Evidence-based Practice Center Technical Brief Protocol

Project Title: Long COVID Models of Care

I. Background and Objectives for the Technical Brief

A large, growing population of persons have experienced severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Although symptoms of acute coronavirus disease 2019 (COVID-19), the disease caused by SARS-CoV-2, typically last ~2 to 4 weeks, accumulating evidence indicates that a significant proportion of recovering patients experience persistent symptoms.[1-5] This condition is referred to as "long COVID," "post-COVID syndrome," or "post-acute sequelae of SARS-CoV-2 (PASC)." Long COVID can affect multiple organ systems, with wide interindividual variability in symptoms and symptom combinations. Common manifestations include neuropsychological symptoms and cognitive impairment; fatigue, often with postexertional malaise; pain; cardio-pulmonary symptoms; anosmia and dysgeusia; headache; gastrointestinal symptoms; and dysautonomia (including postural orthostatic tachycardia syndrome).[1,2,5,6] The duration of long COVID ranges from weeks to years and severity ranges from relatively mild to severely disabling, impacting quality of life, psychological well-being, functioning, and ability to work.[7] The U.S. Department of Health and Human Services has issued guidance that long COVID is considered a disability under the American with Disabilities Act, and describes services available to people with long COVID.[8]

Although there is no specific diagnostic test for long COVID, several case definitions have been proposed. According to the U.S. Department of Health and Human Services, "The signs, symptoms, and conditions are present four weeks or more after the initial phase of infection; may be multisystemic; and may present with a relapsing-remitting pattern and progression or worsening over time."[9] The World Health Organization requires the continuation or development of new symptoms at least 3 months following acute SARS-CoV-2 infection onset and lasting ≥2 months.[10] The UK National Institute for Health and Care Excellence reserves the term "post-COVID-19 syndrome" for symptoms lasting at least 12 weeks [11] and uses the term "ongoing symptomatic COVID-19" for symptoms at 4 to 12 weeks.

The pathophysiology of long COVID appears multifactorial, involving immune dysregulation, microbiota dysbiosis and occult viral persistence, blood clotting and endothelial dysfunction, and dysfunctional neurological signaling.[1,2,5,12] Many features of long COVID resemble those observed in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS),[2,13,14] a syndrome often associated with prior infection. Approximately 50% of persons with long COVID meet criteria for ME/CFS and most persons with long COVID report postexertional malaise, a cardinal ME/CFS feature.[2,15,16] The extent to which long COVID represents a form of ME/CFS or a distinct condition is

uncertain. However, given the observed similarities between ME/CFS and long COVID,[3] experience managing ME/CFS may inform management of long COVID, and some proposed models of care address both conditions.[17]

Long COVID is an important public health issue that has been highlighted as a clinical, policy, and research priority by the U.S. government.[18,19] The risk of long COVID varies according to a number of factors, including acute COVID-19 severity, age, sex, pre-existing conditions, vaccination status, and others. Estimates of long COVID incidence range from 10 to 30% of non-hospitalized cases, 50 to 70% of hospitalized cases, and 10 to 12% of vaccinated cases.[3,7,20,21] With over 146 million cumulative persons with COVID-19 (through September 2021),[22] potentially tens of millions of Americans are or will be impacted. Given the large number of persons who have experienced acute COVID-19, the burden of long COVID is substantial. Long COVID is more common in women (18%) and transgender persons (19%) than men (11%); occurs most frequently in persons 18 to 59 years of age; and is more frequent in Hispanic/Latino persons (20%) than Asian (10%), Black (13%), or White (14%) persons, indicating potential disparities.[23] Data on incidence of long COVID in children are limited, but suggest that it is less common than in adults.[24,25] Emerging evidence suggest disparities in diagnosis of long COVID, with potential underestimation among non-White or Hispanic individuals and persons of lower socioeconomic status.[26]

No curative treatment is currently available for long COVID. Rather, the goal of treatment is to manage symptoms, improve function, and optimize quality of life.[27-30] Evaluation and treatment recommendations are based on expert opinion and consensus. In most patients, fatigue management with an individualized and structured return-to-activity program is a core component of management; other components of treatment are highly variable and tailored for each individual's presentation.[2,3] Because long COVID can manifest as a variety of symptoms affecting multiple organ systems, effective management requires expertise and coordination among multiple specialties, applying a whole-patient perspective that addresses long COVID symptoms within an individual's psychological, social, and medical context.

Models of care broadly define the way health services are organized and delivered for a particular condition or conditions within a health system. Models of care enable provision of necessary services and can impact the quality and outcomes of care. Components or elements that constitute models of care may include the clinical setting (e.g., inpatient or outpatient, primary care or specialty clinic); payment structure and access; multidisciplinary team composition; other staffing required; mechanisms for coordination/collaboration; testing and treatment services provided; education, training, and outreach; use of virtual care or tele-services; provision of home-based care; and others.[31] A variety of long COVID models of care have been proposed or implemented, including primary care integrated, specialty-based, or standalone clinics, with differences in the above factors. [28,31-36] For example, a review of long COVID models of care identified a total of 32 different healthcare professionals and medical specialties proposed to staff long COVID care models, ranging from as few as 3 to as many of 19; all models in the review included rehabilitations services, four integrated primary care, and four had a specialty care component.[31] In this review, all of the models were designed for management of adults.

The purpose of this Technical Brief is to summarize definitions of long COVID and describe what is known about long COVID models of care, including models currently in use, their applicability to the U.S. population, promising new approaches, advantages and disadvantages of different models, barriers and facilitators to implementation, access and equity issues, and needed research.

II. Guiding Questions

The questions below will guide our work in developing a framework and description of research, ongoing efforts, and promising directions in long COVID models of care.

1. How has long COVID been defined?

2. What are the different types or models of care that have been proposed or used in clinical practice?
    a. What are the potential advantages and disadvantages of long COVID models of care?
    b. What are the components of different models of care?

3. Context of models of care:
    a. In what settings and for whom are these models currently implemented?
    b. Are there special considerations for implementing these models for adults, children and disadvantaged populations influenced by social determinants of health?
    c. What are potential facilitators and barriers to implementation, including resources needed, and how do barriers vary according to the setting?
    d. What kinds of training, certification, staffing, and other resources are required to develop and sustain these models of care?

4. What have published and unpublished studies reported on the use of and effectiveness of models of care for long COVID? Describe:
    a. Patient population, practice setting and country/location
    b. Details on model of care, including the types of interventions used and specifics of pharmacological and nonpharmacological treatments, provider type/staffing needs, methods for coordination of care, educational and training components, implementation strategy, mode of delivery, visit frequency, and other factors
    c. Study design/size
    d. Comparator if relevant
    e. Concurrent/prior treatments
    f. Length of follow-up
    g. Outcomes measured
    h. Adverse events/harms/safety issues reported

5. What are gaps in our understanding of long COVID models of care?

III. Methods

As long COVID is a new condition and published literature on models of care is currently limited, the Technical Brief will integrate discussions with Key Informants with searches of the published literature and grey literature to inform the above Guiding Questions.

1. Data Collection:

A. Discussions with Key Informants

In order to ensure that we include information on current and promising long COVID models of care, we will convene a group of Key Informants assembled to provide broad and balanced perspectives relevant to long COVID models of care, including persons with experience in developing and implementing models of care; persons developing guidelines on COVID models of care; persons with expertise in ME/CFS models of care, given similarities to long COVID; and persons providing patient perspectives. The Key Informants will include researchers, clinicians, policymakers, representatives of professional societies and organizations, patient group representatives, and federal representatives. We will select Key Informants to ensure appropriate multidisciplinary representation, including persons with expertise in adult and child/adolescent COVID-19, and aim to include Key Informants with expertise in equity and social determinants of health.

We will organize and facilitate phone discussions with the Key Informants to gain input on the Guiding Questions. Calls will be conducted in a series of small groups (4 to 8 Key Informants) to maximize efficiency and enhance the ability of all Key Informants to provide input. Members of our research team and the Agency for Healthcare Research and Quality (AHRQ) Task Order Officers (TOOs) will attend the calls. On the calls, we will engage Key Informants using an informal group discussion approach to elicit perspectives on specific long COVID models of care, insights on where and how they were established, how they have evolved, and future directions. Topics of discussion with Key Informants will include which long COVID models of care are in use (including models not described in the published literature) and in which settings and populations; insights into what components are critical; challenges or barriers to implementation; applicability to U.S. practice; patient preferences; relevance of ME/CFS models of care; and future directions, including promising new and innovative models and strategies for implementation and sustainability. We will also ask about specific issues to be aware of when reviewing the literature, such as key outcomes, specific populations to be studied, meaningful length of followup, study design issues, and variability between long COVID models of care with regard to intensity, goals, and components of care. We are particularly interested in asking about the feasibility and applicability of models of care implemented in one setting or population to others and about identifying models of care that may be particularly suitable for specific settings and populations. The calls will be recorded, and the key points will be summarized and shared with the group. The feedback from the Key Informants will be integrated with the expertise of our project team and the evidence that we identify through the published and grey literature to develop a

framework for describing long COVID models of care based on key characteristics (e.g., setting, clinical disciplines involved, methods for coordinating care, educational and training components, use of telemedicine, etc.), to help organize and provide a structure for future research and discussions around this topic area.

B. Published Literature Search

An experienced research librarian will create search strategies of search terms and medical subject headings (MeSH) for long COVID models of care and perform searches on the following databases: Ovid Medline, PsycINFO, the Cochrane Library, SocINDEX, Scopus, Embase, and CINAHL. The MEDLINE search strategy is shown in **Table 1.** The searches will be restricted to 2021 or later, corresponding to when long COVID was first described and only publications in the English language will be selected. We will also conduct a supplemental search (no date restriction) for systematic reviews on ME/CFS models of care, which may provide relevant background considerations for long COVID models. We will supplement the searches with a review of reference lists of identified publications for additional relevant studies.

We will update the searches while the report is undergoing peer and public review in order to capture any recently added publications. If any new eligible studies are identified from the update searches or are identified based on peer or public review comments, they will be added to the report prior to finalization of the report.

Table 1. Sample Search Strategy (MEDLINE)

1	SARS-CoV-2/ or COVID-19/
2	(long* or post*).ti,ab,kf.
3	((long* or post*) adj (COVID or COVID-19 or COVID19 or coronavirus* or corona virus* or 2019-nCoV or 19nCoV or 2019nCoV or nCoV or n-CoV or "CoV 2" or CoV2 or SARS-CoV-2 or SARS-CoV2 or SARSCoV-2 or SARSCoV2 or SARS2 or SARS-2 or severe acute respiratory syndrome coronavirus 2 or 2019-novel CoV)).ti,ab,kf.
4	("post-acute sequelae of COVID-19" or "postacute sequelae of COVID-19" or PASC).ti,ab,kf.
5	(1 and 2) or 3 or 4
6	Models, Organizational/
7	exp "Continuity of Patient Care"/
8	exp Patient Care Management/
9	((model* or plan* or deliver* or framework* or multidisciplin*) adj3 (care or healthcare or service*)).ti,ab,kf.
10	or/6-9
11	5 and 10
12	limit 10 to covid-19
13	(long* or post*).ti.
14	12 and 13
15	11 or 14
16	limit 15 to english language
17	limit 16 to yr="2021 -Current"

C. Grey Literature Search.

In order to ensure that we are including studies of long COVID models of care that may be published outside of the standard medical literature, we will supplement our search of standard published literature with searches of the grey literature. We will search websites of national and international government agencies with long COVID initiatives (e.g., the Centers for Disease Control and Prevention [CDC], the National Institute for Health and Care Excellence [NICE] UK, the Canadian Agency for Drugs and Technologies in Health [CADTH], the Health Information and Quality Authority [Ireland], the National Clinical Evidence Taskforce-COVID_19 [Australia], the Provincial Health Services Authority [Canada] and other organizations with long COVID initiatives, such as the Strategy for Patient Oriented Research [SPOR] Evidence Alliance, the Department of Veterans Affairs [VA], the American Academy of Physical Medicine & Rehabilitation [AAPM&R], and Project Extension for Community Healthcare Outcomes [ECHO]). Grey literature studies will be assessed for eligibility using the same approach as described in the published literature search section (Appendix A).

We will also search clinicaltrials.gov and Health Services Research Projects in Progress (HSRProj) for ongoing studies, to inform discussions of future research.

Supplemental Evidence and Data for Systematic Reviews: Supplemental Evidence and Data for Systematic Reviews (SEADs) will be requested for this technical brief through a federal register notice. With AHRQ's assistance, we will also attempt to identify and describe federal efforts to study or described long COVID models of care that are published in the grey literature.

D. Process for Selecting Studies

We will include systematic reviews or primary studies of long COVID models of care. All citations identified through searches will undergo dual independent review by trained members of the research team for eligibility based on whether they address the Guiding Questions. For Guiding Question 4, we will determine eligibility using pre-defined inclusion/exclusion criteria, organized using the PICOTS (population, intervention, comparator, outcome, timing, study design) framework (**Table 2**). Studies marked for possible inclusion by either team member will undergo full-text review. Each full-text article will be independently reviewed by two trained members of the research team for inclusion or exclusion on the basis of the eligibility criteria. If the reviewers disagree, conflicts will be resolved by discussion and consensus or by consulting another member of the research team. Reasons for exclusion at the full text stage will be recorded. We will use DistillerSR to assist in managing the study selection process and EndNote reference management software.

Table 2. Draft Inclusion and Exclusion Criteria for Guiding Question 4 on the Use and Effectiveness of Long COVID Models of Care

PICOT	Include	Exclude
Populations	Patients with long COVID (any definition) -Including adults or children/adolescents	Patients who do not meet definitions for long COVID
Interventions	Long COVID models of care, including concurrent/prior treatments	Studies of interventions for specific long COVID symptoms

PICOT	Include	Exclude
Comparators	Will include studies of long COVID models of care without a comparator, as well as studies that compare long COVID models of care with one another	--
Outcomes	Measures of use or access Quality of life Function Outcomes related to specific long COVID symptoms Patient satisfaction Harms	--
Timing	Any	--
Study Design	Systematic reviews Randomized controlled trials Observational studies, including cohort studies, case control studies, and other experimental and non-experimental study designs	Non-systematic reviews Studies without original data Non-English language Non-human subjects
Setting	Any country	

Abbreviations: COVID = coronavirus disease.

2. Data Organization and Presentation:

A. Information Management

For studies meeting inclusion criteria, data will be entered into abstraction forms summarizing pertinent information from each study, such as characteristics of study populations, model of care details, comparators, outcomes, study designs, settings, and methods. All data abstractions will be reviewed for completeness and accuracy by another member of the team. Data elements to be abstracted into tables are shown in **Table 3,** which will be used to address the Guiding Questions.

Table 3. Proposed Data Elements to be Abstracted into Evidence Tables for Each Study

Data Element	Details
Study characteristics	Study design Inclusion/exclusion criteria Sample size at recruitment and followup rates
Population characteristics	Age Race/ethnicity Sex and gender Long COVID severity and presenting symptoms Definition of long COVID, if known
Intervention characteristics	Description of long COVID program/model of care including: • The types of interventions used • Diagnostic testing strategies • Provider types/disciplines involved • Mode of delivery, including use of telehealth • Educational or training components • Frequency or intensity of visits • Process for coordinating care • Methods of follow-up • Source and duration of funding • Type of patients served (insured/uninsured)
Comparator	Comparator(s), if any
Outcomes examined	Types of outcomes examined in the study, how they were measured, and main findings; identified barriers and facilitators to implementation;

	patient perspectives (preferences, acceptability, satisfaction); impact on equity or disparities
Timing	Timing of outcome measurement (follow-up)
Setting	Clinical setting (e.g., primary care, specialty clinic, or standalone clinic; type of healthcare organization) Country/geographic location

Abbreviations: COVID = coronavirus disease.

B. Data Presentation

We will present our findings in the order of the Guiding Questions. We will categorize and summarize findings from the grey literature and the Key Informant interviews qualitatively in the text of the report, including applicability of different models of care to U.S. practice. Factors to inform applicability assessments include the country/geographic location of the model, clinical setting, patient population (e.g., definition used for long COVID, insurance status), availability of interventions and services offered, and type and feasibility of funding. Models developed and implemented in the U.S. will be highlighted and discussed separately.

We will also develop a conceptual framework for describing long COVID models of care based on key model characteristics and apply the conceptual framework to the most relevant or promising models of care, based on findings from guiding question 4 and input from Key Informants. The primary audience is policymakers and health care professionals, as well as clinicians, researchers, and patients. Our approach to developing a conceptual framework will be informed by a prior technical brief on models of care for medications for addiction treatment that also included a conceptual framework.[37] We will also explore opportunities to present findings graphically in the form of an evidence map to visually represent the state of the science on different long COVID models of care and key research gaps. Our approach to organizing and presenting the evidence map results will be informed by prior evidence mapping efforts and examples of recently produced evidence maps.[38-45]

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V. Definition of Terms

AAPM&R	American Academy of Physical Medicine & Rehabilitation
AHRQ	Agency for Healthcare Research and Quality
CDC	Centers for Disease Control and Prevention
COVID-19	acute coronavirus disease 2019
ECHO	Extension for Community Healthcare Outcomes
EPC	Evidence-based Practice Center
ME/CFS	myalgic encephalomyelitis/chronic fatigue syndrome
NICE	National Institute for Health and Care Excellence
PASC	post-acute sequelae of SARS-CoV-2
PICOTS design	population, intervention, comparator, outcome, timing, study
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SEAD	Supplemental Evidence and Data for Systematic Reviews
SPOR	Strategy for Patient Oriented Research
TOO	Task Order Officer
VA	Department of Veterans Affairs

VI. Summary of Protocol Amendments

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

VII. Key Informants

Within the Technical Brief process, Key Informants serve as a resource to offer insight into the clinical context of the technology/intervention, how it works, how it is currently used or might be used, and which features may be important from a patient or policy standpoint. Key Informants may include clinical experts, patients, manufacturers, researchers, payers, or other perspectives, depending on the technology/intervention in question. Differing viewpoints are expected, and all statements are crosschecked against available literature and statements from other Key Informants. Information gained from Key Informant interviews is identified as such in the report. Key Informants do not do analysis of any kind nor contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The TOO and the Evidence-based Practice Center (EPC) work to balance, manage, or mitigate any potential conflicts of interest identified.

VIII. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodologic expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will be published three months after the publication of the Evidence report.

Potential Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

IX. 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.

X. Role of the Funder

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for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

XI. Appendix A. Long COVID Grey Literature Sources

Shown in associated file.