

COVID-OUT: From Computer Modeling to a Phase III Trial of Early Outpatient Treatment for SARS-CoV-2 Infection

NIH Collaborative Grand Rounds
October 1, 2021

Carolyn Bramante, MD, MPH
Assistant Professor, General Internal Medicine and Pediatrics, UMN
Principal Investigator, COVID-OUT

Thomas Murray, PhD
Assistant Professor, Biostatistics, UMN
Co-Investigator, COVID-OUT

Jared Huling, PhD
Assistant Professor, Biostatistics, UMN
Co-Investigator, COVID-OUT



Overview

- Snap shot of current COVID-OUT Trial
- Background of how the trial developed
 - Why - Scientific background that prompted doing the trial
 - How - Unique funding search
 - What - Initial trial design
 - Current trial design
- Statistical considerations
- Practical adaptations
 - Recruitment
 - Pre-packing IP
 - Shipping
 - Current enrollment
- Possible future directions



Disclosures

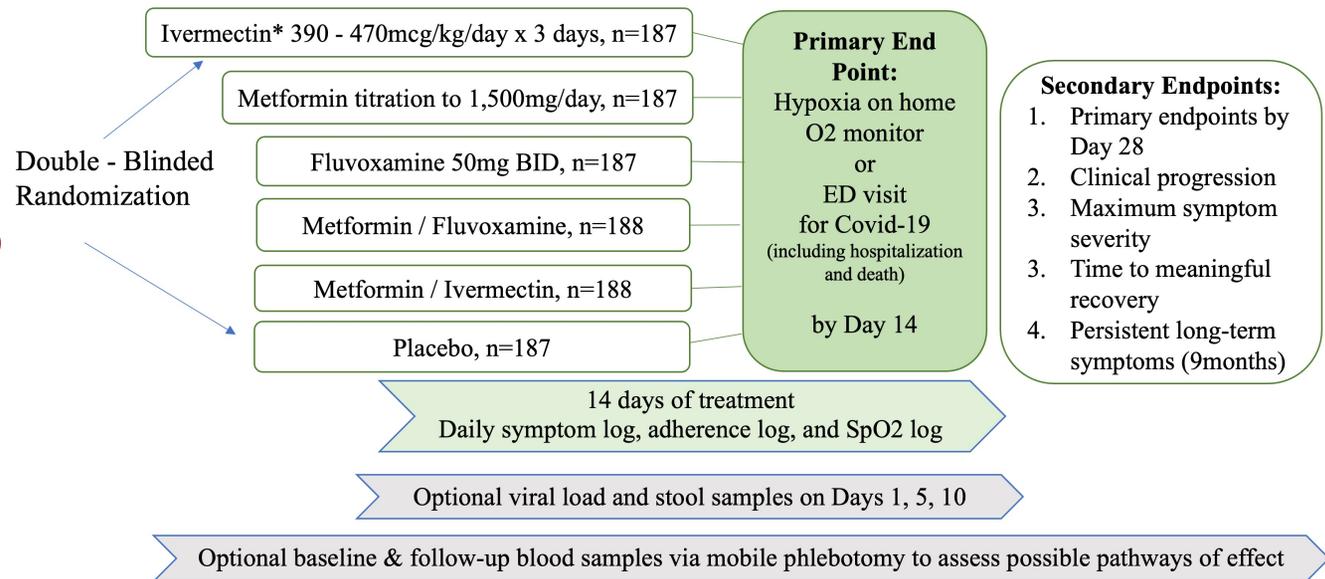
- Trial-related donations:
 - Apotex donated fluvoxamine placebo
 - Edenbridge donated ivermectin and ivermectin placebo



COVID-OUT Trial

COVID-OUT: Early Outpatient Treatment for SARS-CoV-2 infection

- Phase 3, double-blinded, matched placebo-controlled, randomized factorial design study
- Remotely delivered, multi-site clinical trial
- 541 patients enrolled (48%)
- Total Goal: 1,124

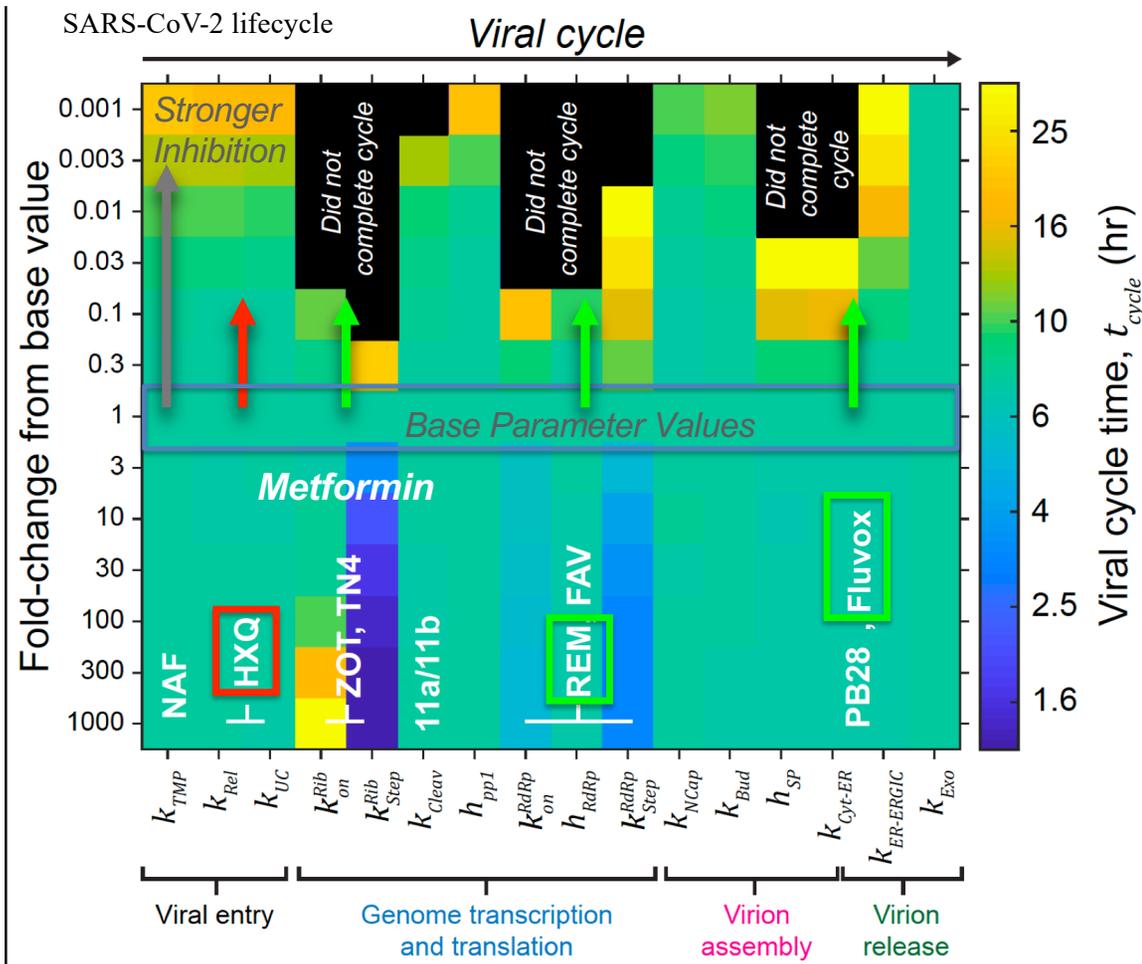


Overview

- Snap shot of current COVID-OUT Trial
- **Background of how the trial developed**
 - Why - Scientific background that prompted doing the trial
 - How - Unique funding search
 - What - Initial trial design
 - Current trial design
- Statistical considerations
- Practical adaptations
 - Recruitment
 - Pre-packing IP
 - Shipping
 - Current enrollment
- Possible future directions



Background for Trial: in silico modeling



Chris Tignanelli, MD MS
Department of Surgery, UMN

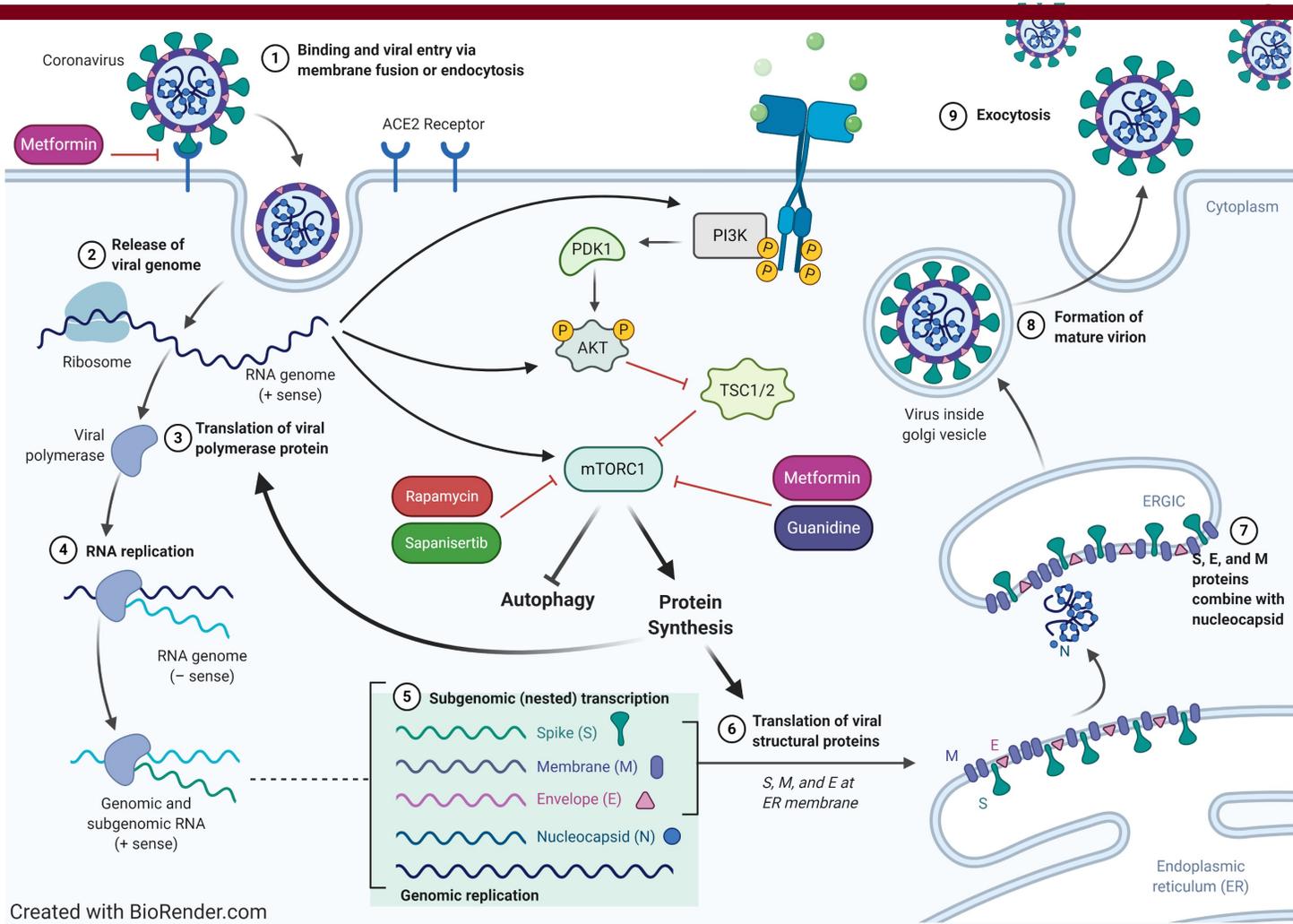


Natural language processing,
Covid clinical trials
Learning Health System Scholar

Natural Language Processing to identify medications with actions on the relevant proteins identified.

Castle *et al.*, biorxiv.org, 2020

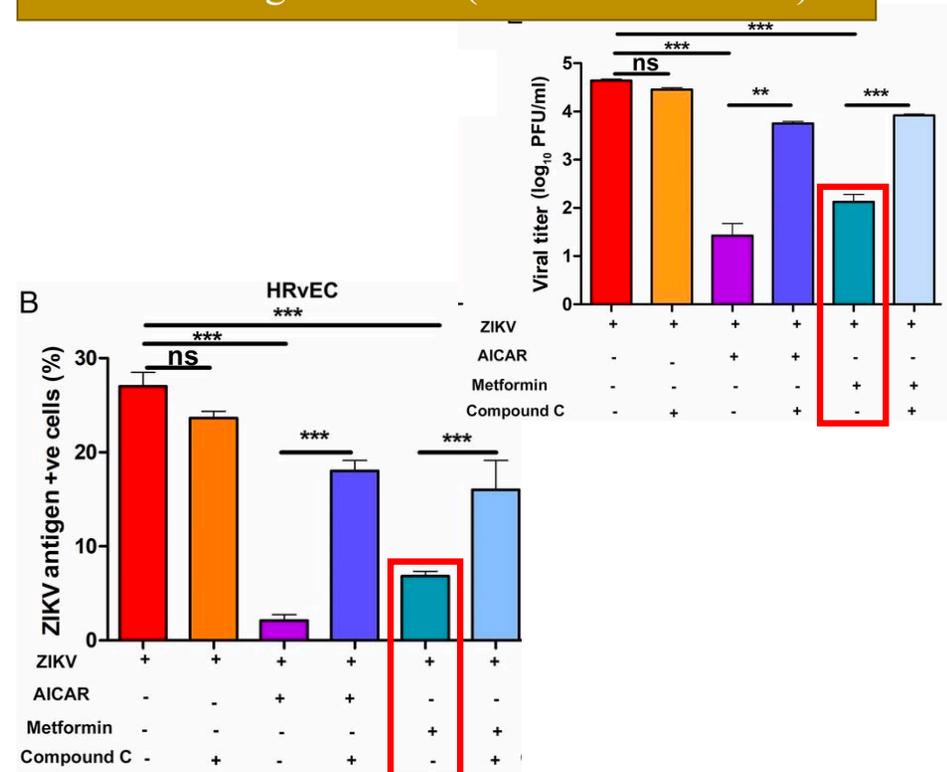
Metformin may inhibit the viral life cycle



Metformin has a history of antiviral properties

- Discovered in 1922
- 1950s, improved outcomes in influenza
 - In 200 patients, metformin (Phenformin) was associated with reduced incidence of H3N2 influenza (5.4 vs 24%, $p < 0.001$)
 - The other biguanides had safety issues
- 1990s FDA approved for diabetes
- 2000s, growing interest in anti-cancer benefits
- 2010 Interest as anti-infectious agent
 - Zika, hep C (autophagy, mTOR inhibition)
 - Was not prospectively assessed in Zika

Effective against Zika (another 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 T1DM, inhibits Hepatitis-B/C, Dengue, Zika, Ebola, HIV-1, 2017

4. Fan Cheng, et al. *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 Infect 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

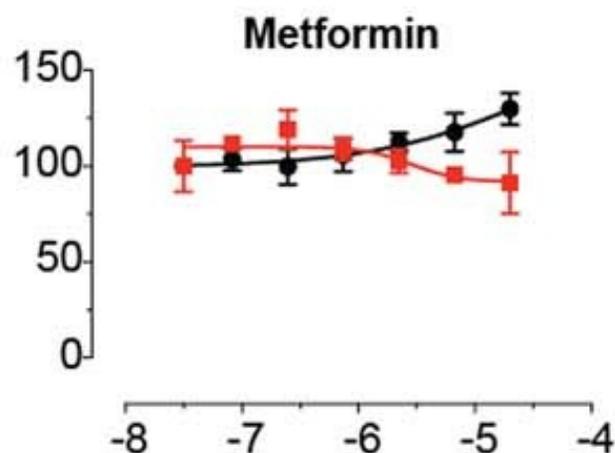
8. Babinski, 1971



In-vitro assays: decreased infection, increased cell viability

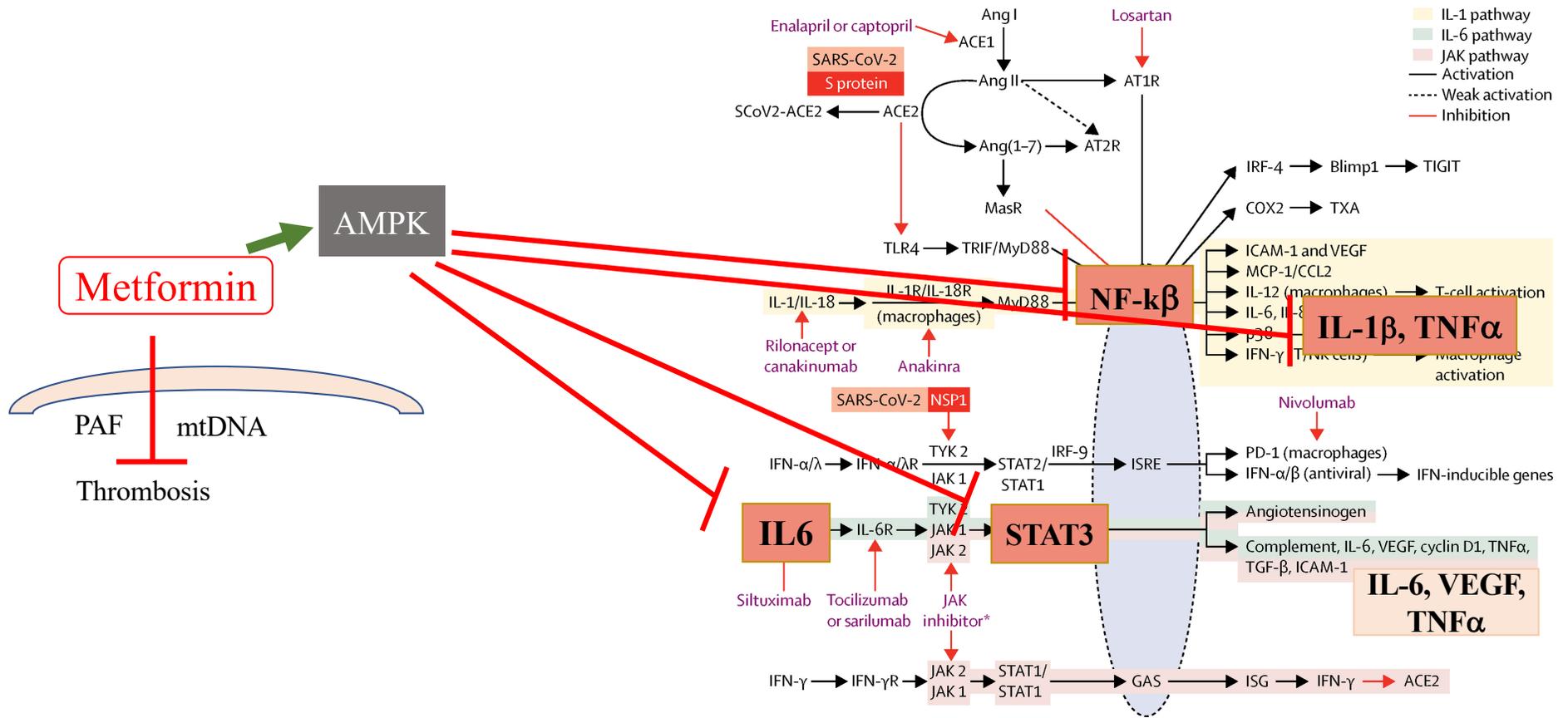
Extended Data Fig. 8: Viral growth and cytotoxicity for compounds tested in New York.

From: [A SARS-CoV-2 protein interaction map reveals targets for drug repurposing](#)



Viral growth (percentage infection; red) and cytotoxicity (black) results for compounds tested at Mount Sinai in New York. TCID₅₀ assay results (green) for zotatifin, hydroxychloroquine and PB28 are also shown. Zotatifin and midostaurin were tested in two independent experiments and data are shown in two individual panels. Data are mean \pm s.d.; $n = 3$ biologically independent samples. The full dataset is available in Supplementary Table 6.

Metformin may inhibit SARS-CoV2 induced cytokine cascade



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



UNIVERSITY OF MINNESOTA
 Driven to DiscoverSM

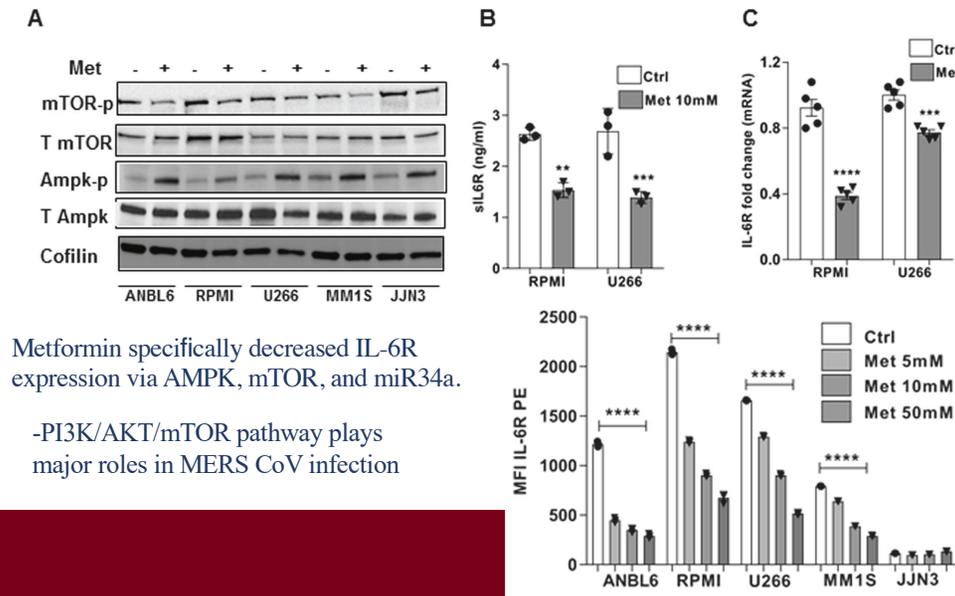
Sample of metformin's reproducible cytokine-reducing effects pre-Covid

- 1) Krysiak et al. *PMID23744427, 24399727* Humans, randomized to 12-weeks of metformin or placebo. Metformin significantly reduced CRP, TNF α , IL-6, interferon gamma. Non-significant reduction of IL-1b and monocyte chemoattractant protein-1 (all patients were already on fenofibrate, which lowers cytokines)
- 2) Andrews et al. Men with obesity & diabetes. Pts on MET had lower hsCRP & lower mRNA relative abundance of TNF α & TLR 2/4 compared to those not on MET
- 3) Hassan et al. Review of Sepsis outcomes. MET decreased acute lung injury by suppressing TLR-4 signaling, mediated via activation of AMPK which reduced LPS-induced expression of TLR4, levels of myeloid differentiation primary response protein 88 (MyD88), NF- κ B, and TNF α .
- 4) Hyun et al. Mice treated with MET for 8 weeks. MET suppresses scavenger receptors in macrophages, down-regulates TNF α , inhibits translocation of NF- κ B in macrophages

5) Mishra, Dingli. *Leukemia* 2019:

Metformin inhibits IL-6 signaling by decreasing IL-6R expression on multiple myeloma cells

269



6) Isoda et al, *Arterioscler Thromb Vasc*:

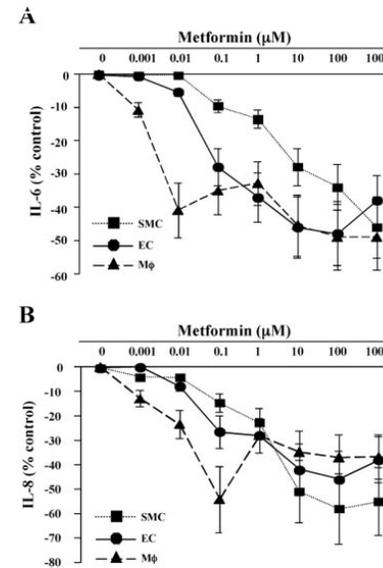


Figure 1. Metformin inhibits IL-1 β -induced cytokine production. Metformin inhibited IL-1 β -induced (1 ng/mL) IL-6 (A) and IL-8 (B) expression from smooth muscle cells (SMCs), endothelial cells (ECs), or macrophages (M ϕ s) in a concentration-dependent manner. Error bars represent SEM. N=7, 7, and 4 for SMCs, ECs, and M ϕ s, respectively. Analyses were performed twice for each donor.

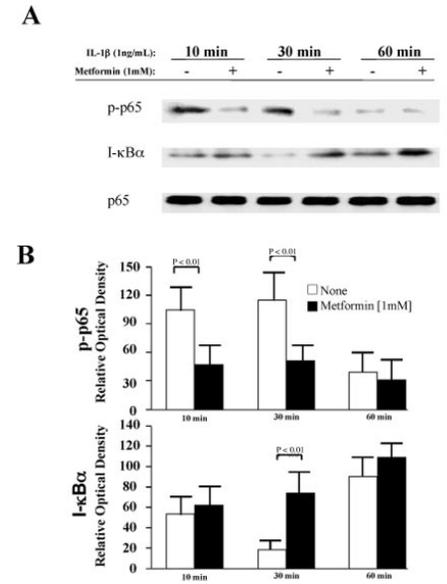


Figure 2. Metformin inhibits IL-1 β -induced NF- κ B activation and suppresses I κ B degradation in SMCs. A, SMCs were pretreated with (+) or without (-) 1 mmol/L metformin for 30 minutes before addition of IL-1 β for 10, 30, or 60 minutes. Western blot analyses were performed to detect phospho-p65 (p-p65) or I κ B protein. Total p65 is provided as a control. B, Densitometry analysis of Western blotting. Data are shown as mean \pm SEM (N=3). Analyses were performed 3 times for each donor.

Observational associations with reduced severity of Covid-19

Author	Patients Hospitalized for Covid-19	Methods	In Hospital Mortality
Luo et al.	283 adults with DM (Wuhan)	104 in metformin, 179 in no-metformin group	4x increased odds of survival OR for survival: 4.36 (1.22-15.59, p=0.02)
Cariou et al.	1,317 adults with DM (France)	Multi-center study, “Coronado Study”	41% reduced odds of death OR for death: 0.59 (0.42, 0.84)
Bramante et al. <i>Lancet Healthy Longevity, in press</i>	6,256 adults with DM2 or obesity (UMN)	Retrospective cohort analysis in collaboration with UnitedHealth Group	25% Reduced odds of death OR for in-hospital mortality 0.759 (0.601, 0.960) by propensity matching, females (ns in males)
Crouse et al. <i>Frontiers Endo.</i>	239 persons with DM2 (UAB)	Review of 25,326 adults tested for Covid-19.	67% Reduced odds of death OR for death: 0.33 (0.13-0.84; p=0.0210)

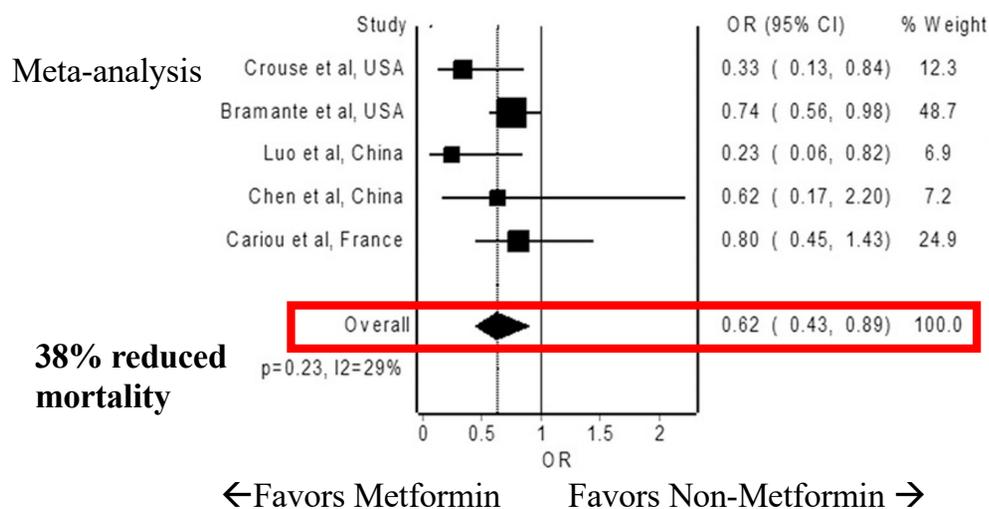


Lab evidence of potential mechanisms in Covid-19

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

Chen et al. Diabetes Care, 2020	136 adults with DM2	Retrospective cohort analysis of outpatient diabetes medications.	Metformin users had lower IL-6: 4.07 vs 11.1, $p=0.02$ 4.77 vs 11.1, $p=0.024$, in PCR confirmed cases
--	---------------------	---	---

*Kow et al,
J Med Virol*



38% reduced mortality

Forest Plot: Pooled risk of mortality in hospitalized COVID-19 patients with diabetes with or without preadmission metformin. (heterogeneity: $I^2 = 29\%$; $p = .23$). COVID-19, coronavirus disease 2019



Metformin is safe, inexpensive, and widely available

- <\$4/month
- Widely available, oral medication
- Primary care physicians are familiar with prescribing it
- Safe in children and pregnancy
- Very few contra-indications
- No follow-up needed (for 12 months or more)
- Well tolerated in most people

A clinical trial for the COVID-19 pandemic 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.*



Many helped with the study design and approach

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



UNIVERSITY OF MINNESOTA
Driven to DiscoverSM

Patient Advisory Board helped design the protocol

I formed patient advisory board as part of my KL2 and Learning Health System training

- To guide research around obesity

We meet monthly

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

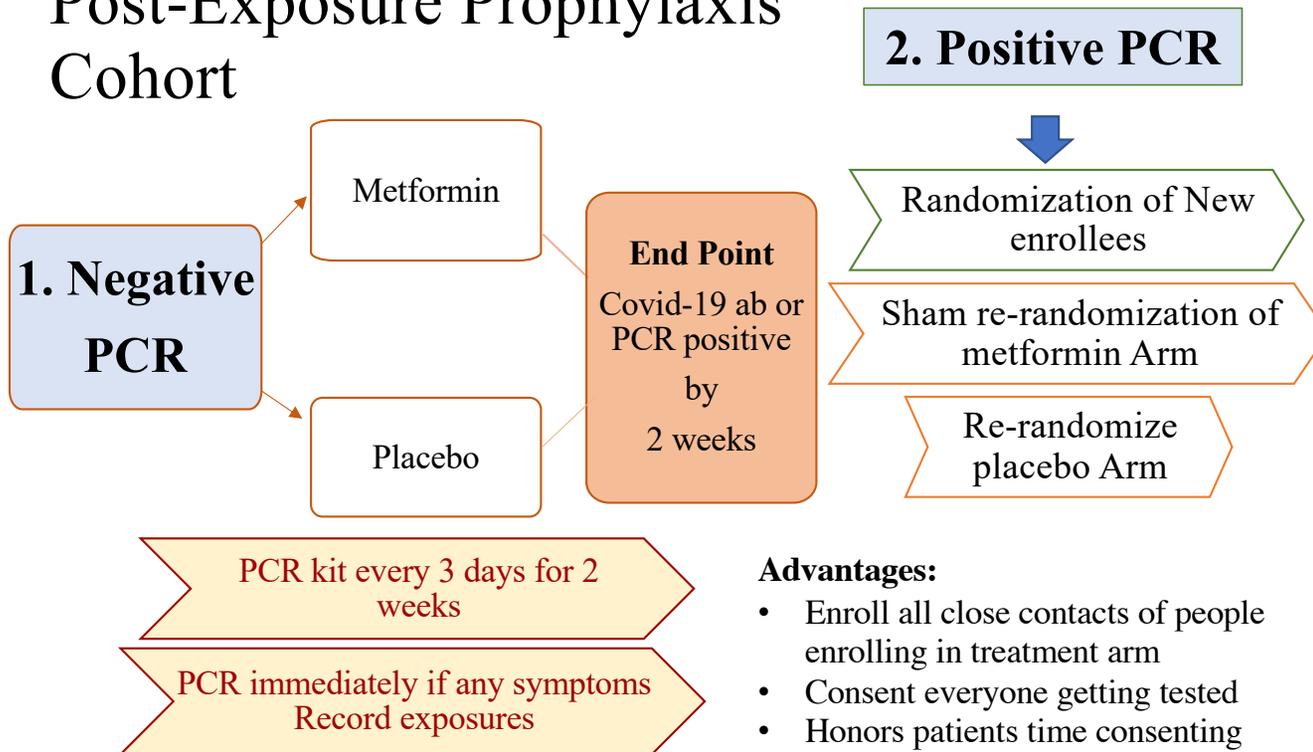


UNIVERSITY OF MINNESOTA

Driven to DiscoverSM

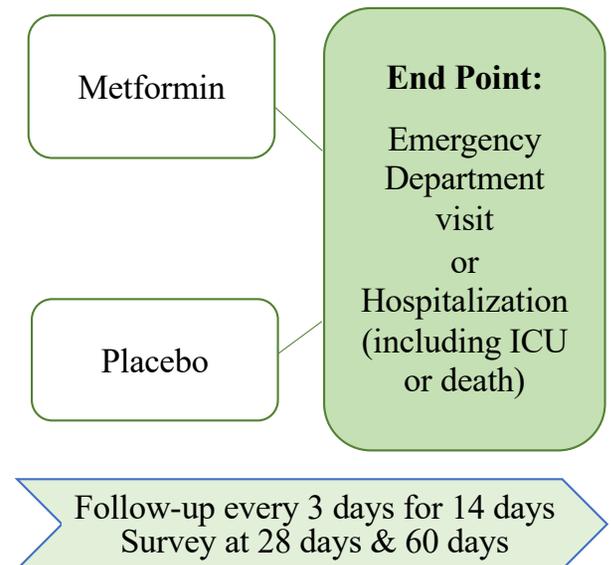
Initial Study Design: parallel PEP and treatment arms

Post-Exposure Prophylaxis Cohort



2. Positive PCR

Treatment Cohort

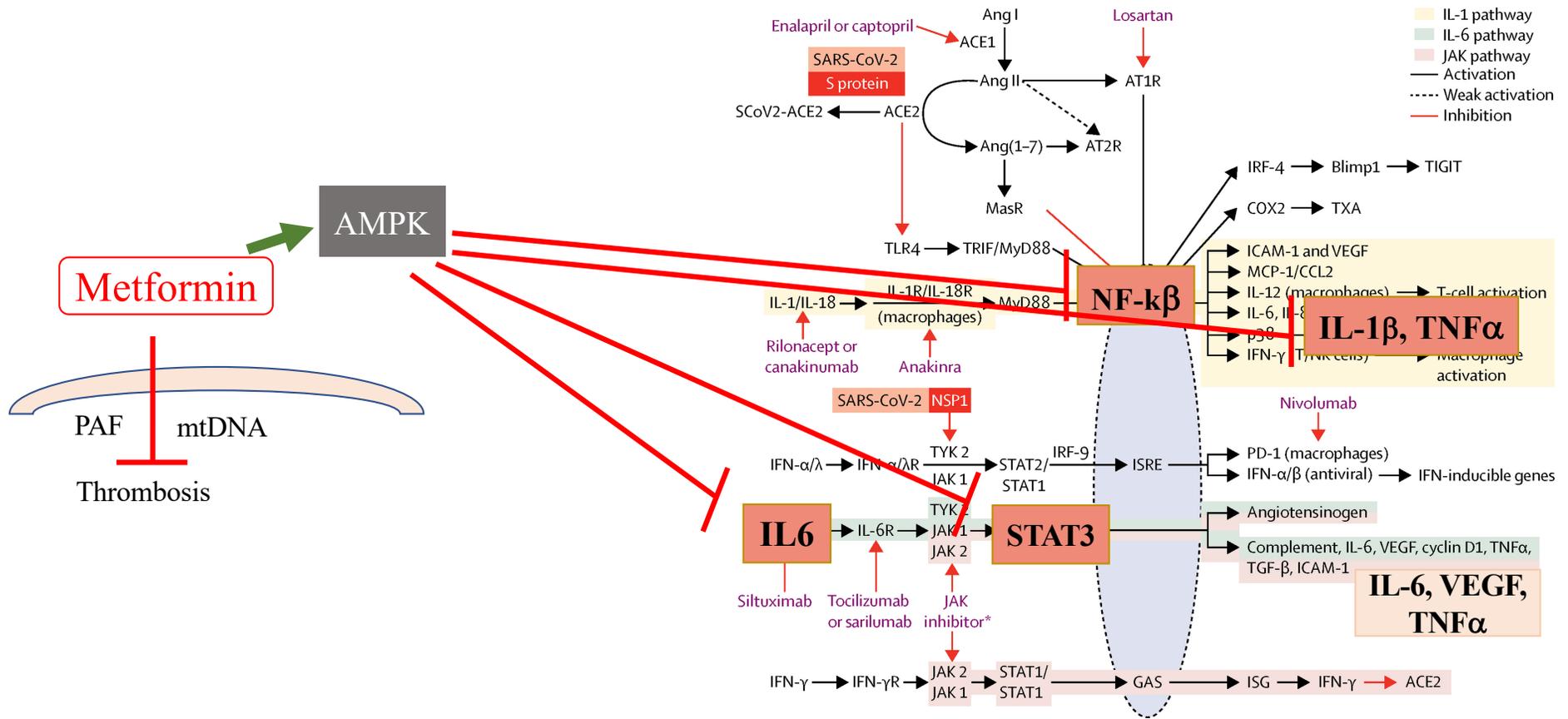


Advantages:

- Enroll all close contacts of people enrolling in treatment arm
- Consent everyone getting tested
- Honors patients time consenting
- **Speeds initiation of study drug**



Subtle immune modulation should start early in disease course

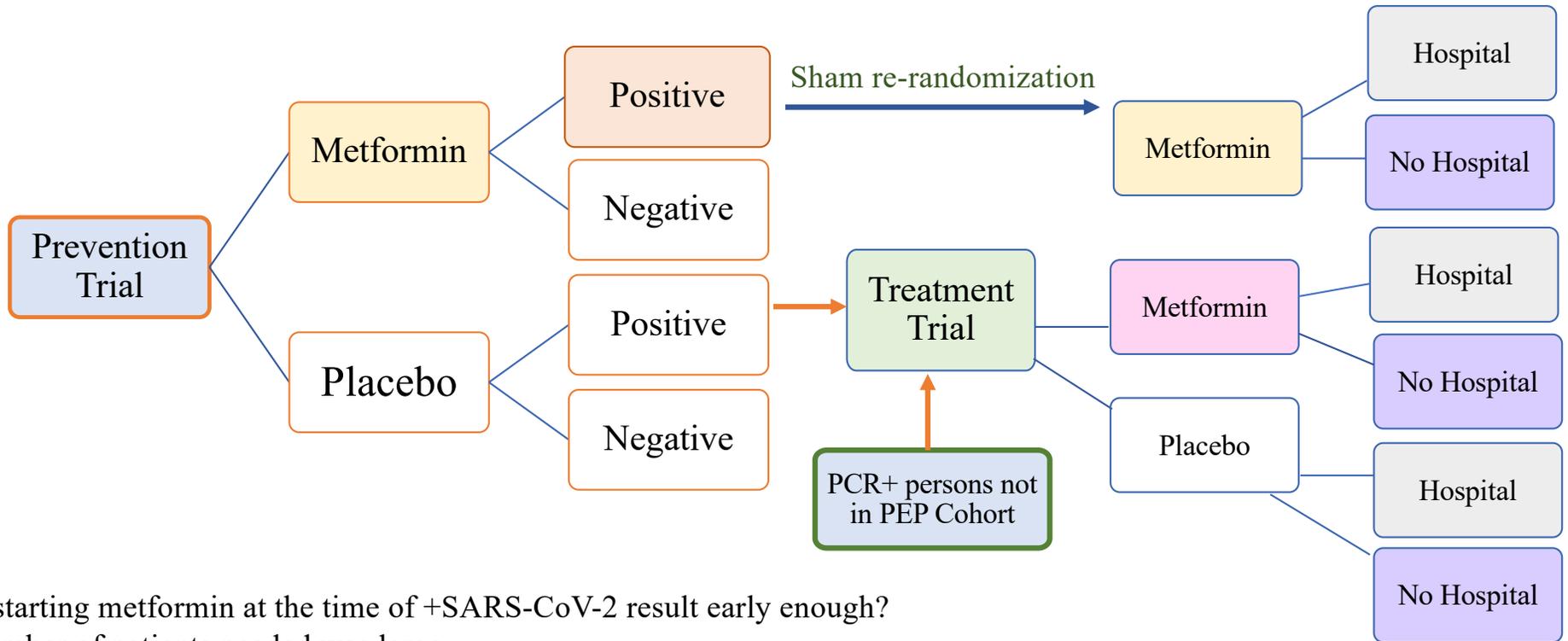


Ingraham N, ..., Tignanelli CJ, Immunomodulation in COVID-19, Lancet Respiratory Medicine, 2020
 Xin et al. 2016.



UNIVERSITY OF MINNESOTA
 Driven to DiscoverSM

Nested SMART Study



Is starting metformin at the time of +SARS-CoV-2 result early enough?
Number of patients needed was large.



Study Population

- +SARS-CoV-2 within 3 days, symptoms not required but if present must be < 7 days of symptoms
- Adults age 30 - 85
- With overweight or obesity
- No severe kidney, liver, or heart failure
- Not excluding patients with diabetes or prediabetes
 - Excluding those on insulin or sulfonylurea
- No known prior infection with SARS-CoV-2
- Pregnancy not excluded

Eligibility Lab: GFR > 45

We will test GFR on persons > 75 or who have a history of heart, liver, or kidney disease



UNIVERSITY OF MINNESOTA

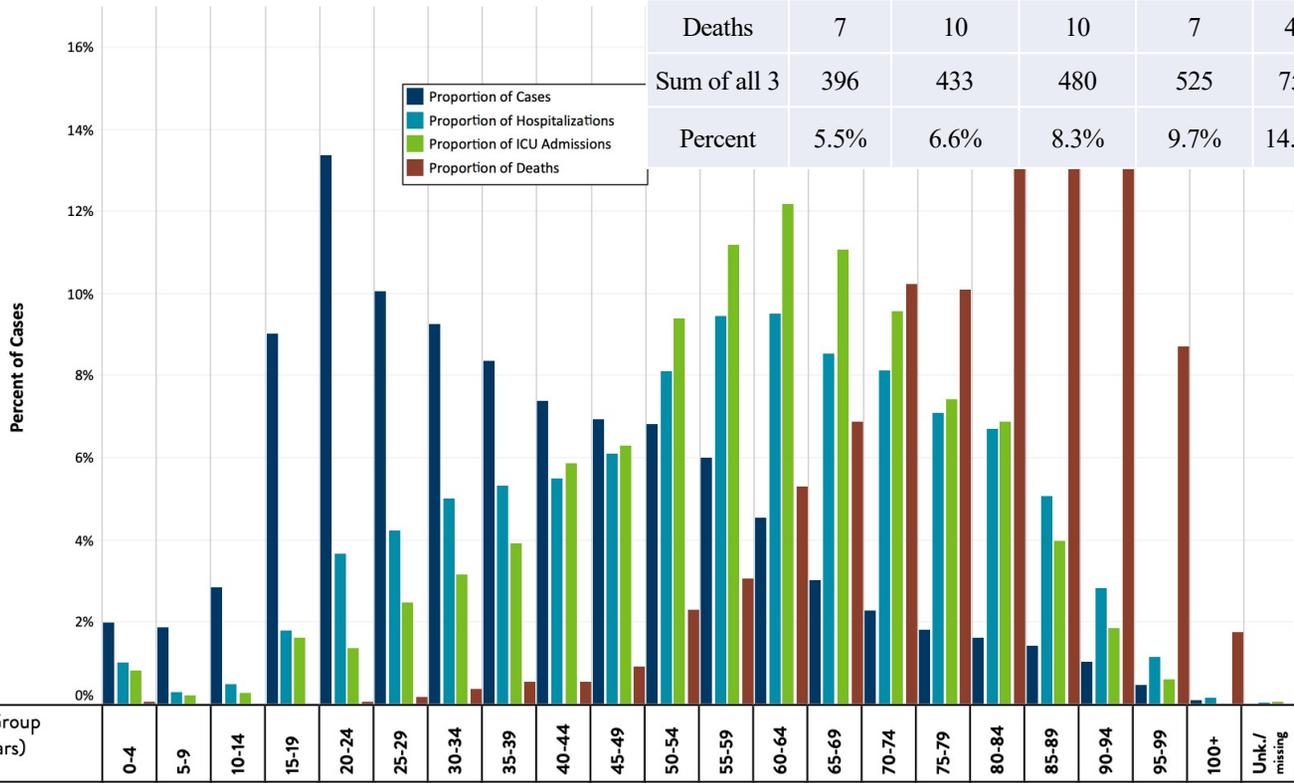
Driven to DiscoverSM

Some of the data used for power calculation

Demographics: Age

Age groups, median age, and range for confirmed cases.

MN	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84
All cases	7228	6,521	5,763	5,412	5,315	4,682	3,535	2,355	1,769	1,411	1,257
Hospitalized	330	350	361	401	534	623	626	562	536	468	441
ICU	59	73	109	117	175	208	227	227	178	138	128
Deaths	7	10	10	7	42	56	97	97	188	185	300
Sum of all 3	396	433	480	525	751	887	950	886	902	791	869
Percent	5.5%	6.6%	8.3%	9.7%	14.1%	18.9%	26.9%	37.6%	51.0%	56.1%	69.1%



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
Ananth Shalev, MD	Endocrinology, Diabetes	Division Director, University of Alabama Birmingham, AL
Ildiko Lingvay, MD	Endocrinology, Diabetes pharmacotherapy	UT Southwestern
Hrishi Belani MD, Art Jeng, MD	GIM, Infectious disease	Director of Primary Care, LA County Olive View-UCLA Medical Center

Angela Reiersen, MD and Eric Lenze, MD, Washington University



UNIVERSITY OF MINNESOTA
Driven to DiscoverSM

Funding Search - Presentations and applications

July 2020: Applied to Fast Grants

July 2020: The Parsemus Foundation reached out to us, arranged a presentation with a larger foundation

Aug 2020: The Parsemus Foundation donated seed money for the IND application

Aug 2020: Met with large insurer

Sept 2020: NIH program officers, clinical trial network

Oct 2020: Updated about new data

Oct 2020: Parsemus Foundation gave larger donation for Stage-1 of a multi-site fully powered phase 3 clinical trial

Enough for about 80 patients as best we could tell

Nov 2020: Applied to BARDA, another PO

Dec 2020: Met with another foundation, applied to Fast Grants

- Is this worth pursuing? -

Jan 2021: Met with Rainwater Foundation, applied to U01

Feb 2021: Met with Rainwater again

Feb 2021: Received Rainwater, Fast Grants, and UnitedHealth Group matching funds

Enough to launch full factorial design, have not yet received the full amount needed for trial

July 2021: Asked Rainwater and Parsemus for small funds for targeted recruitment approaches

Sept 2021: Applied to U01

Sept 2021: **Received small amount of targeted funds**

Funding search is ongoing

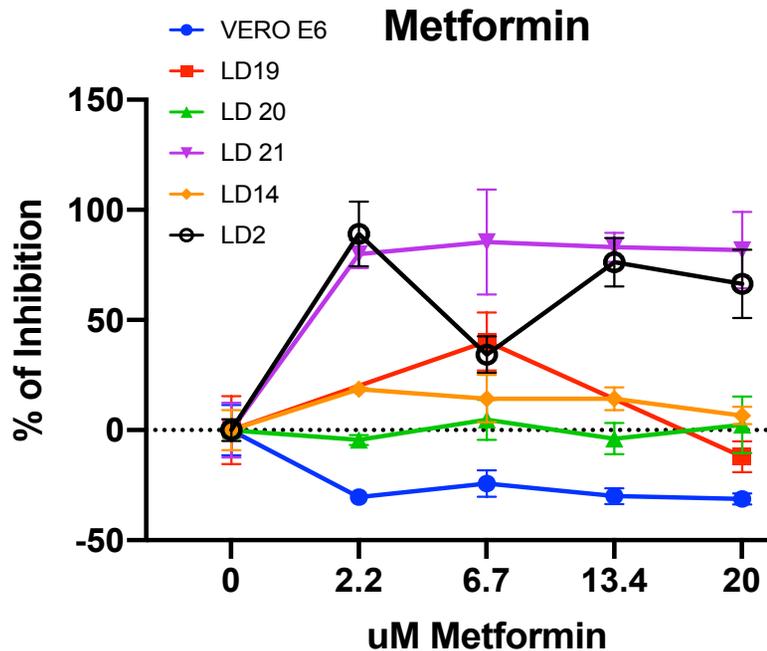


UNIVERSITY OF MINNESOTA

Driven to DiscoverSM

Continuing to pursue funding seemed worth it

Lung epithelial tissue assays



In silico simulator with ongoing success, David Odde Lab:

Drug	Simulator Efficacy Prediction	Status	Simulator Accuracy	Reference
Remdesivir	Effective	Standard of Care (mild hospitalized cases)	Correct	NIH Guidelines
Hydroxychloroquine	Not Effective	Multiple RCT failures	Correct	NIH Guidelines
Lopinavir/Ritonavir	Not Effective	Multiple RCT failures	Correct	NIH Guidelines
Favipiravir	Effective	Ph III success (SOC in multiple countries – not FDA approved)	Correct	Press Release
Fluvoxamine	Effective	Ph II success	Correct	JAMA
Molnupiravir	Effective	Ph II success (Ph II/III underway)	Correct	Clinicaltrials.gov
Plitidespsin	Effective	Ph I success w/efficacy signal (moving to Ph III)	Correct	Press Release
Merimepodib	Effective	Ph II safety failure - development halted	Inconclusive	Press Release
Leflunomide	Effective	No benefit in 1 RCT, additional trials	Inconclusive	Oxford

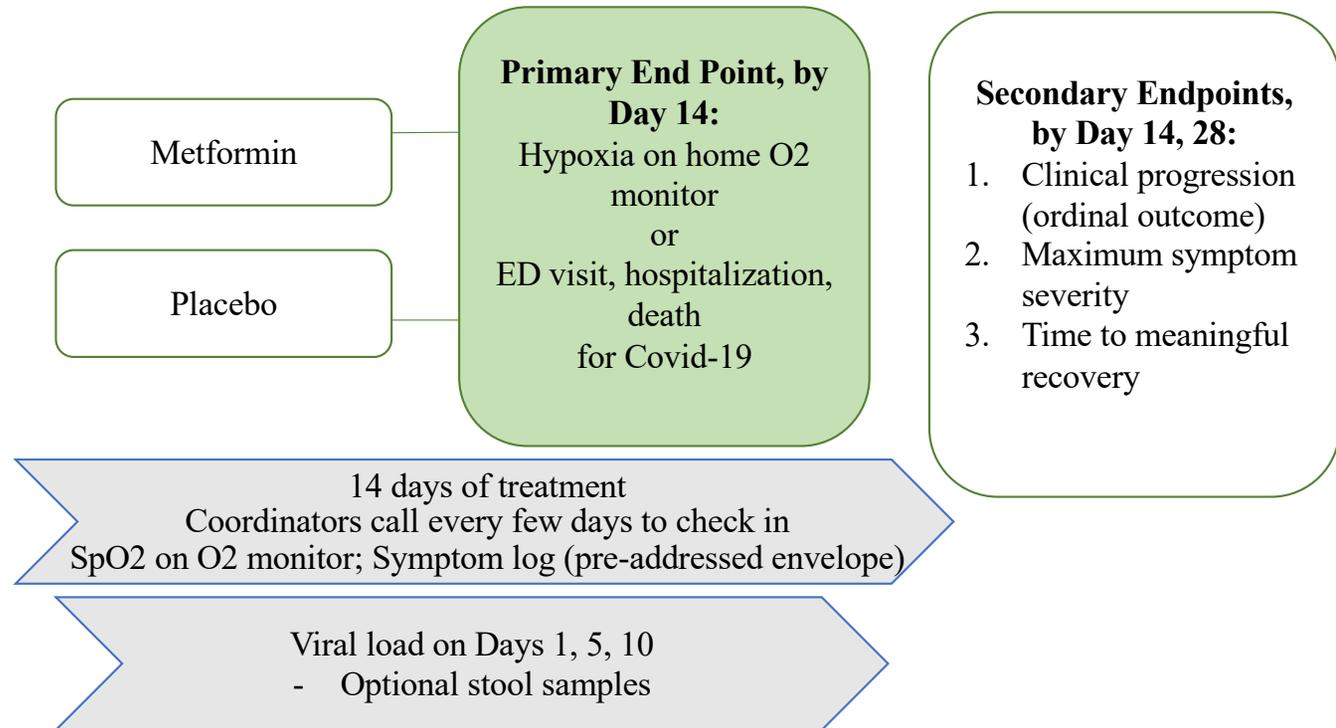
Foundation Funding

- Pre-award work
 - Meetings are important
 - Shorter applications
 - Much faster
- Post-award work
 - Flexible
 - Monthly or > monthly meetings with each funder
 - 2nd half of funds withheld until 1/3 enrollment complete
- Minimal to no indirects
- Funding from multiple sources for one trial
 - Budget for each funder
 - Subcontracts redone for each funder
- Preference for treatment trial, not prevention

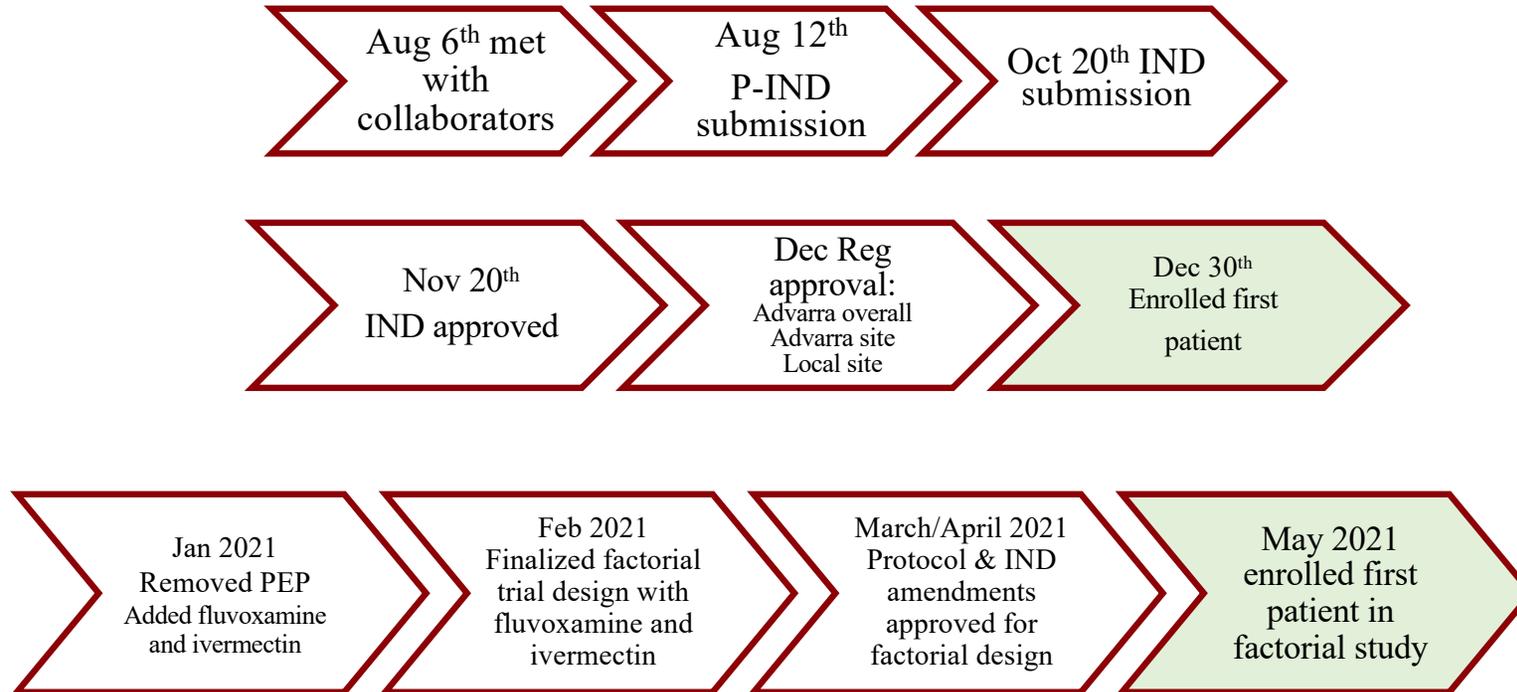


Early Outpatient Treatment Trial

- Pro-active outreach to patients who were recently tested or positive in participating health systems



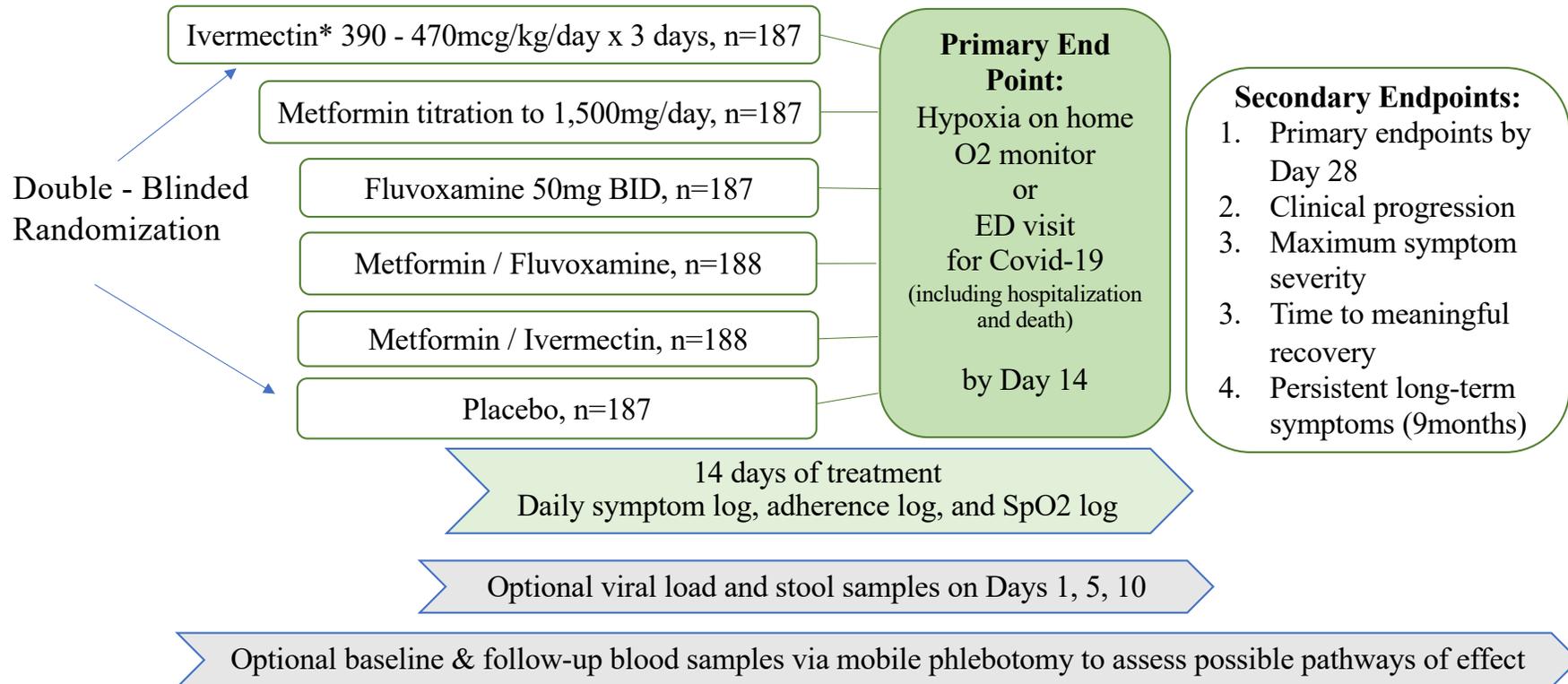
Funding Search & Trial Timeline



UNIVERSITY OF MINNESOTA

Driven to DiscoverSM

6-arm design



*6 weight categories.
Doses to minimize side effects

Each patient gets 2 types of pills

- Maintain the blind
- Represent a real-life pill burden
- Placebo tablets are exact-matching for all 3 medications

	A	B	C	D	E	F	G	H	I	J	K	L	M
1	Pills per pattern	45		63		45		63		45		63	
2		Pill Pattern 1		Pill Pattern 2		Pill Pattern 1		Pill Pattern 2		Pill Pattern 1		Pill Pattern 2	
3		Intervention						Placebo					
4	Every patient gets 2 types of pills	Group 1		Group 2		Group 3		Group 4		Group 5		Group 6	
5		Metformin	Iver*	Metformin	Fluvox	Metformin	Iver*	Fluvox	Met	Iver*	Met	Met	Fluvox
6	Day 1 AM												
7	PM	1	3	1	1	1	3	1	1	3	1	1	1
8	Day 2 AM	1	0	1	1	1	0	1	1	0	1	1	1
9	PM	1	3	1	1	1	3	1	1	3	1	1	1
10	Day 3 AM	1	0	1	1	1	0	1	1	0	1	1	1
11	PM	1	3	1	1	1	3	1	1	3	1	1	1
12	Day 4 AM	1	0	1	1	1	0	1	1	0	1	1	1
13	PM	1	0	1	1	1	0	1	1	0	1	1	1
14	Day 5 AM	1	0	1	1	1	0	1	1	0	1	1	1
15	PM	1	0	1	1	1	0	1	1	0	1	1	1
16	Day 6 AM	1	0	1	1	1	0	1	1	0	1	1	1
17	PM	2	0	2	1	2	0	1	2	0	2	2	1
18	Day 7 AM	1	0	1	1	1	0	1	1	0	1	1	1
19	PM	2	0	2	1	2	0	1	2	0	2	2	1
20	Day 8 AM	1	0	1	1	1	0	1	1	0	1	1	1
21	PM	2	0	2	1	2	0	1	2	0	2	2	1
22	Day 9 AM	1	0	1	1	1	0	1	1	0	1	1	1
23	PM	2	0	2	1	2	0	1	2	0	2	2	1
24	Day 10 AM	1	0	1	1	1	0	1	1	0	1	1	1
25	PM	2	0	2	1	2	0	1	2	0	2	2	1
26	Day 11 AM	1	0	1	1	1	0	1	1	0	1	1	1
27	PM	2	0	2	1	2	0	1	2	0	2	2	1
28	Day 12 AM	1	0	1	1	1	0	1	1	0	1	1	1
29	PM	2	0	2	1	2	0	1	2	0	2	2	1
30	Day 13 AM	1	0	1	1	1	0	1	1	0	1	1	1
31	PM	2	0	2	1	2	0	1	2	0	2	2	1
32	Day 14 AM	1	0	1	1	1	0	1	1	0	1	1	1
33	PM	2	0	2	1	2	0	1	2	0	2	2	1
34	Total Pills	36	9	36	27	36	9	27	36	9	36	36	27

Overview

- Snap shot of current COVID-OUT Trial
- Background of how the trial developed
 - Why - Scientific background that prompted doing the trial
 - How - Unique funding search
 - What - Initial trial design
 - Current trial design
- **Statistical considerations**
- Practical adaptations
 - Recruitment
 - Pre-packing IP
 - Shipping
 - Current enrollment
- Possible future directions



Statistical Considerations - Primary Analysis

- Clinical progression within 14 days
 - O_2 saturation $\leq 93\%$ or supplemental O_2 , ED visit, Hospitalization, Death
- Evaluate main effect of each agent with logistic model
 - Metformin: 1+2+3 vs 4+5+6
 - Fluvoxamine: 1+4 vs 3+6
 - Ivermectin: 2+5 vs 3+6
 - Adjusted for vaccination + other investigational agents
 - Multiple imputation of missing data
- mITT Analysis
 - Received and Ingested 1+ Dose of IP and Met post-randomization eligibility

	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

- 1,124 participants (~204 per arm)
 - Accounts for up to 10% withdrawal
- Metformin main effect (all participants)
 - 90% power for 45% 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 45% relative risk reduction
 - 90% power for 50% relative risk reduction



Data Monitoring

- Bi-weekly Safety Reports to DSMB
 - SAEs/AEs, Side Effects
- Up to 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



Randomization

- Initially, Metformin or Placebo (1:1)
- Currently, Metformin, Ivermectin, Fluvoxamine in 3 x 2 factorial (1:1:1:1:1:1)

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

- Weight-based dosing for ivermectin and ivermectin placebo

- No weight stratum
- Shiny app to allocate pre-packed meds to each enrollee based on weight and random assignment



Randomization Shiny App

Part A: Enter Participant Information

Step 1: Enter all participant information below.

Date of Randomization:
2021-05-02

Study Site:

- University of Minnesota
- Hennepin
- Optum - New West Physicians Network
- Optum - American Health Network
- Northwestern University
- Colorado University
- UCLA/LA County

Randomized By:
Jennifer Proper

Participant ID:
01-100

Participant Weight (kg):
74.8

Drugs Eligible to Receive:

- Metformin Only (Pregnant)
- Metformin+Fluvoxamine+Ivermectin

Step 2: Verify that all participant information has been entered correctly.
Step 3: Click Next.

Next

Part B: Randomize Participant

Step 4: Select the Randomize button to obtain randomization assignment.

Randomize

Covid-Out Randomization				
Date	Participant ID	Weight (kg)	Study Site	Packet ID
2021-05-02	01-100	74.8	University of Minnesota	PK-01-030

Step 5: Click the Download Report button and save this information to an appropriate location.

Download Report

Step 6: Logout when finished.



Secondary Analyses

- Drug-Drug Synergies/Interactions
 - Metformin + Ivermectin / Fluvoxamine
- Subgroup Effect Heterogeneity
 - Assigned Sex at Birth, BMI, Age, Time from Symptom Onset, Vaccination Status
 - Per-protocol / Adherence Analyses
- Secondary Endpoints
 - Labs, Post-acute sequelae, Mortality / Time to Recovery, Symptomatology



Overview

- Snap shot of current COVID-OUT Trial
- Background of how the trial developed
 - Why - Scientific background that prompted doing the trial
 - How - Unique funding search
 - What - Initial trial design
 - Current trial design
- Statistical considerations
- **Practical adaptations**
 - Recruitment
 - Pre-packing IP
 - Shipping
 - Current enrollment
- Possible future directions



Current Status

PI Name Expertise	Site	Primary Patient Population	Recruitment Status
Carolyn Bramante, MD MPH Obesity medicine David Boulware, MD MPH Infectious disease, clinical trials	1. University of Minnesota	Mixed urban, suburban, rural. The hub for online recruiting across nationwide (starting 2/15/21)	Enrolling
Michael Puskarich, MD Director of Research, Emergency Medicine	2. Hennepin County Medical Ctr	Low-income urban population	Enrolling
David Liebovitz, MD Chief Clinical Informatics Officer	3. Northwestern University	Focusing on their suburban and rural sites.	Enrolling
Jacinda Nicklas, MD MPH Perinatal health researcher	4. University of Colorado, Denver	Mixed urban/suburban, access to pregnant patients	Enrolling
Hrishikesh Belani, MD MPH Director of Primary Care, LA County Art Jung, MD Infectious Disease, UCLA	5. Olive-View, UCLA/LA County education center	Low-income urban population, primarily Black and Latinx.	Enrolling
Ken Cohen, MD National Director of Clinical Research, OptumCare clinics (now called OptumLabs); Executive Director Clinical Research, UnitedHealth Group R&D	6. New West Physicians Clinic Network, Denver	Suburban and urban population	Enrolling
	7. American Health Network of Indiana	Suburban and urban population	Enrolling
Blake Anderson, MD Informatics and internal medicine, Emory	8. Emory	Urban and suburban	Transferring patients
Jennifer Thompson, MD, Anupt Challa, Obstetrics and gynecology Vanderbilt University Medical Center	9. Vanderbilt	Urban and suburban	Pregnant women only

Coordinators
answering phone 12
hours/day,
7 days/week



Multi-site design gets patients on study drug quickly

- Study drug is delivered by local courier within 3 hours at all sites
- This mimics real life most closely
 - starting study drug as early as possible in the disease course improves our ability to detect a difference between metformin and placebo
- However, in March we realized that it was challenging to get study drug to patients on the same day
 - Results, pharmacy hours
- Most enrollments were Friday and Saturday
 - Friday → Monday
- With the new study design, we wanted patients to have pill boxes so they took the correct pills (i.e. 3 ivermectin pills, not 3 metformin pills)



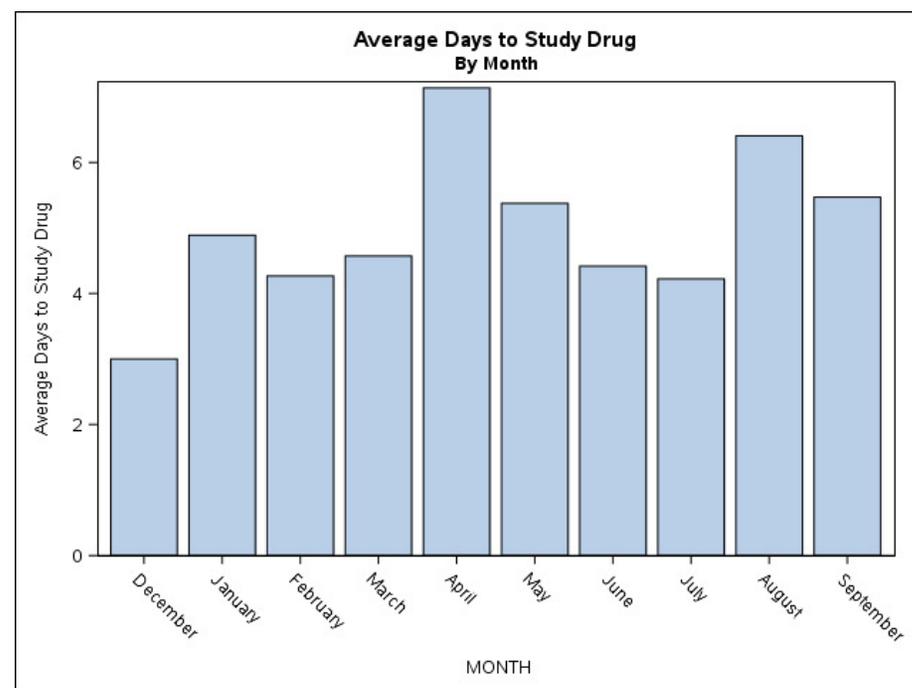
Pre-packing investigational product to speed delivery

- Checked with state boards of pharmacy and medical practice
- We can pre-pack IP if individually labeled



Pre-packing allows faster delivery of IP

- Study team can distribute to courier or FedEx
 - 8:15pm on weekdays, and on weekends
- We decided to pay additional shipping costs
 - FedEx same-day shipping on weekends
 - This is a new, increased cost of trial
 - Will need more funding to finish trial



Pre-packing is 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

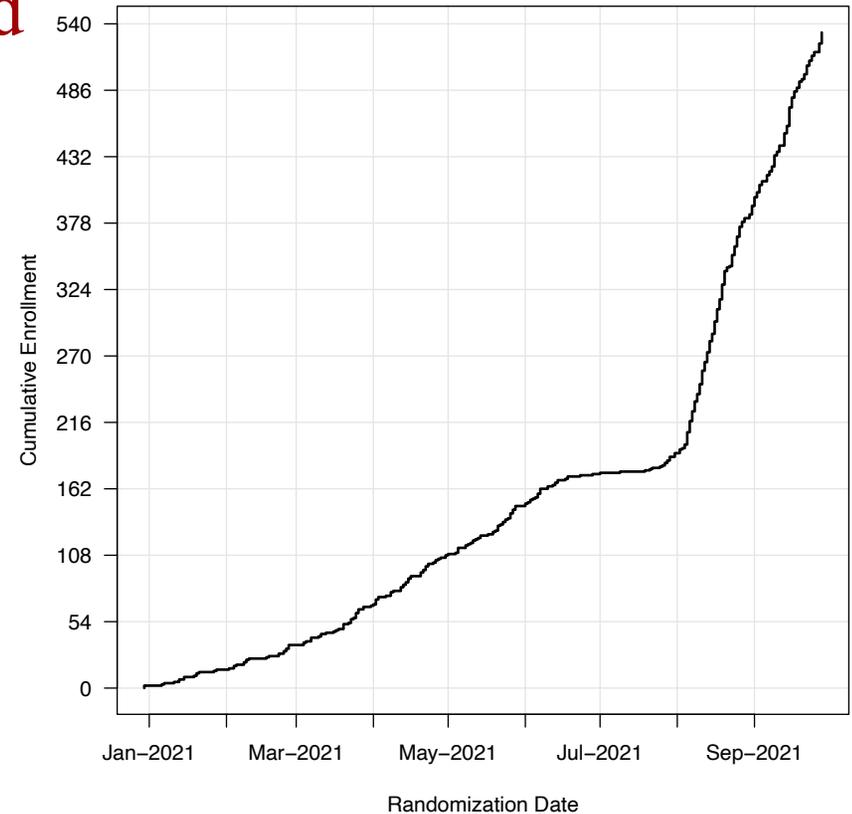


Current Status: Almost 50% enrolled

New approaches to Advertising

- Online advertising
 - Started in May, when cases were dropping
- Research in June/July
- Aug contracted with regional testing locations
 - Most hopeful one starts Monday
- Press releases to local papers in all states

	A	B	C	D	E	F
1	State	Cases (daily avg)	Link	PR sent?	Cost	Distribution
2	Florida >	15,818	https://flpress.com/services/press-	Sent (old)	\$108 w/ discount - paid in	141 daily and weekly newspapers in FL
3	Texas >	9,217	https://www.texaspress.com/press	Sent (old)	\$149 - paid in link	410 paid-circulation newspapers in Texas. Release sent t
4	California >	8,677	https://cnpa.com/services/			Link did not work. Talked with Joe Wirt (Cal Press/New Foundation) and he said the link is dead
5	Louisiana >	4,119	https://www.lapressads.com/press	Sent (old)	\$160 - paid to Mike Rood	Newspaper, news online, radio, and TV across state
6	Georgia >	2,995	http://gapress.org/press-release-si	Sent (old)	\$100 - Dr. B faxed	Sent to GPA members and posted on page
7	Missouri >	2,653	https://mopressservice.com/print-media/			
8	Alabama >	2,391	https://www.alabamapress.org/pre	Sent (old)	\$0 - see comment	120+ daily/weekly newspapers in Alabama
9	North Carolina >	2,372	http://www.ncpress.com/advertisin	Sent (old)	\$0 - see comment	154 newspapers across the state
10	New York >	2,280	https://nynewspapers.com/network	Sent (old)	\$125 - paid to Jill	400 daily and community newspapers across the state
11	Arkansas >	1,869	https://www.arkansaspress.org/pa	Sent (old)	\$200 - paid to Bridgitt	Newspapers all across state
12	Tennessee >	1,773	https://tnpress.com/services/press	See comment	\$150 - see comment	TPA member newspapers across state
13	Arizona >	1,768	https://ananews.com/general-press-release-guidelines/			
14	Illinois >	1,678	https://www.illinoispress.org/Services/PressReleaseService.aspx			
15	Mississippi >	1,475	https://www.mspress.org/page/26			
16	South Carolina >	1,474	https://www.scnewspapernetwork.com/press_releases.html			
17	Oklahoma >	1,351	https://cdn.ymaws.com/okpress.com/resource/resmgr/advertising/press_release_service.pdf			
18	Kentucky >	1,195	https://www.kypress.com/ky-press-service/			
19	Ohio >	1,147	https://www.ohionews.org/aws/ON			Spoke with Chandra (ohio news association and AdOhio) and she said they do not of
20	Nevada >	1,051	https://nevadapress.com/services/pr-media-release/			
21	Washington >	1,004	https://wnpa2.clubexpress.com/co			Spoke with WNPA. They do not have this service and she's not aware of any for the s
22	Indiana >	979	https://www.hsapa.com/contact-us/	Sent (old)	\$100 - paid to Pam	all across state of IN
23		938				Peggy explained PR service is no longer going on: Katrina - I received your voicemail regarding the PR



Current Enrollment

Baseline info	Overall Sample
Age, mean	46 years
Female	57%
Race, Ethnicity	Black, 8.4%
	White, 73.1%
	Asian, 2.5%
	Native American, 2.1%
	Native Hawaiian or Pacific Islander, 0.6%
	Other, 5.1%
	Latinx, 10.3%
	Declined, 1.8%
Average BMI, mean	32 kg/m ²



Spread the word!



GOT COVID?

Volunteer for a research study.

[covidout.com](https://www.covidout.com)

Olive View-UCLA MEDICAL CENTER
University of Colorado Anschutz Medical Campus
Hennepin Healthcare
OPTUM
Northwestern Medicine
HEALTH FAIRVIEW



GOT COVID?

Volunteer for a research study.

[covidout.com](https://www.covidout.com)

Olive View-UCLA MEDICAL CENTER
University of Colorado Anschutz Medical Campus
Hennepin Healthcare
OPTUM
Northwestern Medicine
HEALTH FAIRVIEW

Overview

- Snap shot of current COVID-OUT Trial
- Background of how the trial developed
 - Why - Scientific background that prompted doing the trial
 - How - Unique funding search
 - What - Initial trial design
 - Current trial design
- Statistical considerations
- Practical adaptations
 - Recruitment
 - Pre-packing IP
 - Shipping
 - Current enrollment
- **Possible future directions**



Potential Future Directions

1. Analyze the Day 1, 5, and 10 viral samples
 - Could these medications be creating selective pressure?
2. Ongoing shedding of virus in stool samples
3. Reduced risk of re-infection
(metformin associated with improved T cell immunity in Mice)
4. Children



More children at risk for poor outcomes from COVID-19

Percentage of children with obesity went up in all age categories analyzed from 2020 to 2021:

Table. Weight Changes in Youths Over an 11-Month Period Before and During the Pandemic^a

Age group, y	Prepandemic			Pandemic			
	Start	End	Change 1 ($\Delta 1$, 95% CI)	Start	End	Change 2 ($\Delta 2$, 95% CI)	$\Delta 2 - \Delta 1$ (95% CI)
Obesity (≥ 95 th percentile), rate (SD), % ^b							
5-11	17.27 (0.18)	18.38 (0.18)	1.11 (0.83 to 1.39)	18.79 (0.21)	26.11 (0.25)	7.32 (6.84 to 7.80)	6.21 (5.66 to 6.76)
12-15	19.19 (0.25)	19.06 (0.25)	-0.13 (-0.47 to 0.22)	18.58 (0.27)	23.20 (0.30)	4.62 (4.06 to 5.18)	4.75 (4.09 to 5.42)
16-17	18.18 (0.37)	17.97 (0.37)	-0.21 (-0.70 to 0.28)	18.41 (0.41)	20.07 (0.41)	1.66 (0.93 to 2.39)	1.87 (0.99 to 2.75)

^a Total body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) measures included in the models totaled 425 855 from March 2019 to January 2020 (2.22 BMI measures per youth) compared with 283 718 from March 2020 to January 2021 (1.48 BMI measures per youth).

^b All models are adjusted for race and ethnicity (Asian or Pacific Islander, Hispanic, non-Hispanic Black, non-Hispanic White [reference], and other race), state-subsidized health care [reference, none], parks (no parks,

≥ 2 , reference, 1 park), neighborhood education, and neighborhood income. Estimates are shown for the reference group. After initial decrease, in-person well-child visits were back to 84% of prepandemic visits by June 2020.

^c Models for distance from the median BMI for age and body weight were also adjusted for baseline weight class (<5th, 5th-84th, 85th-94th, 95th-97th, >97th; reference, 5th- \leq 85th), the model for body weight is adjusted for height.

More children may die

Outcomes among children hospitalized for COVID-19, pre- and post- Delta-variant period:

	Pre-Delta n=3,116 (3/1/20 – 6/19/21)	Post-Delta n=164 (6/20/21-7/31/21)	p value
ICU admission	827 (26.5%)	38 (23.2%)	0.34
Ventilation	190 (6.1%)	16 (9.8%)	0.06
Death	21 (0.7%)	3 (1.8%)	0.12

- When there are more events in the Delta variant period, the p values may drop below 0.05
- A decrease in ICU admission may only reflect hospitals greater experience with treating COVID-19.

Site Principal Investigators

Hennepin Healthcare, Michael Puskarich, MD



Optum Labs, New West Physicians, Ken Cohen, MD



Optum Labs, American Health Network of IN, Andrew Daluga, MD



Northwestern University, Dave Leibovitz, MD



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



UNIVERSITY OF MINNESOTA
Driven to DiscoverSM

Participating Site Research Coordinators

Samuel Lee
Jannis Brea
Naveen Reddy
Bristol Pavol
Gwen Carangi
Amber Voit
Amber Bretz

Audrey Hendrickson
Walker Tordsen
Lucas Brown
Olivia Kaus
Nicole Rudin
Radhika Edpuganti
Leah Stodieck
Jane Ude

Riannon Atwater
Nikita Deng
Alex Pedowitz
Rosario Machicado
Mary Schmoll
Melissa Denny
Sara Slaughter



UNIVERSITY OF MINNESOTA
Driven to DiscoverSM

University of Minnesota



Surgery CTO:

Lisa Rogers
Dave Ankarlo
Mary Farnsworth

FDA Prep:

Harvey Arbit
Wrenda Temple

Pharmacists:

Darlette Luke
Theresa Christiansen
Derek LaBar

Statisticians:

Jennifer Proper
Lianne Siegel
Sara Lindberg

ADRL:

Bob Janicke
Jamie Lavalle

Fairview
Research:

Jill Cordes
Andrew Snyder
Pa Chia Yang
Melissa Schedler
Sarah Zwagerman
Erik Kuehl
Madeline Zolik

BME:

Bo Connelly

DOM:

Sara Eischen
Leslie Kennedy
Alicia Callahan
Ashlee Janecke

CPOM: Cameron Naughton
Juanita Jenson
Lucas Simmons

GIM: Kate Brekke
Jill Charles
HR

CTSI: Casey Dahl
Study Monitor

SPA: contracts



UNIVERSITY OF MINNESOTA
Driven to DiscoverSM

University of Minnesota



Research Coordinators:

Paula Campora



Grace Christensen

Kristi Fordyce

Regina Fricton

Gwen Griffiths

Aubrey Hagen



Daniela Parra



Barkha Patel

Via Rao



Manju Nayar

Mercury Wu



University of Minnesota



Medical Students:

Katrina Hartman
Hanna Saveraid
Tannon Tople
Arman Quraishi
Neha Reddy
Rumbidzai Ngonyama
Sarah Fenno
Megan Schramski
Spencer Erickson
Nandini Avula

Undergrad Students:

Hanna Saveraide
Faith Fairborn



UNIVERSITY OF MINNESOTA
Driven to DiscoverSM

Extra slides



UNIVERSITY OF MINNESOTA
Driven to DiscoverSM

Thank you

- Appreciate any questions, discussion



UNIVERSITY OF MINNESOTA
Driven to DiscoverSM