LONG COVID WEB

RECLAIM

Update on Trials in Long COVID

Angela M. Cheung MD, PhD, FRCPC

Tuesday June 17, 2025

Source: https://tati.on.ca/about/land-acknowledgement/

NONE

OBJECTIVES

1) Trials with published results

2) RECLAIM Trial

1) Trials expecting to have results later this year

CAN COV

Shortness of Breath

Fatigue

Headaches

Tachycardia

Brain Fog

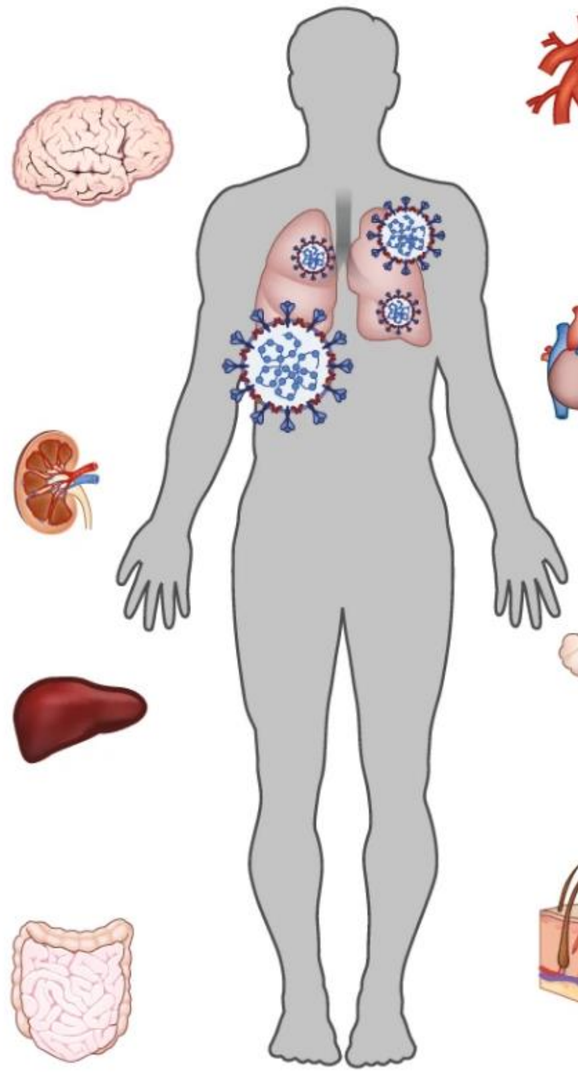
Insomnia

Neurologic
Headaches
Dizziness
Encephalopathy
Guillain-Barré
Ageusia
Myalgia
Anosmia
Stroke

Renal
Acute kidney injury
Proteinuria
Hematuria

Hepatic
Elevated aminotransferases
Elevated bilirubin

Gastrointestinal
Diarrhea
Nausea/vomiting
Abdominal pain
Anorexia



Thromboembolism
Deep vein thrombosis
Pulmonary embolism
Catheter-related thrombosis

Cardiac
Takotsubo cardiomyopathy
Myocardial injury/myocarditis
Cardiac arrhythmias
Cardiogenic shock
Myocardial ischemia
Acute cor pulmonale

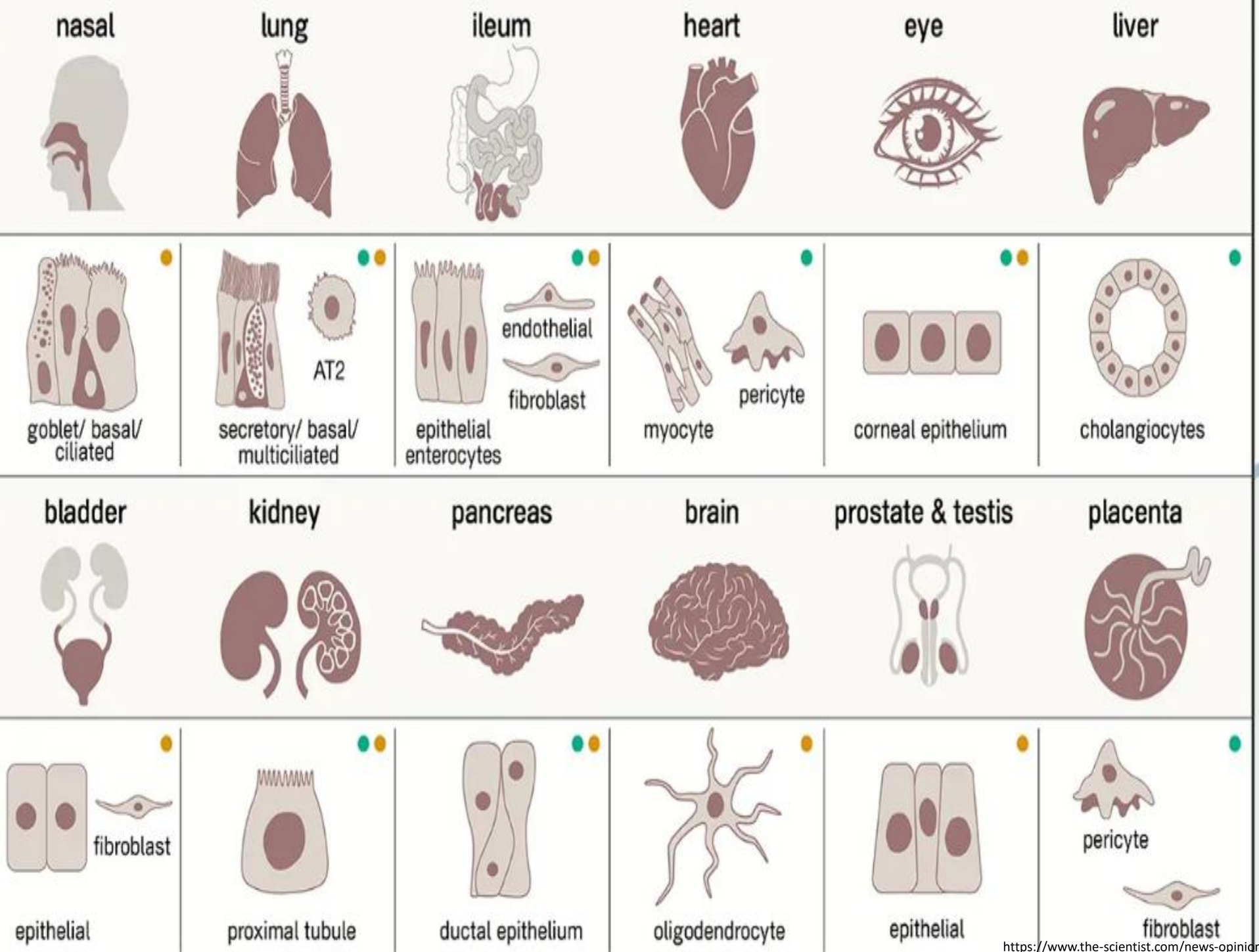
Endocrine
Hyperglycemia
Diabetic ketoacidosis

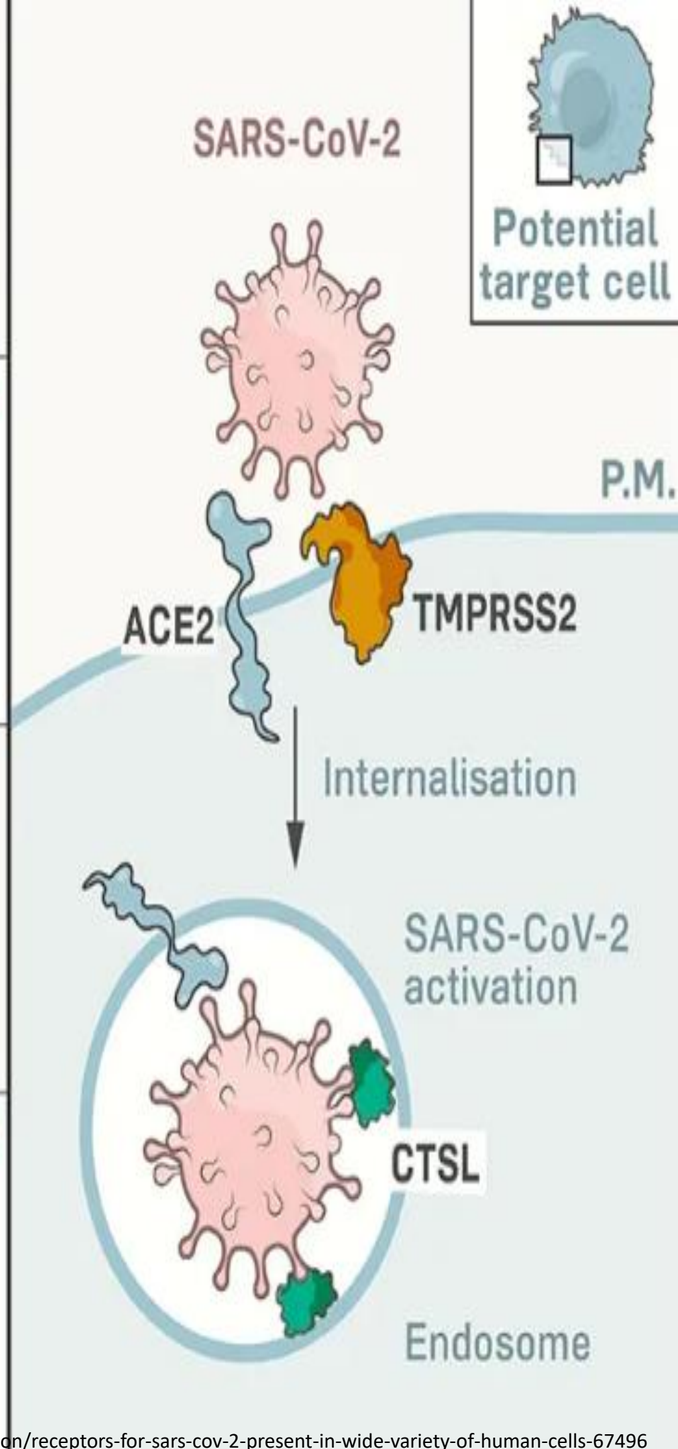
Dermatological
Petechaie
Livedo reticularis
Erythematous rash
Urticaria
Vesicles
Pernio-like lesions

UHN Toronto General Toronto Western Princess Margaret Toronto Rehab

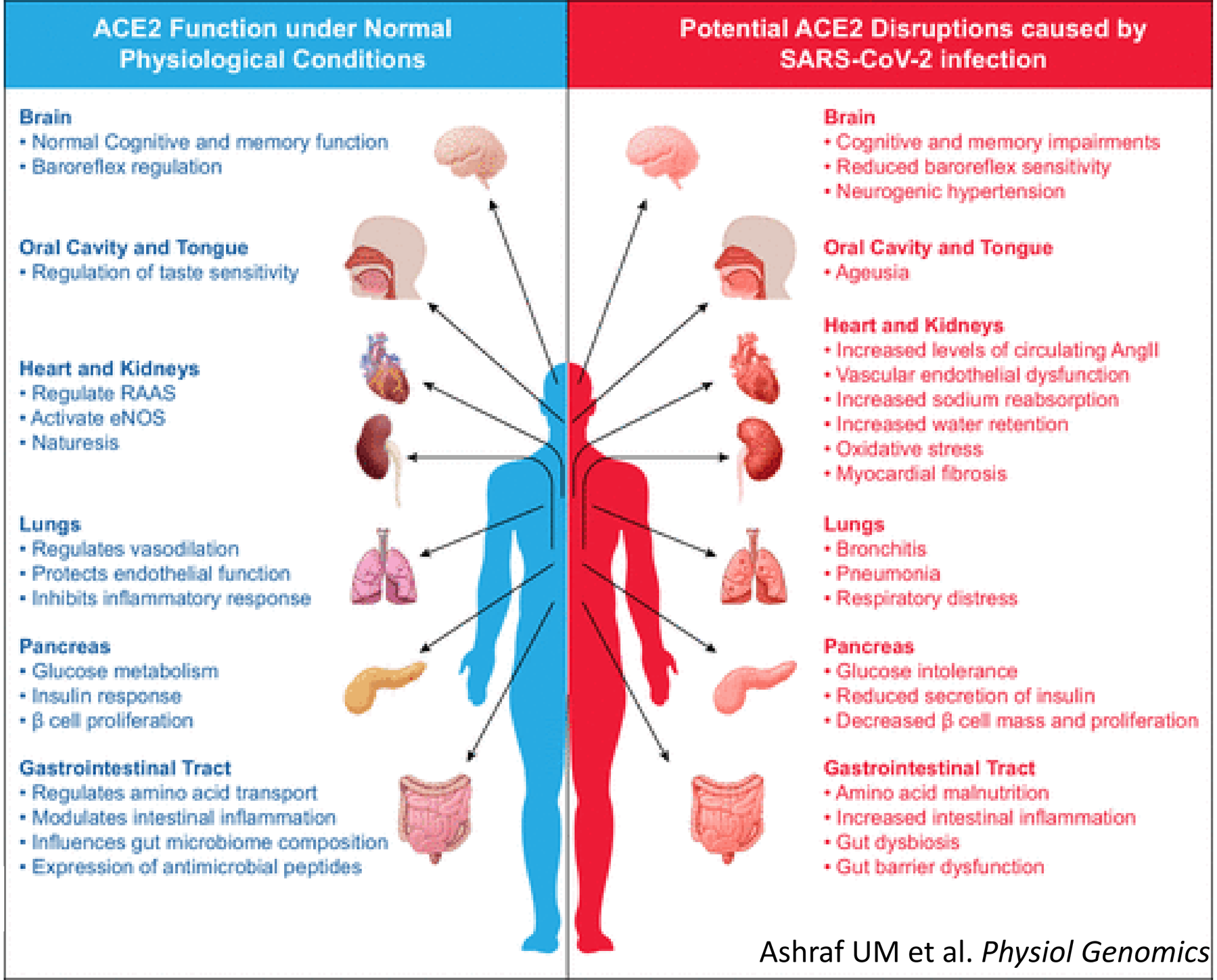
Medicine UNIVERSITY OF TORONTO

Nature Medicine **26**, 1017–1032(2020)





https://www.the-scientist.com/news-opinion/receptors-for-sars-cov-2-present-in-wide-variety-of-human-cells-67496

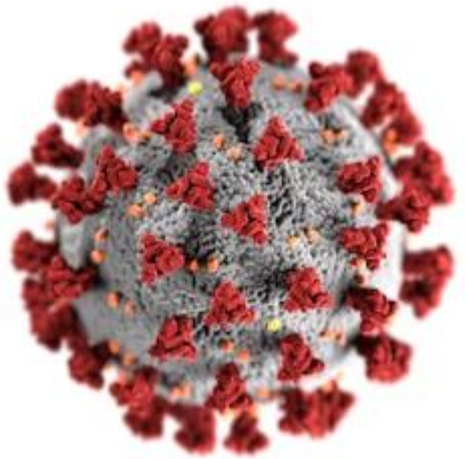


Ashraf UM et al. *Physiol Genomics* 53: 51–60, 2021

Pathogenic Mechanisms

Potential pathogenic mechanisms (based on WHO report*):

1) Immune dysregulation
2) Inflammation
3) Endothelial dysfunction
4) Viral or viral particle persistence
5) Thrombotic microclots
6) Mitochondrial dysfunction
7) Perturbations to microbiome



*WHO Report: Expanding our understanding of Post COVID-19 condition. 2021. ISBN 978-92-4-002503-5

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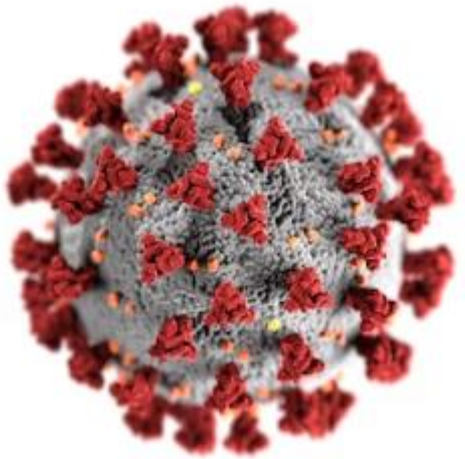

*WHO Report: Expanding our understanding of Post COVID-19 condition. 2021. ISBN 978-92-4-002503-5

JAMA Internal Medicine | Original Investigation

Nirmatrelvir-Ritonavir and Symptoms in Adults With Postacute Sequelae of SARS-CoV-2 Infection
The STOP-PASC Randomized Clinical Trial

Linda N. Geng, MD, PhD; Hector Bonilla, MD; Haley Hedlin, PhD; Karen B. Jacobson, MD; Lu Tian, DSc; Prasanna Jagannathan, MD; Phillip C. Yang, MD; Aruna K. Subramanian, MD; Jane W. Liang, PhD; Sa Shen, PhD; Yaowei Deng, MA; Blake J. Shaw, MS; Bren Botzheim, MS; Manisha Desai, PhD; Divya Pathak, MS; Yasmin Jazayeri, MPH; Daniel Thai, BS; Andrew O'Donnell, MA; Sukanya Mohaptra, BS; Zenita Leang, BS; Gabriella Z. M. Reynolds, BS; Erin F. Brooks, MS; Ami S. Bhatt, MD, PhD; Robert W. Shafer, MD; Mitchell G. Miglis, MD; Tom Quach; Anushri Tiwari; Anindita Banerjee, PhD; Rene N. Lopez, MPH; Magdia De Jesus, PhD; Lawrence R. Charnas, MD, PhD; Paul J. Utz, MD; Upinder Singh, MD

IMPORTANCE There is an urgent need to identify treatments for postacute sequelae of SARS-CoV-2 infection (PASC).

OBJECTIVE To assess the efficacy of a 15-day course of nirmatrelvir-ritonavir in reducing the severity of select PASC symptoms.

DESIGN, SETTING, AND PARTICIPANTS This was a 15-week blinded, placebo-controlled, randomized clinical trial conducted from November 2022 to September 2023 at Stanford University (California). The participants were adults with moderate to severe PASC symptoms of 3 months or longer duration.

JAMA Internal Medicine | Original Investig

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of 3 months or longer duration.

INTERVENTIONS Participants were randomized 2:1 to treatment with oral nirmatrelvir-ritonavir (NMV/r, 300 mg and 100 mg) or with placebo-ritonavir (PBO/r) twice daily for 15 days.

MAIN OUTCOMES AND MEASURES Primary outcome was a pooled severity of 6 PASC symptoms (fatigue, brain fog, shortness of breath, body aches, gastrointestinal symptoms, and cardiovascular symptoms) based on a Likert scale score at 10 weeks. Secondary outcomes included symptom severity at different time points, symptom burden and relief, patient global measures, Patient-Reported Outcomes Measurement Information System (PROMIS) measures, orthostatic vital signs, and sit-to-stand test change from baseline.

RESULTS Of the 155 participants (median [IQR] age, 43 [34-54] years; 92 [59%] females), 102 were randomized to the NMV/r group and 53 to the PBO/r group. Nearly all participants (n = 153) had received the primary series for COVID-19 vaccination. Mean (SD) time between index SARS-CoV-2 infection and randomization was 17.5 (9.1) months. There was no statistically significant difference in the model-derived severity outcome pooled across the 6 core symptoms at 10 weeks between the NMV/r and PBO/r groups. No statistically significant between-group differences were found at 10 weeks in the Patient Global Impression of Severity or Patient Global Impression of Change scores, summative symptom scores, and change from baseline to 10 weeks in PROMIS fatigue, dyspnea, cognitive function, and physical function measures. Adverse event rates were similar in NMV/r and PBO/r groups and mostly of low grade.

CONCLUSIONS AND RELEVANCE The results of this randomized clinical trial showed that a 15-day course of NMV/r in a population of patients with PASC was generally safe but did not demonstrate a significant benefit for improving select PASC symptoms in a mostly vaccinated

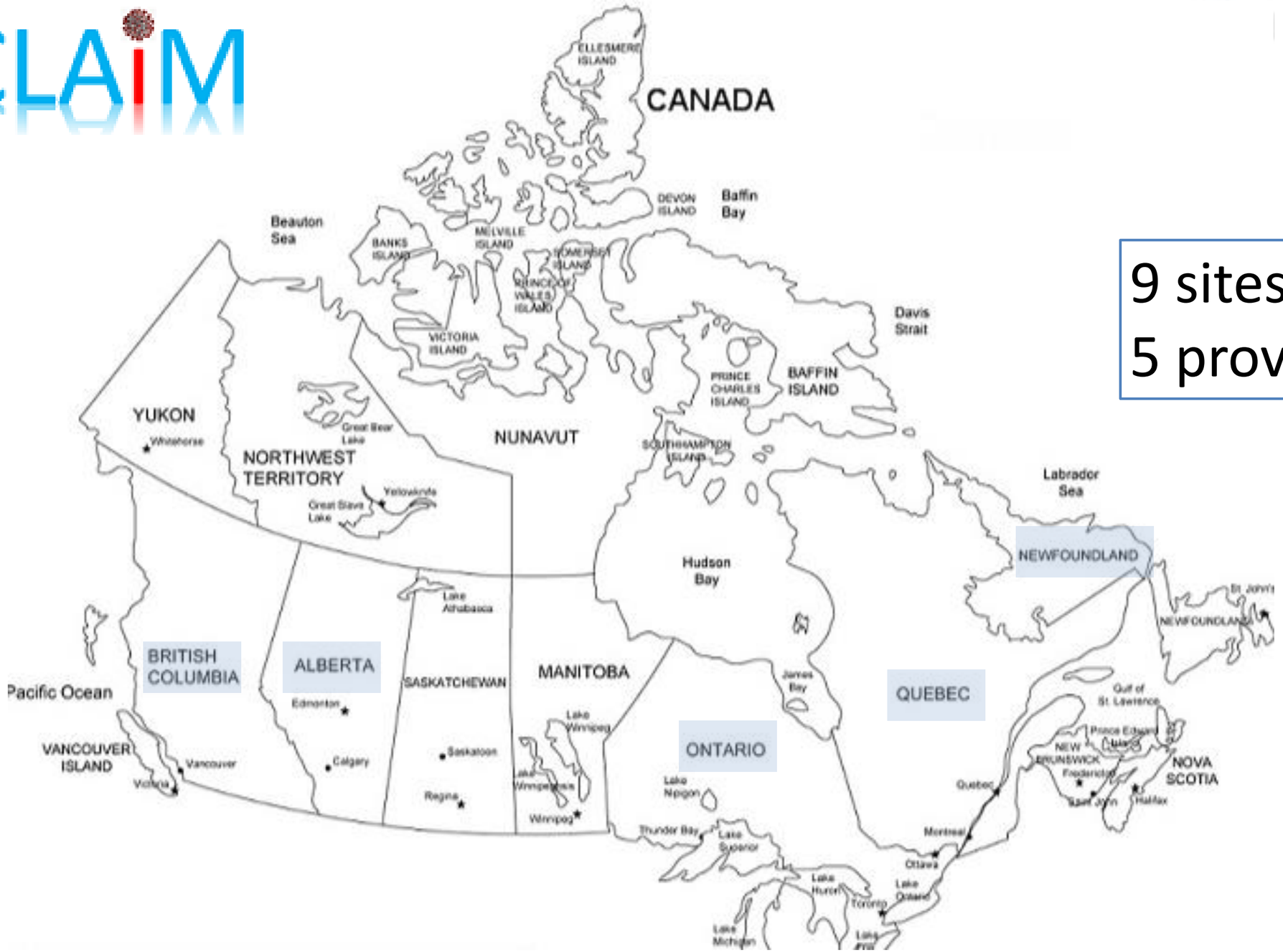
The RECLAiM Trial

REcovering from
COVID-19
Lingering Symptoms
Adaptive
Integrative
Medicine

Adaptive Platform Trial

CIHR IRSC

RECLAIM

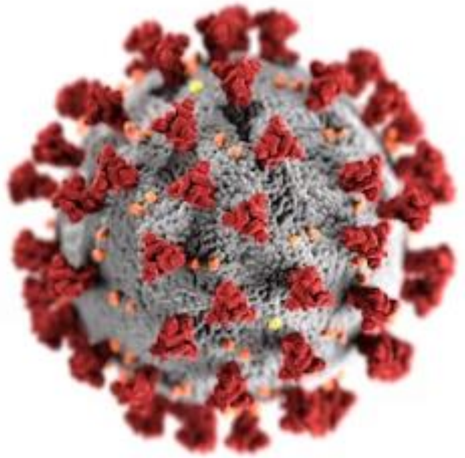


9 sites
5 provinces

What are the Interventions in RECLAIM?

Potential pathogenic mechanisms (based on WHO report*) that we are targeting:

1) Immune dysregulation
2) Inflammation
3) Endothelial dysfunction
4) Viral or viral particle persistence
5) Thrombotic microclots
6) Mitochondrial dysfunction
7) Perturbations to microbiome



Investigators, patient partners, outside experts met Sept 10, 2021 and voted on the first round of therapies to be tested

WHO Report: Expanding our understanding of Post COVID-19 condition. 2021. ISBN 978-92-4-002503-5

RECLAIM trials

Pentoxifylline (PEN)

Ibudilast (IBU)

Hyperbaric oxygen therapy (HBOT)

(HiOxSR)

Taurine (TAU)

Cordyceps (COR) – Traditional Chinese Medicine (TCM)

Ibudilast (MN-166)

Small Molecule / Oral meds

Same Active ingredient approved in 1989 in Japan with lower dose

- Asthma (20mg/day) Post-stroke symptoms (30mg/day)

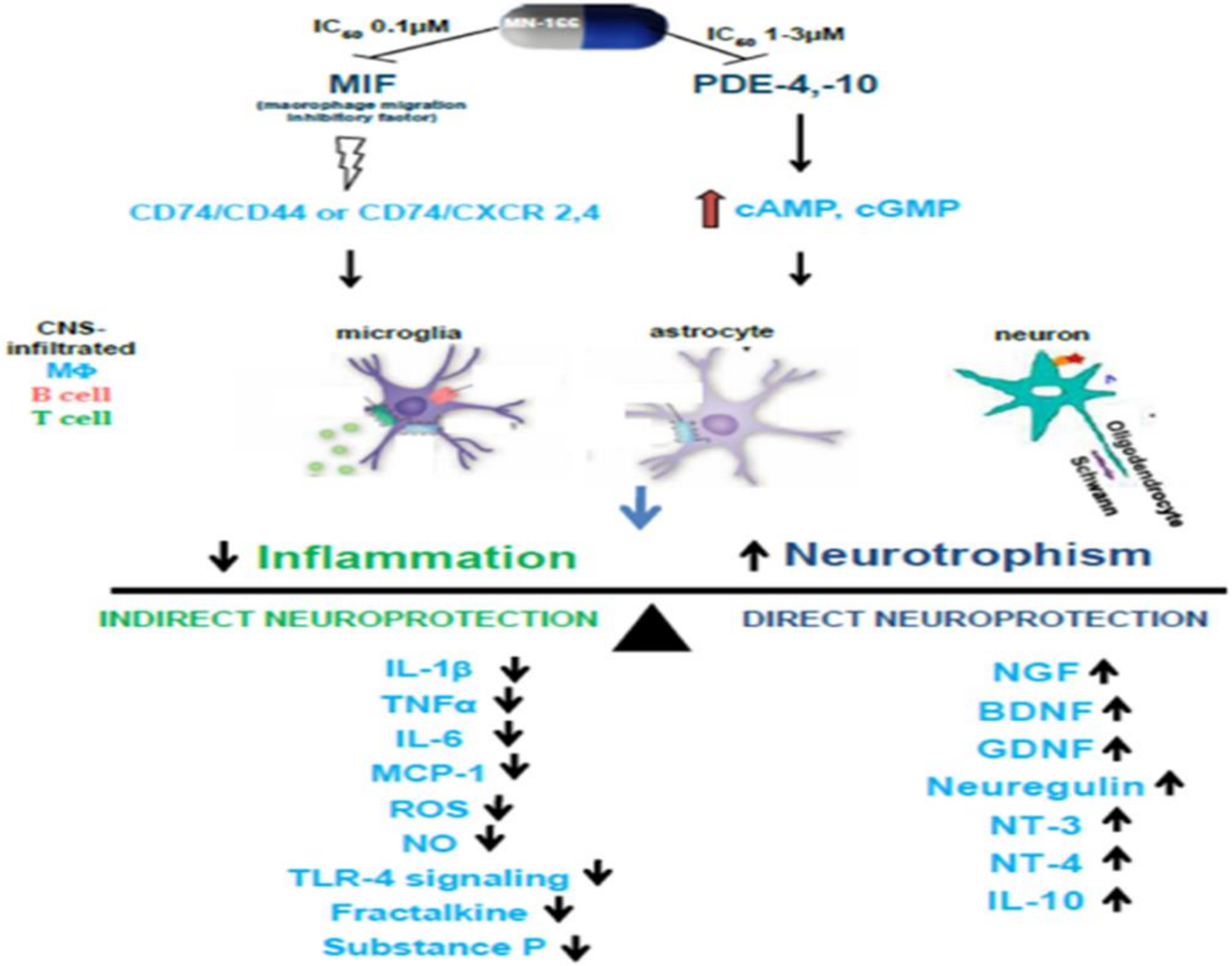
Mechanism of action

- PDE 3,4,10,11 inhibition
- MIF inhibition (Macrophage migration inhibitory factor)
- TLR4 inhibition

Expected Clinical Effects in Neurological Indication

- Anti-platelet aggregation / Vasodilation=> **increase cerebral blood flow**
- **Anti-inflammation**
- Glia attenuation
- **Neuroprotective** cytokine /chemokine

MN-166 Mechanism of Action



Pentoxifylline

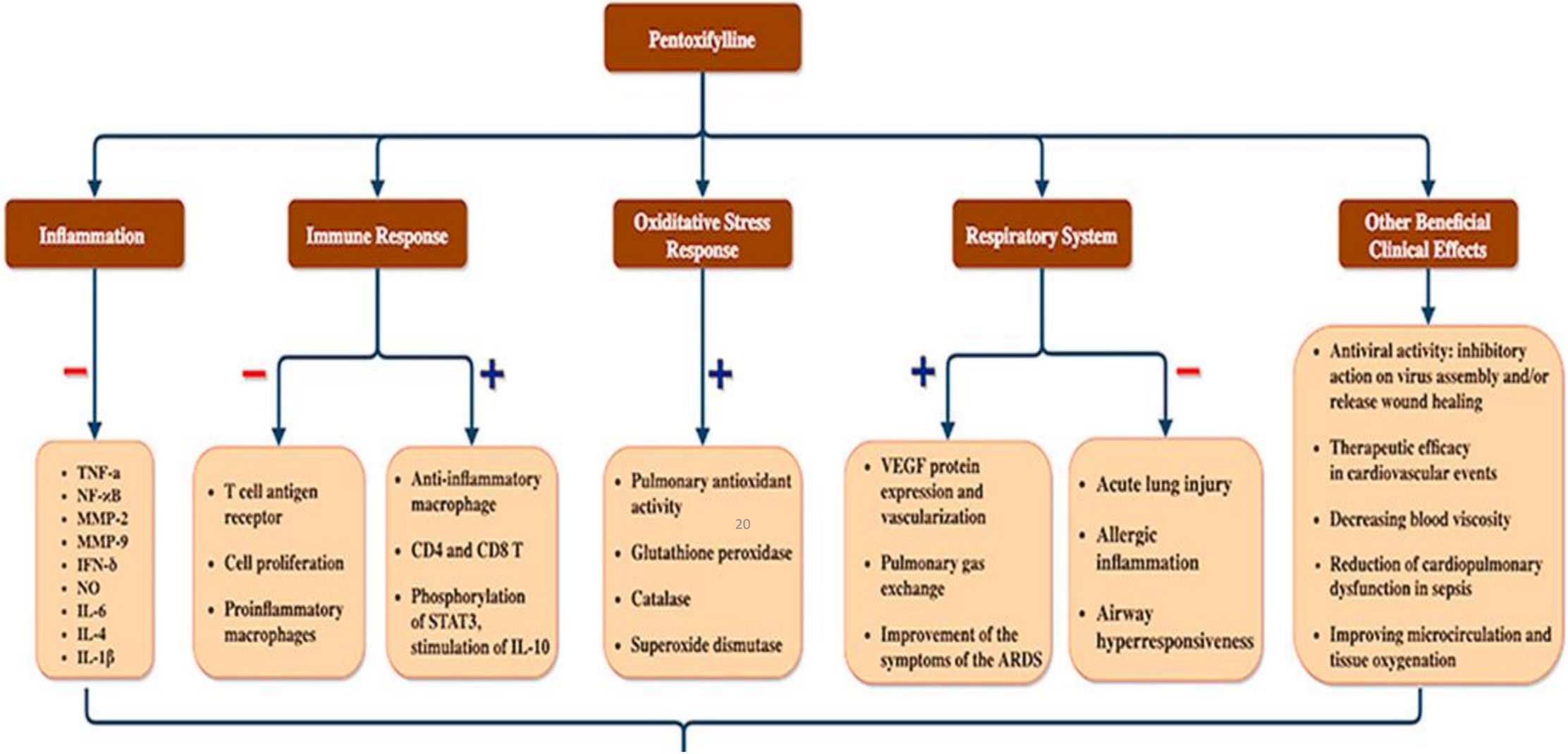
- Xanthine derivative (1H-Purine-2,6-dione, 3,7-dihydro-3,7-dimethyl-1-(5-oxohexyl)-xanthine)
- Oral medication taken 3 times a day
- Used for occlusive vascular disease / intermittent claudication for decades in Canada
- First approved in Europe in 1972

Pentoxifylline Mechanism of Action

1. Increases red blood cell flexibility
   - Increase erythrocyte ATP
   - Increase cyclic nucleotide levels
2. Reduces viscosity of blood
   - Decrease erythrocyte aggregation
   - Stimulate fibrinolysis and reduce plasma fibrinogen concentration
3. Phosphodiesterase (PDE) inhibitor
   - Increase cyclic AMP
   - Inhibits thromboxane
   - Increase prostaglandin synthesis

   → Decrease platelet aggregation
4. Vasodilation in skeletal muscles vascular bed
5. Inhibits leukocyte-derived free radicals (generated by not enough O2)
6. Has immunomodulatory effects
   - Decrease production of inflammatory cytokines

Pentoxifylline Mechanism of Action



https://doi.org/10.1016/j.ejphar.2020.173561

Inclusion and Exclusion Criteria

- Age 18 and over
- WHO criteria of Post-COVID Condition
  - Lingering symptoms for 3 months or more
  - Last at least 2 months
  - Non-explainable by other conditions
- Exclude those on mechanical ventilation or ECMO

Who are the Subjects?

Inclusion criteria:

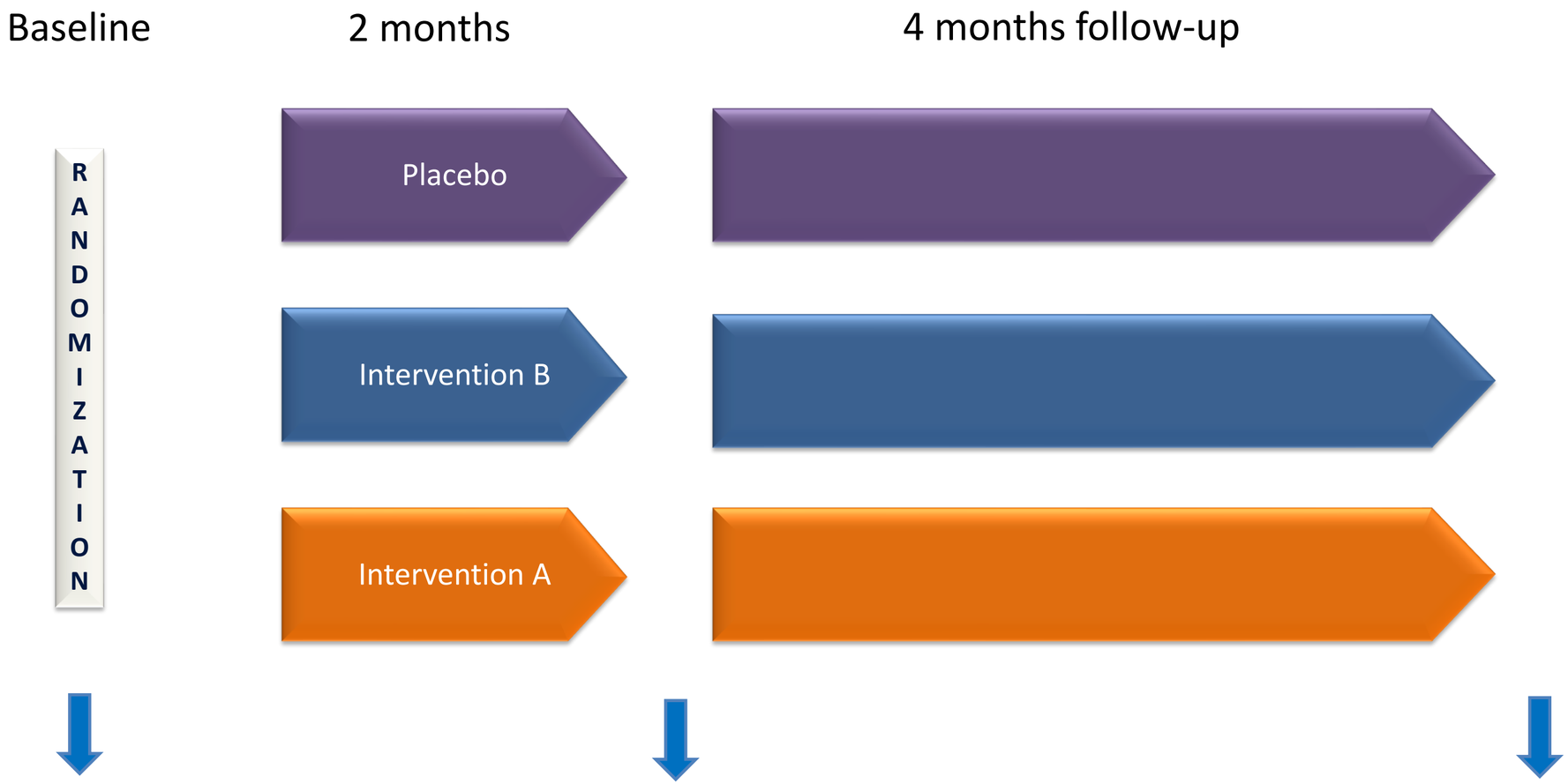
1. Age ≥18 years;
2. Positive COVID-19 test (RT-PCR test, RAT, antibody tests at least 3 months prior to randomization)
   OR
   Presumed COVID-19 assessed by the site investigator (no positive COVID-19 test) with acute illness after October 15, 2019, and at least 3 months prior to randomization.
3. Treated with standard of care therapies for at least 4 weeks prior to entry into trial.
4. Lingering COVID-19 symptoms beyond 3 months from onset of acute COVID and symptoms have lasted at least 2 months. The onset of COVID is considered the earliest of two dates: the date of positive testing or the date of first symptoms.
5. Lingering symptoms from COVID-19 present at the time of randomization.
6. Female patients of childbearing potential (as assessed by the overseeing Investigator) who are sexually active must agree to practice true abstinence or use at least one highly effective method of contraception while on study treatment. Highly effective methods of contraception must be discussed and approved by the overseeing Investigator (refer to Section 5 Contraception).
7. Must be able to provide informed consent and both willing and able to comply with study requirements.

Who are the Subjects?

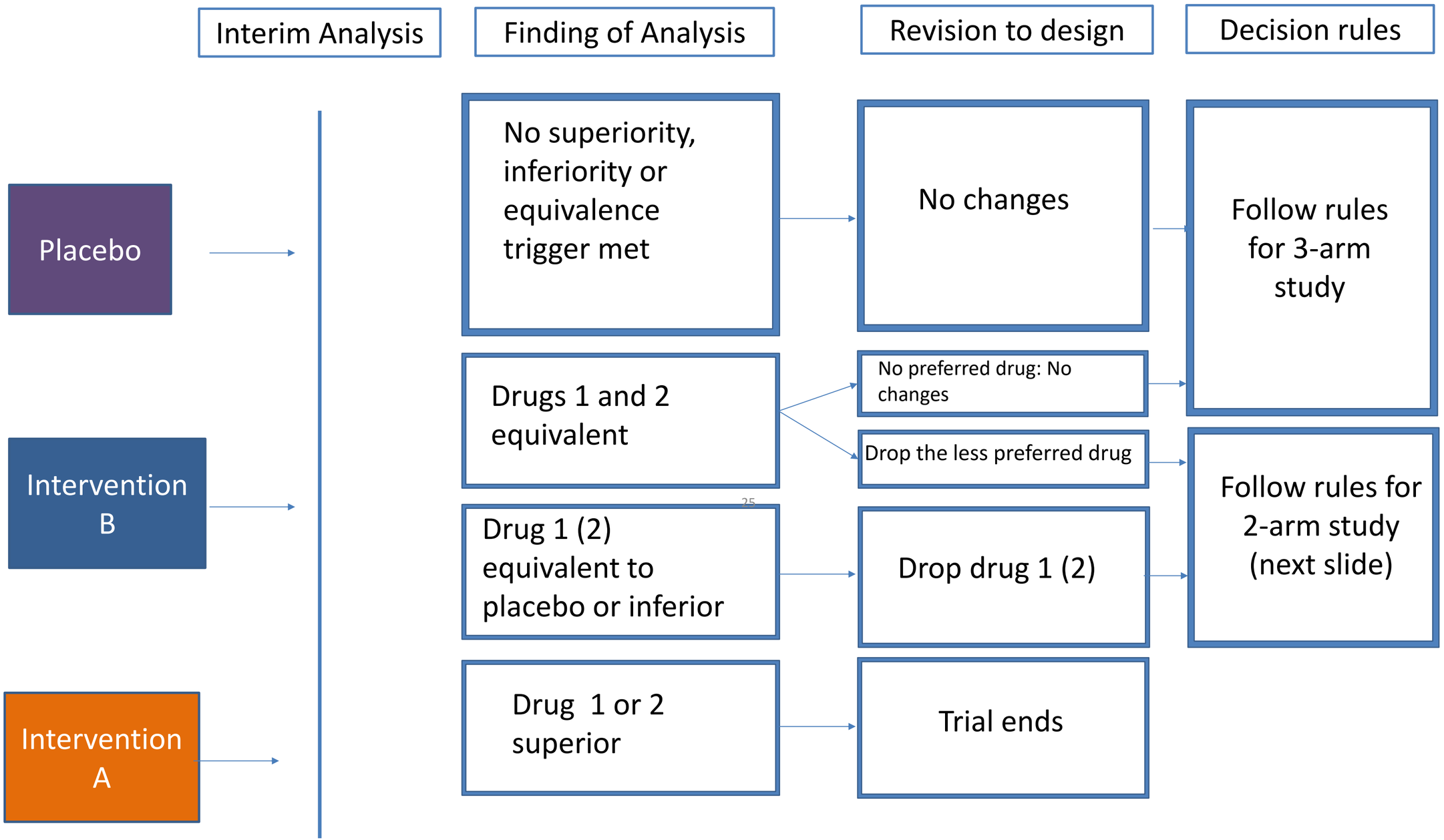
Exclusion criteria:

1. Patients who had mechanical ventilation or extracorporeal membrane oxygen (ECMO) for COVID-19.
2. Current end-organ failure, organ transplantation, or current hospitalization in acute care hospital.
3. Contraindications to all of the study interventions,
4. Co-enrollment in another interventional trial (co-enrolment in an observational study is permitted).
5. Currently pregnant or breastfeeding.

Structure of RECLAIM



RECLAIM ADAPTATION: Rules for three-arm study



SECONDARY OBJECTIVES

1. Symptoms:
    - Three point Likert scale assessing how bothersome symptoms are on a weekly basis for two months then monthly until end of study, as reported by the participant: to provide a granular, detailed picture of the symptom trajectory.
    - Symptom Checklist (adapted from the De Paul Symptom Questionnaire (DSQ2), the World Health Organization Global COVID-19 Clinical Platform's Post COVID-19 CRF and the Symptom Burden Questionnaire for Long COVID): to track symptom trajectory.
2. Six minute walk test scores (with oximetry): to assess functional capacity.
3. A selected number of measures developed through the TestMyBrain.org: to assess cognitive impairment.
4. Post COVID19 functional status scale (0-4) scores: to evaluate functional limitations due to COVID-19.

SECONDARY OBJECTIVES

5. Re-integration to Normal Living Index (RNLI) scores: to determine the degree to which participants reintegrate into normal social activities.

6. Fatigue: using the Brief fatigue inventory and Fatigue Scale (adapted from the DSQ-2), to evaluate the severity and impact of fatigue.

7. Post-Exertional Malaise: will be assessed using the DePaul Post-Exertional Malaise Questionnaire (DPEMQ)

8. Mental Health: using the PCL-5 (to assess post-traumatic stress disorder), PHQ-9 (to assess depression), and GAD-7 (to assess anxiety).

9. Mental health-related quality of life: will be assessed with the Mental Composite Score (MCS) of the SF-36 (v.1).

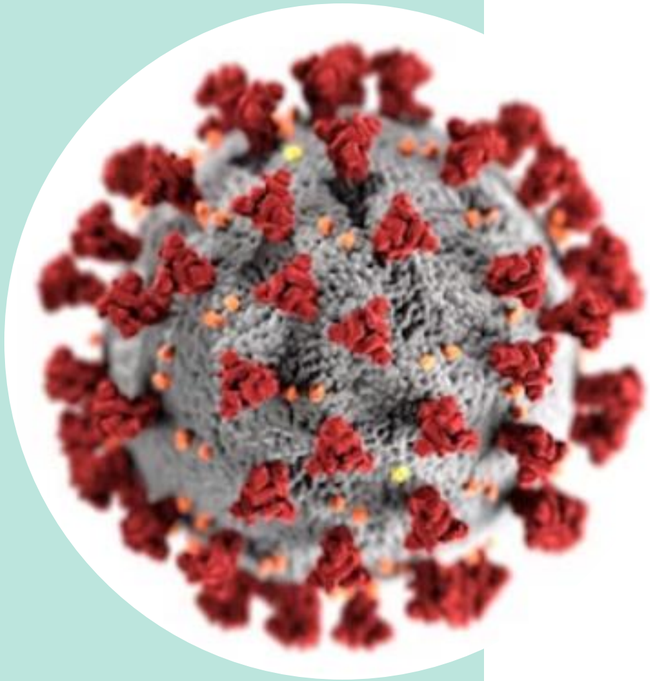
SECONDARY OBJECTIVES

10. Dyspnea: to assess levels of self-reported shortness of breath at rest and during activity using the Modified Borg Dyspnea Scale.

11. Biospecimens to assess potential biomarkers and genetic, transcriptomic, epigenomic and immunological predictors of outcomes following study intervention.

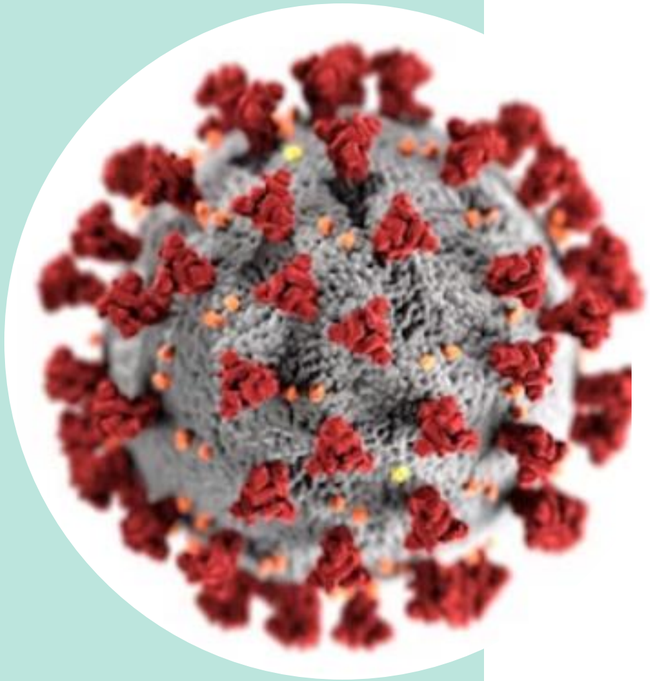
PRELIMINARY RESULTS

RECLAIM June 16, 2025



RECLAIM – DRUG TRIAL

- FIRST PT – MAY 31, 2023
- LAST PT – DEC 20, 2024
- N= 460
- ~80 HAVE NOT REACHED 6-MONTH ENDPOINT



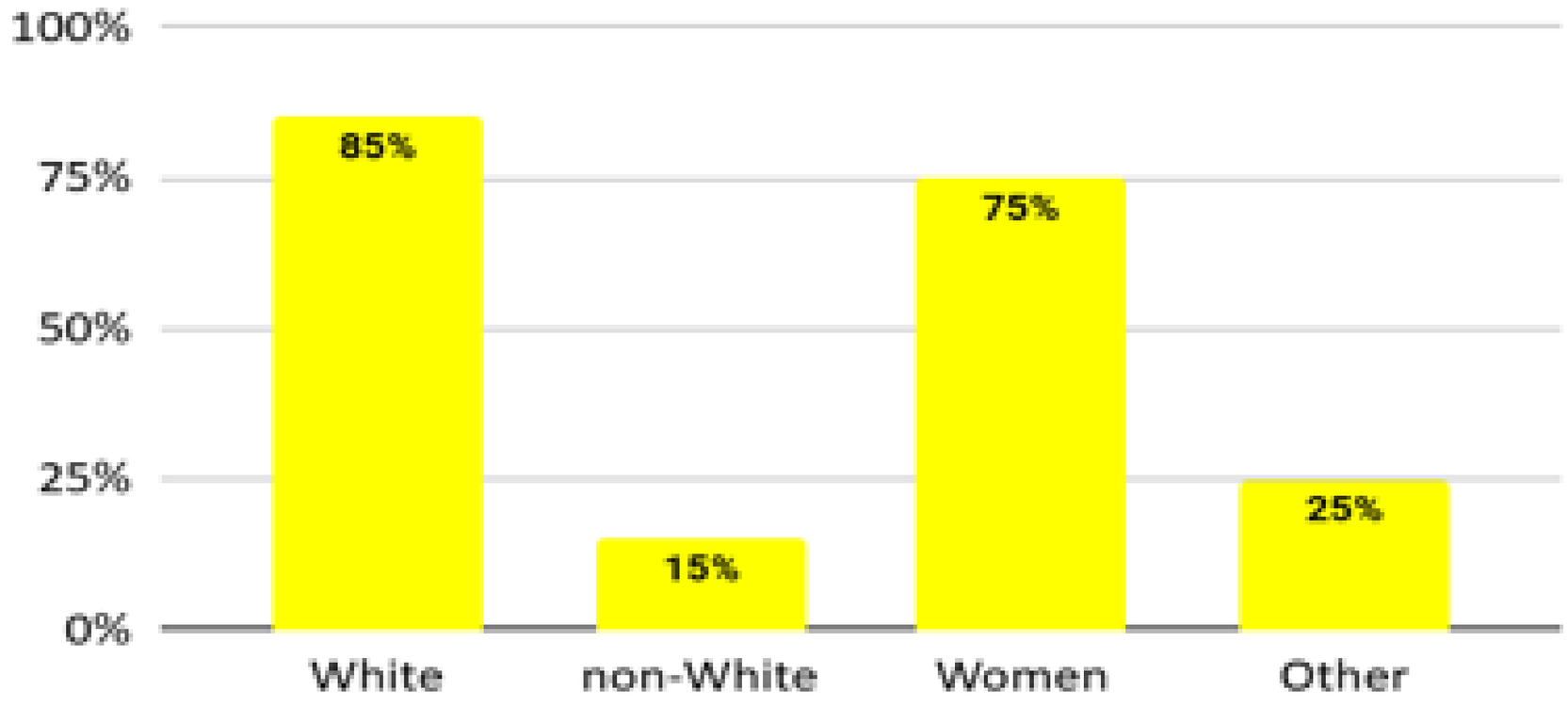
RECLAIM – DRUG TRIAL

Ibudilast vs placebo:	p=0.89
Pentoxifylline vs placebo	p=0.87
Ibudilast vs pentoxifylline	p=0.96

Stigma

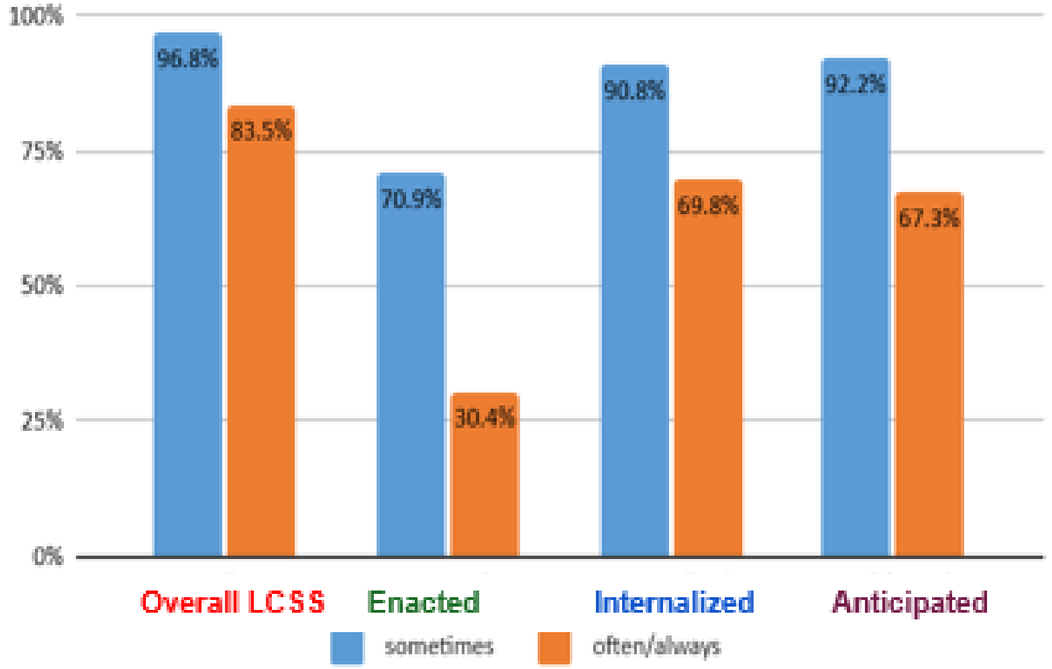
- Total RECLAIM participants: 460. Only 437 participants completed the baseline stigma scale.
- Mean age: 48 years (SD: 11.7, range 18-84 years)

Figure 1: Race and Gender Distribution



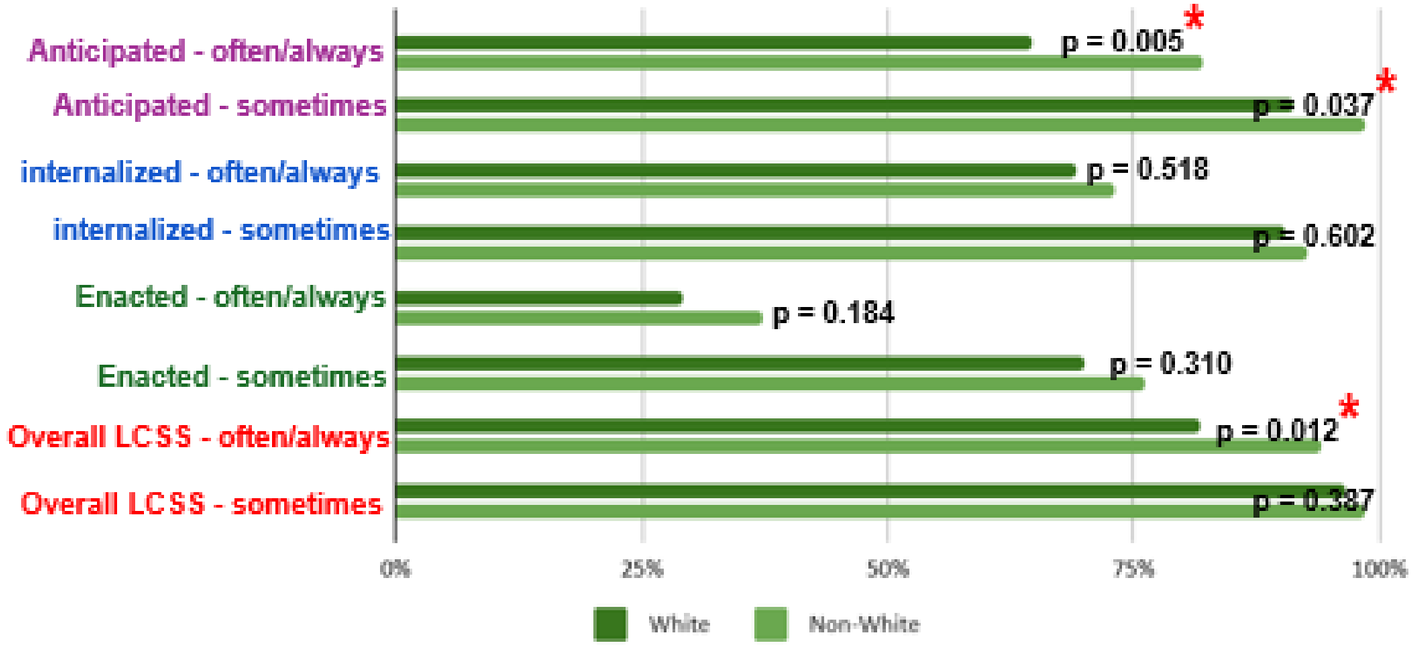
Stigma

Figure 2 :Stigma response for the full sample (n=437)



Note: Percentages are based on the total number of participants in each subgroup

Figure 3: Stigma response by Race



Note: Percentages are based on the total number of participants in each subgroup; *p<0.05 before Bonferroni correction.

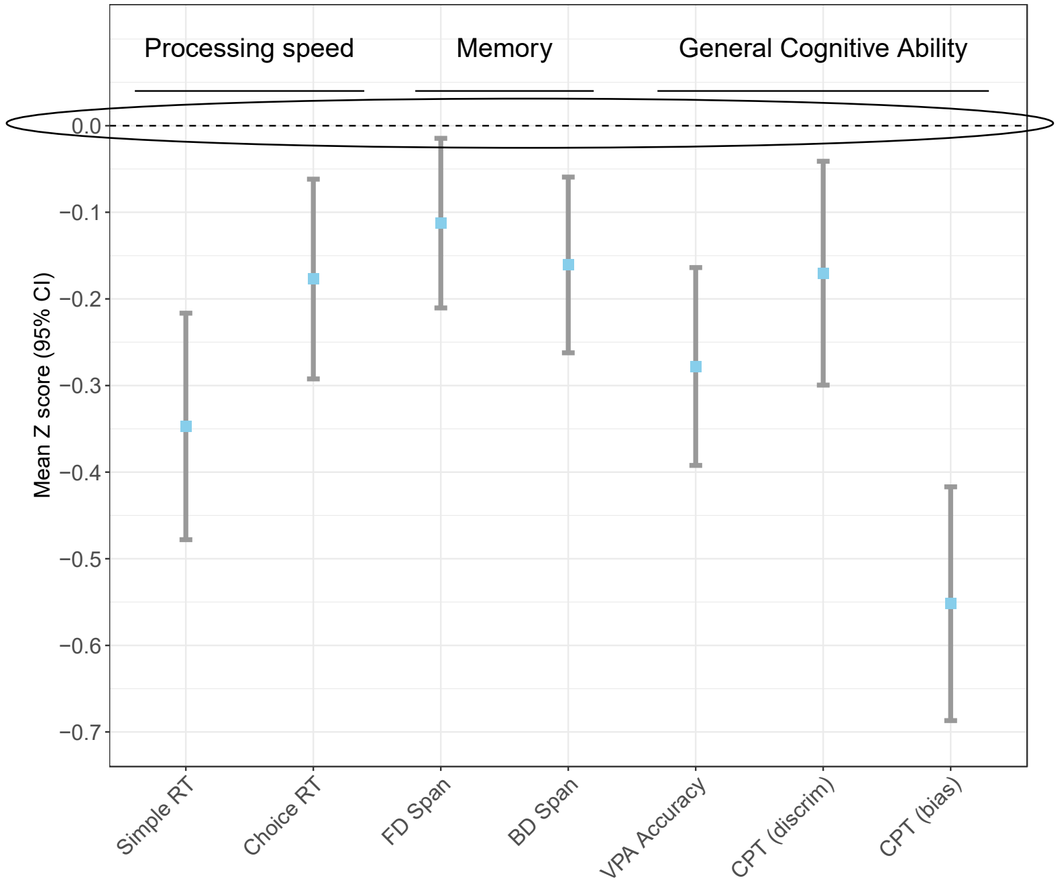
Neurocognitive Outcomes at Baseline

Compared to the TMB reference population

(SRT n= 46539, VPA n= 9716),

- **Significantly lower Z-scores in both SRT and VPA**
  - *(mean (SD): -0.35 (1.19), p< 0.001, and -0.28 (1.03), p< 0.001)*
- All other cognitive tasks also demonstrated **decreased scores**
- Gradual Onset Continuous Performance Task **(CPT) bias showed the most impairment**
  - *(mean (SD): -0.55 (1.22), p< 0.001)*

Figure 2. TMB Z-score results of 317 participants



Other upcoming RECLAIM trials

- Pentoxifylline (PEN) ✓
- Ibudilast (IBU) ✓
- Hyperbaric oxygen therapy (HBOT)
- (HiOxSR)
- Taurine (TAU)
- Cordyceps (COR) – Traditional Chinese Medicine (TCM)

scientific reports

Article | Open Access | Published: 12 July 2022

Hyperbaric oxygen therapy improves neurocognitive functions and symptoms of post-COVID condition: randomized controlled trial

Shani Zilberman-Itskovich, Merav Catalogna, Efrat Sasson, Karin Elman-Shina, Amir Hadanny, Erez Lang, Shachar Finci, Nir Polak, Gregory Fishlev, Calanit Korin, Ran Shorer, Yoav Parag, Marina Sova & Shai Efrati ✉

Scientific Reports **12**, Article number: 11252 (2022) | Cite this article

HI-OXSR

Phase 1

- 4 weeks from acute infection
- 14 days of twice daily 30min treatments
- Followed for 1 month after

Preliminary results: positive

UHN Toronto General Toronto Western Princess Margaret Toronto Rehab

Medicine UNIVERSITY OF TORONTO

OTHER TRIALS

Published as of June 16, 2025

What do the RECOVER clinical trials study?

RECOVER clinical trials study possible causes of Long COVID and possible treatments for Long COVID symptoms. The RECOVER team has developed a set of clinical trials based on what researchers are learning from RECOVER studies and conversations with people living with Long COVID. RECOVER clinical trials are studying multiple treatments across 5 focus areas:

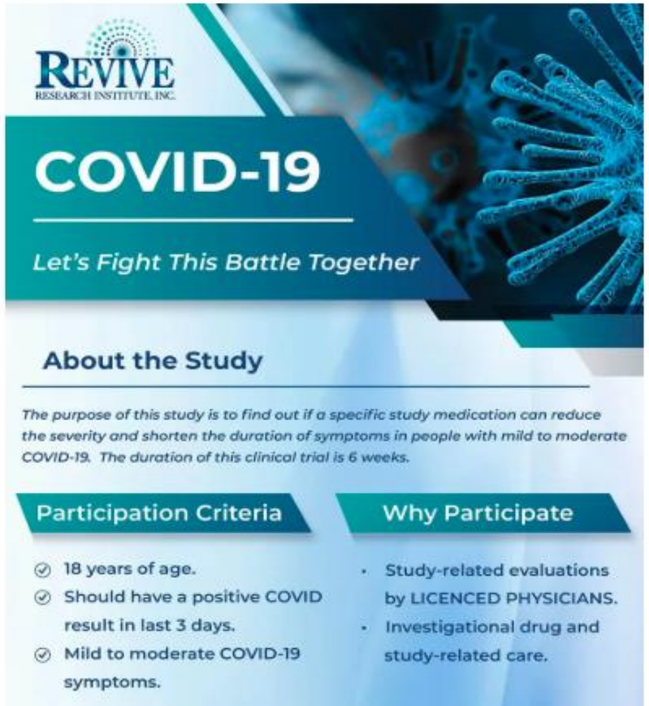
- **Autonomic Dysfunction**: Dizziness, fast heart rate, shortness of breath, upset stomach, or other changes in body functions that happen automatically
- **Cognitive Dysfunction**: "Brain fog," trouble thinking clearly, memory changes, slowed attention, and other symptoms related to brain function
- **Exercise Intolerance and Fatigue**: Exhaustion or low energy that interferes with daily activities
- **Sleep Disturbances**: Changes in sleep patterns or the ability to sleep
- **Viral Persistence**: When the virus that causes COVID stays in the body and damages organs or affects the immune system

RECOVER-SLEEP Hypersomnia (Modafinil/Solriamfetol)	Modafinil and solriamfetol are repurposed drugs used to help people stay awake during the day.	News Release RECOVER-SLEEP Study Record Hypersomnia (Modafinil/Solriamfetol) Study Record Complex Sleep Disturbances (Melatonin + Light Therapy) Study Record Protocol →
RECOVER-SLEEP Complex Sleep Disturbances (Melatonin + Light Therapy)	Melatonin is a natural hormone in the brain that helps regulate the timing of sleep. Light therapy is exposure to a bright light that may help improve and regulate sleep-wake patterns.	
RECOVER-ENERGIZE Exercise Intolerance (Personalized Cardiopulmonary Rehabilitation)	Personalized Cardiopulmonary Rehabilitation is a program that combines exercise training with education to help participants with exercise intolerance improve their quality of life and ability to exercise. The program is tailored to the participant's level of functioning and progress.	Website → News Release RECOVER-ENERGIZE Study Record Exercise Intolerance (Cardiopulmonary Rehabilitation) Study Record Post-Exertional Malaise (Pacing) Study Record Protocol →
RECOVER-ENERGIZE Post-Exertional Malaise (Structured Pacing)	Structured Pacing is a program to help participants get to know, control, and minimize PEM symptoms with the assistance of a Pacing Coach. The goal of the program is to help people experience more stable function in everyday life with less frequent and less severe PEM symptoms.	

CLINICAL TRIAL	DESCRIPTION	LEARN MORE
RECOVER-VITAL Viral Persistence (PAXLOVID)	PAXLOVID (nirmatrelvir and ritonavir) is an antiviral drug that works to stop the virus that causes COVID-19 from multiplying.	Website → Enrollment Announcement RECOVER-VITAL Study Record Viral Persistence (PAXLOVID) Study Record Protocol →
RECOVER-NEURO Cognitive Dysfunction (BrainHQ, PASC-CoRE, & tDCS)	BrainHQ is an interactive online brain training program designed to improve memory, attention, and brain processing speed.	Website → Enrollment Announcement RECOVER-NEURO Study Record Cognitive Dysfunction (BrainHQ, PASC CoRE, and tDCS Intervention) Study Record Protocol →
	PASC Cognitive Recovery (PASC-CoRE) is an online goal management training program.	
	Transcranial Direct Current Stimulation (tDCS) is a safe, noninvasive form of brain stimulation.	
RECOVER-AUTONOMIC Severe POTS (IVIG)	Gamunex-C, a form of intravenous immunoglobulin (IVIG), is a repurposed drug that contains antibodies to help the body protect itself against infection from various diseases.	Website → Enrollment Announcement RECOVER-AUTONOMIC Study Record Severe POTS (IVIG) Study Record Moderate POTS (Ivabradine) Study Record Protocol →
RECOVER-AUTONOMIC Moderate POTS (Ivabradine)	Ivabradine is a repurposed drug that reduces heart rate.	

COVID-19

Clinical Trial Excellence in Internal Medicine



COVID-19

Combat the Pandemic with Revive's COVID 19 Clinical Trials

Covid-19 is a contagious disease caused by SARS-CoV-2, a new coronavirus variant. It was declared a global pandemic by WHO in March 2020.

Revive Research Institute, as a rising leader in clinical research, is dedicated to finding treatments and enhancing healthcare services. We are currently conducting covid-19 clinical trials and working tirelessly to help make lives better for a brighter future, free of masks.

Our coronavirus clinical research center employs skilled specialists with backgrounds in a wide range of medical conditions to guarantee that you receive the finest COVID treatment available.

Join us in our clinical trial to bring a change.

PARTICIPATION CRITERIA:

COVID-19

Clinical Trial Excellence in Internal Medicine

Intervention / Treatment

- Drug: Fluvoxamine Maleate 100 MG
- Drug: Placebo
- Drug: Metformin Extended Release Oral Tablet

SUMMARY

- PUBLISHED TRIALS
- RECLAIM – IBU AND PEN ARE DONE, 4 MORE TO OPEN SHORTLY
- EXPECT RESULTS FROM VARIOUS TRIALS AT THE END OF THE YEAR 2025

LONG COVID WEB

MEMORIAL UNIVERSITY

3rd Canadian Symposium on Long COVID

Registration Open

October 20 - 21, 2025

VIRTUAL and IN-PERSON

Emera Innovation Exchange
Conference Centre,
Memorial University of Newfoundland
St. John's, Newfoundland and Labrador

Questions/ Comments