Evidence-based Practice Center Rapid Review Protocol

Project Title: *Adverse Events Associated with COVID-19 Pharmaceutical Treatments*

I. Background and Objectives for the Systematic Review

The Public Readiness and Emergency Preparedness Act of 2005 (PREP Act) authorizes the Countermeasures Injury Compensation Program (CICP) to support the development, distribution, and use of countermeasures by providing compensation for serious injuries or death directly caused by the administration or use of covered countermeasures.[1] To provide compensation to eligible individuals who sustain a covered injury, the CICP must establish that a covered injury was sustained as the direct result of the administration or use of a covered countermeasure based on "compelling, reliable, valid medical, and scientific evidence." Eligible individuals may be compensated by showing an injury is the direct result of a covered countermeasure, or if an injury meets the requirements of a covered countermeasure injury table unless there is another more likely cause.

A countermeasure injury table lists and explains injuries presumed to be caused by a covered countermeasure and provides a rebuttable presumption that the covered countermeasure was the cause of the injury, if the injury occurred within the listed time period, while meeting the severity requirement. Serious physical injuries, as defined in 42 CFR 110.3(z), are "physical biochemical alterations leading to physical changes and serious functional abnormalities at the cellular or tissue level in any bodily function may, in certain circumstances, be considered serious injuries. As a general matter, only injuries that warranted hospitalization (whether the person was actually hospitalized) or injuries that led to a significant loss of function or disability (whether or not hospitalization was warranted) will be considered serious injuries." Disability is defined as "a physical or mental impairment that substantially limits one or more major life activities of an individual." Minor side effects from a countermeasure—such as soreness, headache, or fatigue—are not included. An injury as the direct result of the covered condition or disease for which the countermeasure was administered or used, and not the covered countermeasure, is not a covered injury.

Since the beginning of the COVID-19 pandemic, over 11,000 COVID-19 claims have been filed in the CICP. For compensation of a claim, there must be compelling, reliable, valid medical, and scientific evidence that the injury was directly caused by the countermeasure. Temporality alone is not sufficient to establish that an alleged injury was directly caused by a countermeasure. Thus, there is an urgent need for a rapid product to summarize the best available evidence on adverse events associated with authorized treatments for COVID-19. The Agency for Healthcare Research & Quality (AHRQ) has

commissioned a rapid review using abbreviated methods to provide an assessment of evidence in a compressed timeframe to inform the end-user's decision.

Purpose of the Review

The purpose of the Rapid Review is to provide an overview of the risk, severity, and timing of adverse events associated with treatments for COVID-19 approved under Emergency Use Authorization or previously approved by the Food & Drug Administration (FDA). The project's sponsor, the federal Health Resources & Services Administration (HRSA) will use the report to inform a countermeasure injury table and relevant amendments by identifying potential injuries and grading the strength of evidence between these interventions and potential injuries; once a table and any relevant amendments are published, it will be used to make decisions in compensating individuals for covered injuries or deaths.

II. Key Question

KQ1: What are the serious adverse effects or events directly caused by the use or administration of medications approved by the FDA to prevent or treat COVID-19 infection?

> KQ1a: In what timeframe are the adverse effects or events noted in KQ1 expected to occur (considering elimination half-life, etc.)?

III. Methods

Criteria for Inclusion/Exclusion of Studies in the Review

The eligibility criteria are shown in the table below.

Table 1. Eligibility Criteria

Domain	Inclusion criteria	Exclusion criteria
Population	Pediatric and adult patients with a confirmed SARS-CoV-2 infection (positive Nucleic Acid Amplification Test plus symptoms consistent with COVID-19), or in close contact with someone with confirmed COVID-19, requiring medication to prevent or treat COVID-19	Animal studies
Interventions	1. COVID-19 convalescent plasma 2. Anti-viral medications • Remdesivir • Nirmatrelvir and ritonavir • Molnupiravir 3. Monoclonal antibodies • Tocilizumab • Bamlanivimab / Etesevimab	Vaccines Use of intervention for reason other than prevention or treatment of COVID-19

	• Bebtelovimab • Sotrovimab • Casirivimab and Imdevimab • Tixagevimab and cilgavimab 4. Interleukin Antagonist: Anakinra	
Comparators	Placebo, treatment as usual, no treatment	Active comparators
Outcomes	• Serious physical injury as a result of treatment that warrant hospitalization (whether or not the person was actually hospitalized) or injuries that led to a significant loss of function or disability • Mortality as a result of the intervention	Non-major and non-serious adverse events, effectiveness outcomes,
Timing	No restriction	NA
Study Design	Randomized controlled trials, controlled clinical trials, observational studies with a comparison group, case-control studies	Uncontrolled studies, case series, case reports
Setting	Inpatient and outpatient studies conducted in the US or studies that include US patients	Conducted solely outside the US
Other Limiters	English language publications	Studies reported in abbreviated format only (e.g., conference abstract rather than in a journal publication, trial record, or FDA submission) will be excluded, studies only reported in non-English publications

Abbreviations: NA = Not applicable

Recent relevant systematic reviews and meta-analyses will be reference-mined. Publications reporting on the same participants will be consolidated into one study record.

Searching for the Evidence: Strategies for Identification of Relevant Studies

The search strategy is displayed in Appendix A. To find signals of adverse events, we will review the product labels and conduct a search on causality of adverse events associated with the interventions, regardless of medical indication.

We will search PubMed (including LitCOVID) and the Cochrane Database of Systematic Reviews to systematically identify existing research syntheses. Identified systematic reviews will be screened for relevancy and reference mined for studies of the interventions listed in Table 1. We will also retrieve the NIH/Infectious Disease Society of America guidelines for context and download submissions from the Food and Drug

Administration database for interventions that received Emergency Use Authorization. We will also reference mine the international COVID Network Meta-analysis database.

We will use the pre-established criteria listed in Table 1 to determine eligibility for inclusion and exclusion of publications in accordance with the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[2] To reduce reviewer errors and bias, all citations and abstracts will be reviewed by the project leader.

Each full-text article will be independently reviewed for eligibility by a literature reviewer and checked by the project leader. We will maintain a record of studies excluded at the full-text level with reasons for exclusion.

Data Abstraction and Data Management

The review team will create data abstraction forms in DistillerSR, an online program for systematic reviews. Forms include detailed guidance to support reviewers to aid both reproducibility and standardization of data collection. One researcher will abstract the data and the project leader will check for accuracy and completeness. Forms will be pilot tested with a sample of included articles to ensure that all relevant data elements are captured, and that ambiguity is avoided.

The following data will be abstracted

- Study identifier (author) and publication year
- Study design
    - Randomized Controlled Trial (RCT)
    - Controlled Clinical Trial
    - Retrospective cohort
    - Prospective cohort
    - Case control
    - Other, specify _____
- Setting
    - Inpatient
    - Outpatient
- Interventions
    - Category (Convalescent plasma, Anti-viral, Monoclonal antibodies, Interleukin Antagonist)
    - Specific intervention
    - Dosage
- Comparator
    - Placebo
    - No treatment
    - Usual care
    - Other, specify _____
- Population
    - Pregnant women
    - Elderly (65 years and older)
    - Children & adolescents (up to 18 years old)
    - Co-morbidities

    - COVID-19 severity level
- Adverse events
    - Common Terminology Criteria for Adverse Events (CTCAE) severity category[3]
    - CTCAE event name
    - Timing (days since the beginning of treatment)
    - Timing category
        - Less than or equal to 45 days
        - Greater than 45 days
    - Number of participants in each group experiencing adverse events.

Final abstracted data will be uploaded to SRDR+.

Assessment of Methodological Risk of Bias of Individual Studies

Several study designs are eligible for the review. We believe that studies can still be compared across study designs, and we will apply a set of evaluation criteria that focuses on methodology for collection and reporting of adverse events. To assess the quality of adverse events collection, we will abstract the following, based on the McHarm instrument[4]: whether reporting was passive (i.e., outpatients contacted researchers if they experienced an event rather than the researchers actively contacting each patient and asking about a pre-determined list of events); whether the authors report the proportion of patients experiencing each event (e.g., rather than the total number of events).

We will incorporate the risk of bias result into the rating of evidence certainty and downgrade our confidence in the findings.

Data Synthesis

Abstracted adverse events data will be converted to rates for intervention and comparison groups; rates will be used to compute risk ratios to estimate effects (where not reported as effect sizes). We will narratively summarize the risk ratios for each intervention class and each specific intervention within the class, as well as for specific population categories such as children, elderly, those hospitalized for COVID-19, and those with pre-existing medical conditions.

Rating the Certainty of Evidence

We will provide a statement of certainty on the association of each countermeasure with each serious adverse event or death. The assessment will clearly document uncertainty, outline the reasons for insufficient evidence where appropriate, and communicate our confidence in the findings. The project leader will create the ratings; the center director and content expert will review and provide feedback. The system, described below, comes from the Institute of Medicine 2012 report Adverse Effects of Vaccines: Evidence and Causality.[5]

High: Two or more studies with negligible methodological limitations that are consistent in terms of the direction of the effect, and taken together provide high confidence.

Moderate: One study with negligible methodological limitations, or a collection of

studies generally consistent in terms of the direction of the effect, that provides moderate confidence.

Limited: One study or a collection of studies lacking precision or consistency that provides limited, or low, confidence.

Insufficient: No epidemiologic studies of sufficient quality

Use of Artificial Intelligence and/or Machine Learning

All citation and full text decisions will be checked for reviewer errors by a machine learning algorithm in the software DistillerSR.

V. References

1. Federal Register. December 23, 2023. https://www.federalregister.gov/documents/2022/12/23/2022-28013/notice-of-amendment

2. Agency for Healthcare Research and Quality. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville, MD; 2022. https://effectivehealthcare.ahrq.gov/products/collections/cer-methods-guide. Accessed on August 3, 2023.

3. National Institutes of Health, Institute NC. Common Terminology Criteria for Adverse Events (CTCAE) Version 5. November 27, 2017. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_8.5x11.pdf. Accessed on May 10, 2023.

4. Santaguida P, Raina P. The Development of the McHarm Quality Assessment Scale for adverse events: Delphi Consensus on important criteria for evaluating harms McMaster University. 2012.

5. Institute of Medicine (US). Committee to Review Adverse Effects of Vaccines, Kathleen R. Stratton, and Ellen Wright Clayton. Adverse effects of vaccines: evidence and causality. 2012

VI. Definition of Terms

None

VII. Summary of Protocol Amendments

None

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Invited peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism instead.

XII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than $1,000 will usually disqualify EPC core team investigators.

XIII. Role of the Funder

This project was commissioned and funded by the Health Resources and Services Administration through a contract with the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The AHRQ Task Order Officer reviews contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by HRSA, the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

XIV. Registration

This protocol will be registered in the international prospective register of systematic reviews (PROSPERO).

Appendix A. Search strategies

Pubmed
COVID-19 Treatment (PubMed Filter)
AND
convalescent plasma OR Anti-viral medications OR Remdesivir OR Veklury OR (Nirmatrelvir AND ritonavir) OR Paxlovid OR (Tixagevimab AND cilgavimab) OR Evusheld OR Molnupiravir OR Lagevrio OR Monoclonal antibodies OR Tocilizumab OR (Bamlanivimab AND Etesevimab) OR Bebtelovimab OR Sotrovimab OR (Casirivimab AND imdevimab) OR REGEN-COV OR Interleukin antagonists OR Anakinra OR Kineret
Filters: Systematic Reviews

Cochrane Database of Systematic Reviews
MeSH descriptor: [COVID-19] explode all trees OR ("severe acute respiratory syndrome coronavirus" OR coronavirus* or corona virus* or Covid 19 or Covid19 or SARS CoV* or SARSCov*):ti,ab,kw (Word variations will be searched)
AND
(convalescent plasma OR Anti-viral medications OR Remdesivir OR Veklury OR (Nirmatrelvir AND ritonavir) OR Paxlovid OR (Tixagevimab AND cilgavimab) OR Evusheld OR Molnupiravir OR Lagevrio OR Monoclonal antibodies OR Tocilizumab OR (Bamlanivimab AND Etesevimab) OR Bebtelovimab OR Sotrovimab OR (Casirivimab AND imdevimab) OR REGEN-COV OR Interleukin antagonists OR Anakinra OR Kineret):ti,ab,kw (Word variations will be searched)