)	72/275 (3)	1.04 (0.71 to 1.52)
Body Mass Index (BMI)			
< 30 kg/m^2	80/344 (3)	78/326 (4)	1.01 (0.70 to 1.45)
≥ 30 kg/m^2	74/308 (8)	101/327 (3)	0.71 (0.50 to 1.01)
Symptom onset to drug initiation			
< 4 days	63/290 (6)	73/298 (5)	0.90 (0.61 to 1.32)
≥ 4 days	85/352 (5)	103/337 (2)	0.74 (0.53 to 1.04)
Unknown	6/10 (0)	3/18 (0)	
Age			
< 45 years	53/303 (5)	61/309 (4)	0.93 (0.61 to 1.42)
≥ 45 years	101/349 (6)	118/344 (3)	0.78 (0.56 to 1.08)
Covid−19 Variant Time Period			
Alpha	27/78 (1)	35/80 (0)	0.66 (0.34 to 1.28)
Delta	101/434 (6)	113/426 (5)	0.87 (0.63 to 1.19)
Omicron	26/140 (4)	31/147 (2)	0.87 (0.48 to 1.57)
Vaccinated, primary series			
No	87/293 (8)	112/322 (5)	0.80 (0.57 to 1.12)
Yes	67/357 (2)	67/329 (2)	0.90 (0.62 to 1.32)
Unknown	0/2 (1)	0/2 (0)	
Preganant			
Not Pregnant	151/630 (10)	175/630 (6)	0.84 (0.65 to 1.09)
Pregnant	3/22 (1)	4/23 (1)	0.77 (0.14 to 4.21)

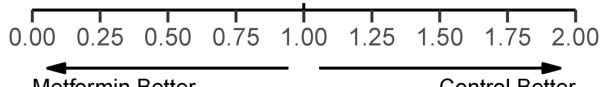


Figure S1B.

Effect of ivermectin vs. control for the primary outcome, overall and by subgroups.

Subgroup	Ivermectin	Control	Adjusted Odds Ratio (95% CI)
	n events /	n (n missing)	
All Participants	105/407 (3)	96/391 (7)	1.05 (0.76 to 1.45)
Sex			
Female	54/214 (2)	56/224 (2)	1.01 (0.65 to 1.55)
Male	51/193 (1)	40/167 (5)	1.12 (0.69 to 1.84)
Body Mass Index (BMI)			
< 30 kg/m^2	52/215 (1)	45/206 (4)	1.12 (0.71 to 1.78)
≥ 30 kg/m^2	53/192 (2)	51/185 (3)	0.98 (0.62 to 1.55)
Symptom onset to drug initiation			
< 4 days	46/198 (2)	41/182 (4)	0.99 (0.61 to 1.62)
≥ 4 days	58/205 (1)	53/202 (3)	1.10 (0.70 to 1.71)
Unknown	1/4 (0)	2/7 (0)	
Age			
< 45 years	33/176 (2)	40/187 (2)	0.80 (0.47 to 1.36)
≥ 45 years	72/231 (1)	56/204 (5)	1.17 (0.77 to 1.78)
Covid−19 Variant TIme Period			
Alpha	5/11 (0)	4/11 (0)	1.20 (0.14 to 9.89)
Delta	69/276 (2)	70/270 (5)	0.92 (0.62 to 1.37)
Omicron	31/120 (1)	22/110 (2)	1.43 (0.76 to 2.67)
Vaccinated, primary series			
No	62/184 (3)	50/166 (4)	1.16 (0.74 to 1.82)
Yes	43/222 (0)	46/224 (3)	0.93 (0.59 to 1.49)
Unknown	0/1 (0)	0/1 (0)	
Dose, µg/kg)			
≤ 430	52/202 (1)	96/391 (7)	1.03 (0.69 to 1.52)
> 430	53/205 (2)	96/391 (7)	1.07 (0.72 to 1.58)

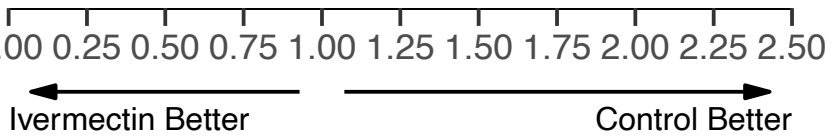
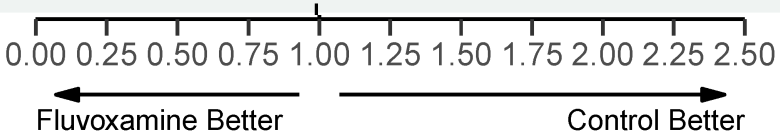


Figure S1C.

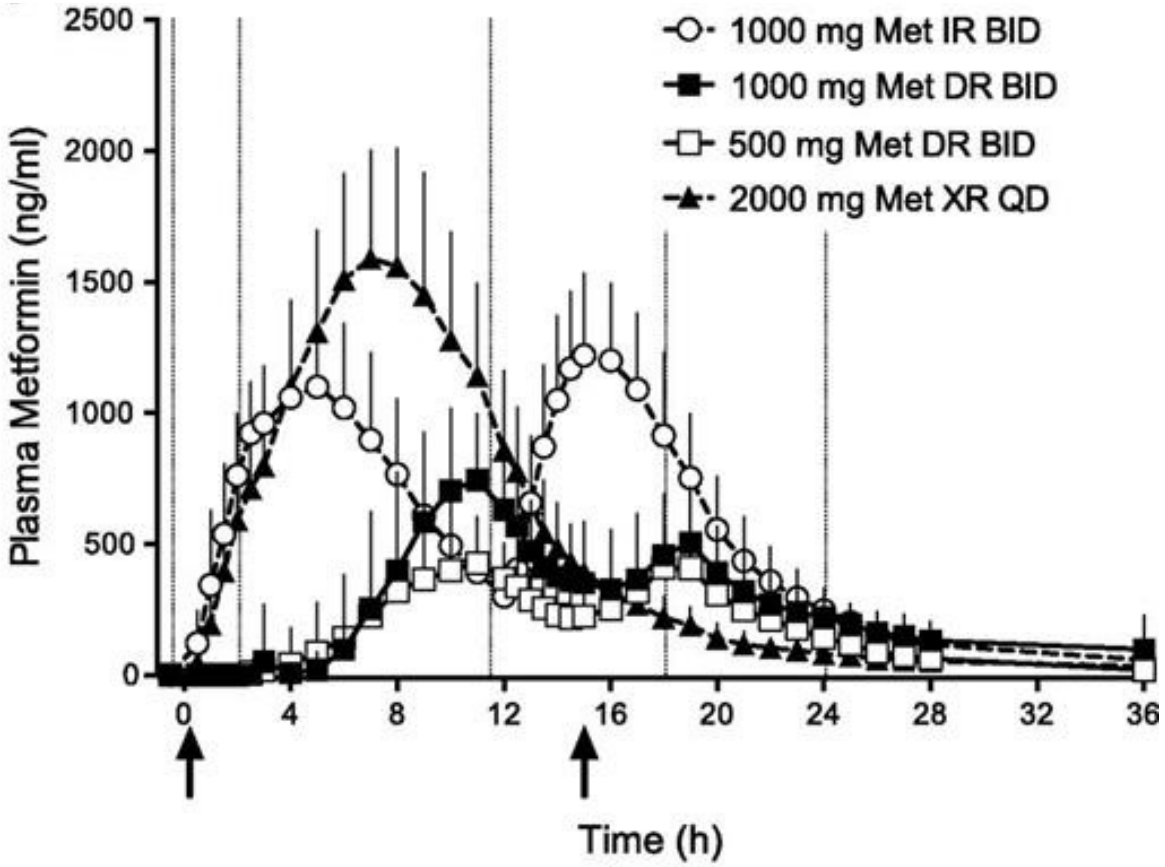
Effect of fluvoxamine vs. control for the primary outcome, overall and by subgroups.

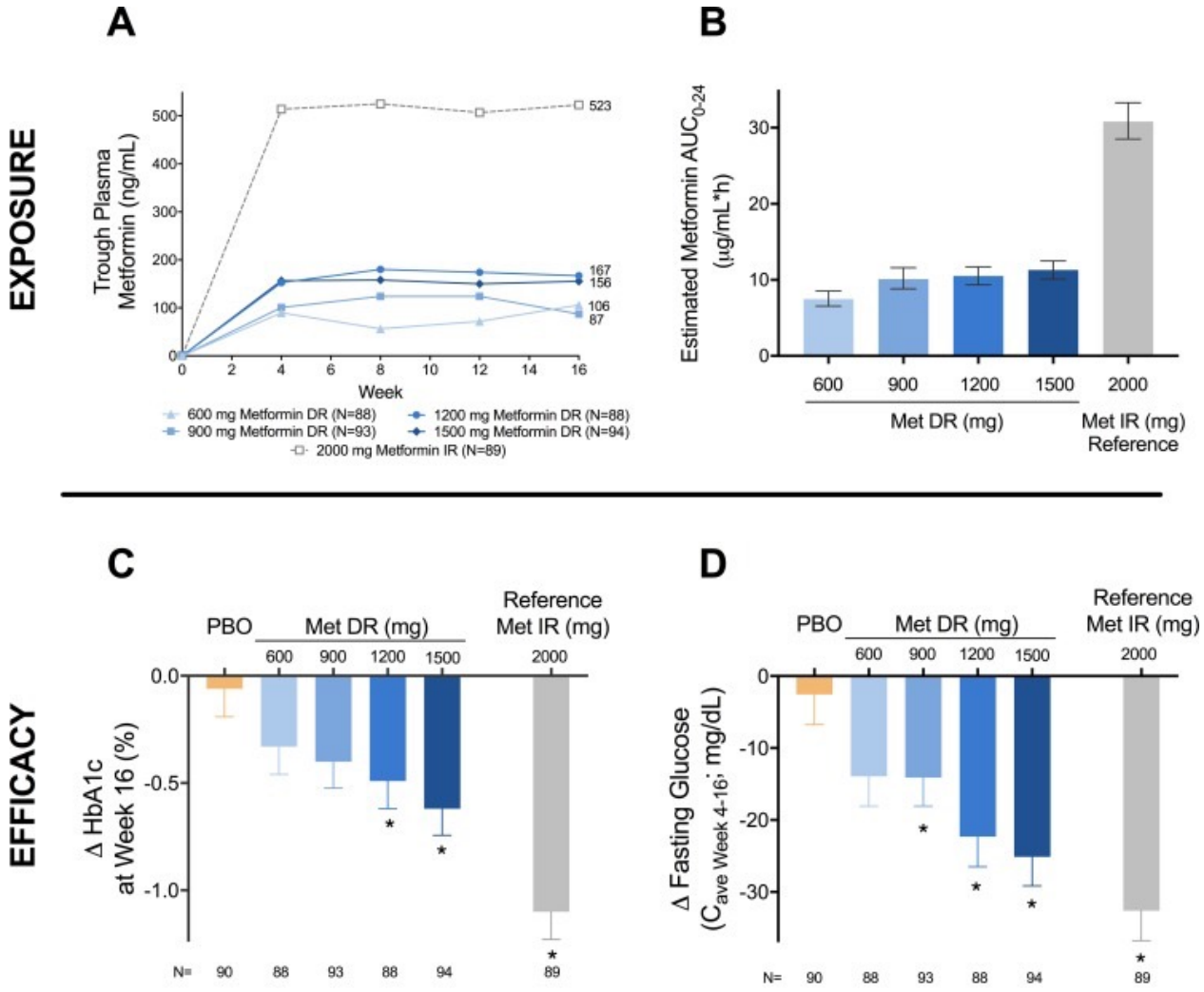
Subgroup	Fluvoxamine	Control	Adjusted Odds Ratio (95% CI)
	n events /	n (n missing)	
All Participants	79/329 (5)	80/321 (6)	0.94 (0.66 to 1.35)
Sex			
Female	42/166 (4)	49/187 (1)	0.94 (0.58 to 1.52)
Male	37/163 (1)	31/134 (5)	1.00 (0.57 to 1.76)
Body Mass Index (BMI)			
< 30 kg/m^2	39/179 (1)	37/167 (3)	0.97 (0.58 to 1.62)
≥ 30 kg/m^2	40/150 (4)	43/154 (3)	0.94 (0.56 to 1.58)
Symptom onset to drug initiation			
< 4 days	35/145 (4)	34/150 (3)	1.03 (0.59 to 1.78)
≥ 4 days	42/180 (1)	45/166 (3)	0.84 (0.51 to 1.38)
Unknown	2/4 (0)	1/5 (0)	
Age			
< 45 years	23/150 (3)	38/170 (2)	0.65 (0.36 to 1.15)
≥ 45 years	56/179 (2)	42/151 (4)	1.12 (0.69 to 1.83)
Covid−19 Variant Time Period			
Alpha	7/12 (0)	4/11 (0)	4.14 (0.42 to 40.87)
Delta	68/274 (3)	70/270 (5)	0.93 (0.63 to 1.37)
Omicron	4/43 (2)	6/40 (1)	0.58 (0.14 to 2.31)
Vaccinated, primary series			
No	43/143 (4)	44/135 (4)	0.87 (0.52 to 1.45)
Yes	36/184 (1)	36/185 (2)	1.02 (0.60 to 1.71)
Unknown	0/2 (0)	0/1 (0)	



Extra slides

IR metformin has higher systemic exposure than ER





John B. Buse, Ralph A. DeFronzo, Julio Rosenstock, Terri Kim, Colleen Burns, Sharon Skare, Alain Baron, Mark Fineman; The Primary Glucose-Lowering Effect of Metformin Resides in the Gut, Not the Circulation: Results From Short-term Pharmacokinetic and 12-Week Dose-Ranging Studies. *Diabetes Care* 1 February 2016; 39 (2): 198–205

Henry RR, Frias JP, Walsh B, et al. Improved glycemic control with minimal systemic metformin exposure: Effects of Metformin Delayed-Release (Metformin DR) targeting the lower bowel over 16 weeks in a randomized trial in subjects with type 2 diabetes. *PloS one.* 2018;13(9):e0203946.

Previous trial with evidence of benefit

Numbers in supplement tables (2nd supplement document):

ED Visits		**ITT**			**Per protocol**		**% in Per**
	N (patients)	N (events)	%	N (patients)	N (events)	%	**Protocol**
Metformin	216	8	3.70%	171	7	4.10	0.79
Placebo	205	11	5.37%	181	10	5.50	0.88
All	421	19	4.50	352	17	4.80	0.84
		OR	0.67	OR	0.73		
		RR	0.69	RR	0.75		
		ARR	1.66%	ARR	1.40		

Numbers in supplement tables:

Hospitalizations		**ITT**			**Per protocol**		**% in Per**
	N (patients)	N (events)	%	N (patients)	N (events)	%	**Protocol**
Metformin	215	24	11.2%	168	8	4.76%	0.78
Placebo	203	24	11.8%	179	14	7.82%	0.88
All	418	48	11.5%	347	22	6.34%	0.83
		OR	0.94	OR	0.61		
		RR	0.944	RR	0.61		
		ARR	0.66%	ARR	3.06%		

The risk of side effects increase at a dose of 2,000mg daily. 2,500 per day would likely cause side effects and discontinuation.

Henry RR, Frias JP, Walsh B, et al. Improved glycemic control with minimal systemic metformin exposure: Effects of Metformin Delayed-Release (Metformin DR) targeting the lower bowel over 16 weeks in a randomized trial in subjects with type 2 diabetes. *PloS one.* 2018;13(9):e0203946.