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# The UPMC OPTIMISE-C19 (OPtimizing Treatment and Impact of Monoclonal antIbodieS through Evaluation for COVID-19) trial: a structured summary of a study protocol for an open-label, pragmatic, comparative effectiveness platform trial with response-adaptive randomization

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## Abstract

**Objectives:** The primary objective is to evaluate the comparative effectiveness of COVID-19 specific monoclonal antibodies (mABs) with US Food and Drug Administration (FDA) Emergency Use Authorization (EUA), alongside UPMC Health System efforts to increase patient access to these mABs.

**Trial design:** Open-label, pragmatic, comparative effectiveness platform trial with response-adaptive randomization

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**Participants:** We will evaluate patients who meet the eligibility criteria stipulated by the COVID-19 mAB EUAs who receive mABs within the UPMC Health System, including infusion centers and emergency departments. EUA eligibility criteria include patients with mild to moderate COVID-19, ≤10 days of symptoms, and who are at high risk for progressing to severe COVID-19 and/or hospitalization (elderly, obese, and/or with specific comorbidities). The EUA criteria exclude patients who require oxygen for the treatment of COVID-19 and patients already hospitalized for the treatment of COVID-19. We will use data collected for routine clinical care, including data entered into the electronic medical record and from follow-up calls.

**Intervention and comparator:** The interventions are the COVID-19 specific mABs authorized by the EUAs. All aspects of mAB treatment, including eligibility criteria, dosing, and post-infusion monitoring, are as per the EUAs. As a comparative effectiveness trial, all patients receive mAB treatment, and the interventions are compared against each other.
When U.S. government mAB policies change (e.g., FDA grants or revokes EUAs), UPMC Health System policies and the evaluated mAB interventions will accordingly change. From November 2020 to February 2021, FDA issued EUAs for three mAB treatments (bamlanivimab; bamlanivimab and etesevimab; and casirivimab and imdevimab), and at trial launch on March 10, 2021 we evaluated all three. Due to a sustained increase in SARS-CoV-2 variants in the United States resistant to bamlanivimab administered alone, on March 24, 2021 the U.S. Government halted distribution of bamlanivimab alone, and UPMC accordingly halted bamlanivimab monotherapy on March 31, 2021. On April 16, 2021, FDA revoked the EUA for bamlanivimab monotherapy. At the time of manuscript submission, we are therefore evaluating the two mAB treatments authorized by EUAs (bamlanivimab and etesevimab; and casirivimab and imdevimab).

**Main outcomes:** The primary outcome is total hospital free days (HFD) at 28 days after mAB administration, calculated as 28 minus the number of days during the index stay (if applicable – e.g., for patients admitted to hospital after mAB administration in the emergency department) minus the number of days readmitted during the 28 days after treatment. This composite endpoint captures the number of days from the day of mAB administration to the 28 days thereafter, during which the patient is alive and free of hospitalization. Death within 28 days is recorded as -1 HFD, as the worst outcome.

**Randomisation:** We will start with equal allocation. Due to uncertainty in sample size, we will use a Bayesian adaptive design and response adaptive randomization to ensure ability to provide statistical inference despite variable sample size.
When mABs are ordered by UPMC physicians as a generic referral order, the order is filled by UPMC pharmacy via therapeutic interchange. OPTIMISE-C19 provides the therapeutic interchange via random allocation. Infusion center operations teams and pharmacists use a mAB assignment application embedded in the electronic medical record to determine the random allocation.

**Blinding (masking):** This trial is open-label. However, outcome assessors conducting follow-up calls at day 28 are blinded to mAB assignment, and investigators are blinded to by-mAB aggregate outcome data until a statistical platform trial conclusion is reached.

**Numbers to be randomised (sample size):** Sample size will be determined by case volume throughout the course of the pandemic, supply of FDA authorized mABs, and by that needed to reach a platform trial conclusion of inferiority, superiority, or futility of a given mAB. The trial will continue as long as more than one mAB type is available under EUA, and their comparative effectiveness is uncertain.

**Trial Status:** Protocol Version 1.0, February 24, 2021.
Recruitment began March 10, 2021 and is ongoing at the time of manuscript submission. The estimated recruitment end date is February 22, 2022, though the final end date is dependent on how the pandemic evolves, mAB availability, and when final platform trial conclusions are reached. As noted above, due to U.S. Government decisions, UPMC Health System halted bamlanivimab monotherapy on March 31, 2021.

**Trial registration:** ClinicalTrials.gov Identifier: NCT04790786. Registered March 10, 2021

**Full protocol:** The full protocol is attached as an additional file, accessible from the Trials website (Additional file 1). In the interest in expediting dissemination of this material, the familiar formatting has been eliminated; this Letter serves as a summary of the key elements of the full protocol.

**Keywords:** COVID-19, pragmatic trial, randomised controlled trial, protocol, monoclonal antibodies, bamlanivimab, etesevimab, casirivimab, imdevimab

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-021-05316-3.

**Additional file 1.**

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### Authors' contributions

All authors contributed to the design and execution of the study and approved the manuscript.

### Funding

The Federal COVID Response Team (formerly called Operation Warp Speed) supplies mABs to UPMC, participates in design discussions, and is provided regular updates. UPMC supports this trial with resources and internal funds, and leadership was involved in all aspects of the trial including design, analysis, data interpretation, and manuscript preparation.

### Availability of data and materials

Data will be made available from the author on reasonable request and pursuant to contractual agreements, via contacting David T. Huang at huangdt@upmc.edu.

## Declarations

### Ethics approval and consent to participate

University of Pittsburgh IRB STUDY21020179, approved March 1, 2021. UPMC Quality Improvement Review Committee Project ID 3280, approved April 20, 2021. We certify this trial has received ethical approval from the appropriate committees as described above.

OPTIMISE-C19 is a quality improvement (QI) study, governed by approvals from both the UPMC QI committee and the University of Pittsburgh IRB. Currently, mAB therapy is approved for use under EUA issued by the FDA. There are no data on the relative benefits of one mAB versus any other. mABs are ordered by UPMC physicians as a generic referral order and the order is filled by UPMC pharmacy via therapeutic interchange. The selection of mABs available within pharmacy is overseen by the UPMC pharmacy and therapeutics committee. OPTIMISE-C19 provides the therapeutic interchange via random allocation. The UPMC Quality Improvement Committee approved the OPTIMISE-C19 study, including the random therapeutic interchange. The University of Pittsburgh IRB considered the randomized therapeutic interchange to be quality improvement and approved the additional data collection and analyses.

Patients provide verbal consent to receive mAB therapy. UPMC requires physicians to provide and review with patients the EUA Fact Sheet for each mAB, and explain that the patient could receive any of the EUA-governed mABs. As per EUA requirements, physicians discuss the risks and benefits of mABs with patients, and patients consent to receive a mAB as part of routine care, should they desire mAB treatment. Patients are told which mAB they are receiving, and physicians and patients can agree to the assigned mAB or request a specific mAB. It is the treating physicians' and patients' choice to accept the assigned mAB or not. The QI committee considered these steps to represent adequate consent to participate. The IRB considered that the provision of mAB therapy therefore fell under quality improvement and only the additional data collection and analyses represented research. The IRB waived any additional consent requirements.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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