

Consensus methodology for the development of postacute sequelae of SARS-CoV-2 guidance statements

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INTRODUCTION

Many patients who have been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continue to experience a constellation of symptoms long after they have recovered from the acute stages of their COVID-19 illness. Often referred to as “long COVID,” these symptoms can persist for months and can range from mild to incapacitating. Although still being defined, these effects are referred to as post-acute sequelae of SARS-CoV-2 infection (PASC). The magnitude of the problem is not yet known, but given the number of individuals of all ages who have been, or will be, infected with SARS-CoV-2, the health impacts are likely to be profound and long lasting.¹⁻⁴ At present, lack of rigorous scientific evidence limits the creation of evidence-based clinical guidelines for PASC care. Given the number of patients presenting around the United States and worldwide with these symptoms, there is an urgent need for clinical guidance in the assessment and treatment of PASC in the outpatient setting.

The American Academy of Physical Medicine and Rehabilitation (AAPM&R) Multi-Disciplinary PASC Collaborative was created, in part, to develop expert recommendations and guidance from established PASC

centers with extensive experience in managing patients with PASC. The collaborative is following an iterative, modified Delphi approach⁵⁻⁷ to achieve consensus on assessment and treatment recommendations for a series of Consensus Guidance Statements focused on the most prominent PASC symptoms.

AAPM&R established a modified-Delphi approach to achieve consensus at the individual assessment and treatment recommendation statement level. These statements integrate current experience and expertise with limited available evidence to provide tools to clinicians treating patients in ambulatory settings including primary care, specialty clinics, and PASC clinics. Existing literature on PASC is limited and descriptive in nature—these data inform our approach; however, the absence of evidence necessitated the use of highly specialized PASC centers to achieve consensus on the assessment and treatment of PASC. In addition, experts in treating chronic fatigue and cognitive impairment provided insight from pre-COVID-19 clinical experience, and literature from relevant pre-COVID-19 clinical domains informed our work. Our PASC Collaborative focused on the most prevalent symptoms of PASC, as well as important additional considerations including health equity and pediatric care.

OBJECTIVES

We sought to develop consensus-based clinical recommendations and guidance for the assessment and

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treatment of PASC. These guidance statements are being developed to achieve the following:

- Discuss and establish best practices and protocols, including assessment and treatment principles
- Engage patient/caregiver partners to provide perspectives from the PASC patient community and inform clinical recommendations of importance from patients
- Promote patient-centeredness and health equity

Ultimately, we intended to develop the guidance statements for ready translation into resources for the medical community and specifically for primary care providers and those who are striving to implement PASC clinics.

SUMMARY OF CONSENSUS METHODOLOGY

Based on the urgent need for clinical guidance in the assessment and treatment of PASC in the outpatient setting, the PASC Collaborative initiated an iterative, modified-Delphi approach to developing Consensus Guidance Statements^{5,6} (described in Table 1).

Topic identification and literature review

Each Consensus Guidance Statement topic was identified via the PASC Collaborative clinical cochairs. This involved conducting an initial literature review and considering the most prevalent and disabling symptoms (Table 1). Based on the evolving nature of the knowledge base surrounding PASC, literature reviews were conducted on an ongoing monthly basis and augmented with new studies as released.

The AAPM&R Multi-Disciplinary PASC Collaborative officially launched in March 2021 and guidance statement development started immediately. Given the absence of any prospective data for PASC assessment and treatment at the outset of this effort, all members were asked to integrate their experience, professional judgment, and knowledge of pre-COVID-19 literature to guide statement development.

For each topic, relevant literature was reviewed to understand incidence, prevalence, and emerging patient experience from April 2020 through May 2021. Searches were conducted through Google Scholar and PubMed, and preprint documents were considered through medrxiv given the rapidly evolving nature of the PASC literature, as well as referral of relevant peer-reviewed publications by collaborative participants. Search of English-language literature in the publication window of March 2020 to May 2021 was conducted first including terms “SARS-CoV-2,” “COVID,” or “COVID-19.” Manuscripts were then narrowed to include studies with additional terms “long COVID,” “long hauler,” “postacute,”

“postacute sequelae of COVID-19,” “PASC,” “long-term outcomes,” or “persistent symptoms” to identify candidate manuscripts. For each symptom-based subgroup, this search was further refined using terms related to the symptom of interest; for example, on March 25, 2021 the review of fatigue literature was conducted, narrowing the candidate manuscripts with the additional terms “fatigue,” “chronic fatigue syndrome,” “myalgic encephalomyelitis,” “CFS,” and “ME/CFS.” In addition, where available and applicable, existing pre-COVID clinical guidelines from appropriate medical specialties were reviewed to augment support for assessment and treatment recommendations and discussion sections.

PASC collaborative guidance statement development

The PASC Collaborative is a multidisciplinary expert group of physicians, therapists, patients, government representatives, and others who have expertise in a range of areas, including, but not limited to, physiatry and rehabilitation medicine, neuropsychiatry, neurology, pulmonology and critical care, cardiology, primary care, speech language pathology, physical therapy, and comprehensive approaches used in postinfectious disease and chronic care management. The collaborative is composed of 27 established post-COVID-19 or PASC centers; and over 50 experts spanning clinical disciplines and specialties participate in the monthly meetings. Individual guidance statements include the total number of authors at the time of the publication, given the evolving nature of this group. Participating PASC centers were asked to designate one expert to be the voting member to assess consensus. Patient representatives were also permitted to vote.

Participation on writing groups/author teams is voluntary. Clinical experts are recruited from the 27 collaborative members with the goal of cross-discipline and cross-specialty representation. Participants are assigned to specific topics based on clinical expertise and ensuring diversity of representation from physical medicine and rehabilitation as well as any specific specialty for each symptom area. For example, for the cognitive impairment topic, a physiatrist is the clinical lead and is supported by authors representing neurology, neuropsychology, and speech-language pathology. We aim to include at least five members in each symptom-based writing group.

Consensus statement structure and content

In order to promote consistency in the PASC Guidance Statement set, the PASC Collaborative developed a statement outline used for each topic area:

TABLE 1 AAPM&R Multi-Disciplinary PASC Collaborative consensus methodology

1. Given a goal of symptom-driven consensus guidance generation, PASC clinical cochairs conducted literature review and initial discussion of likely priorities based on existing PASC data informing the most prevalent and disabling symptoms.
2. At an initial meeting of the PASC collaborative, expert clinicians and patients experiencing PASC discussed and refined priority areas. These initial areas included fatigue, cognitive impairment, breathing discomfort, and dysautonomia. In addition to symptoms, there was complete consensus that health equity would require a dedicated writing group to address this critical topic in the context of PASC. The group also outlined future areas of focus to be addressed in subsequent guidance statements.
3. The PASC Collaborative, consisting of 27 U.S., geographically distributed centers, convened to discuss experience with assessment and treatment of PASC symptoms in two-hour meetings for each symptom domain. These meetings began in April 2021, have convened once per month since then, and are ongoing as the collaborative works through each domain of interest.
4. Within the membership of the PASC collaborative, clinicians were identified with specific expertise in each area of focus and amongst them, a small writing group was formed to develop each consensus statement. These experts represent a broad array of specialties (eg, brain injury specialists, speech language pathologists and cognitive neurologists for cognition; pulmonologists, cardiopulmonary rehabilitation physiatrists, and physical therapists for breathing discomfort).
5. The smaller writing group considered initial PASC collaborative discussion, reviewed existing literature, and generated an initial document of recommendations for assessment and treatment of the PASC symptom. The health equity writing group followed a similar process to consider equity in the context of PASC. The members of the writing group then conducted anonymous electronic voting (Alchamer) to designate areas they deemed important for inclusion as assessment and treatment recommendations.
6. All recommendations were discussed, but those that did not meet an "importance" vote from the majority of writing group members did not progress as candidate recommendation statements. The writing group was directed to consider any of those recommendations that did not meet majority in the discussion section of the guidance statement. The remaining "important" recommendations are discussed further by the writing group to move them toward a second round of voting by the full PASC collaborative.
7. Each individual assessment and treatment recommendation statement, as proposed by the writing group, was presented within a survey to all PASC Collaborative members. Members are provided the opportunity to vote as "agree," "agree with consideration," or "disagree" with initial recommendation statements.
8. Statements for which 80% consensus was achieved were retained, and statements with "agree with consideration" were then discussed among the full PASC collaborative and shared with the writing group for further refinement.
9. Statements for which >60 to <80% consensus was achieved were discussed among the full PASC collaborative and a determination was made if the recommended concept should be refined, excluded, or included in the discussion section of the consensus statement. For reference, prior groups examining clinical and research guidance regarding long-term sequelae of critical illness used a number of consensus thresholds varying from 60% to 80%. For example, in the "Society of Critical Care Medicine's International Consensus Conference on Prediction and Identification of Long-Term Impairments After Critical Illness," 80% agreement indicated a strong recommendation and 60% indicated a weak recommendation. We felt that the absence of data and limited experience with this condition supported the need for more discussion of those statements not meeting an 80% agreement threshold.
10. The writing group finalized the assessment and treatment recommendation tables, which were voted on as sets by the entire PASC Collaborative with options of "approve" or "do not approve." Consensus of the set of assessment and treatment recommendations were considered final with 80% approval by the full collaborative, consistent with earlier discussion of consensus threshold.⁸ Collaborative participants are provided the opportunity to comment further, and additional discussion may be added to the full consensus statement document.
11. The writing group was responsible for final consensus statement approval and an author assigned for publication submission.

- I. Introduction: Includes topic/symptom prevalence, incidence, key factors for identification
 - a. Brief methodology statement
- II. Assessment Recommendation Set
 - a. Assessment Discussion
- III. Treatment Recommendation Set
 - a. Treatment Discussion
- IV. Future Directions or statement where more research is needed, if applicable
- V. Health Equity Considerations

These guidance statements are intended to assist clinicians in clinical decision making by describing a range of generally acceptable approaches to the assessment and treatment of PASC. The recommendation statements attempt to define practices that meet the needs of most patients in most circumstances. The ultimate judgment regarding care of a particular patient must be made by the clinician and patient in light of all the circumstances presented by that patient. Clinical decision making should involve consideration of the quality and

availability of expertise in the area where care is provided.

Patient input

The Patient-Led Research Collaborative are members of the PASC Collaborative, providing input and participating in voting throughout the process of guidance statement development. Each symptom discussed includes their input into the patient experience and aspects of symptoms, diagnosis, and treatment from their unique perspective. This experience is incorporated throughout the document and considered extensively in the development of this work.

Health equity subcommittee/workgroup

A health equity workgroup of patients and clinicians was convened to discuss health equity in PASC and

the content of our guidance statements. Each Consensus Clinical Guidance Statement was developed with the belief that acknowledging institutional and individual bias in the health care setting is the initial step toward mitigating the harms of structural racism and systemic oppression on patient health and well-being. To this end, the PASC Collaborative, with guidance from the health equity workgroup, pursued the following steps to identify if information exists regarding how populations could be differentially affected by the symptom or condition under consideration, the institutional and individual biases that may contribute to those differences, and the potential impact of any proposed assessment or treatment recommendation on all people and particularly vulnerable populations:

1. In the generation of draft guidance statements, writing groups assessed issues of differential effect of symptoms on vulnerable populations, inequities in access and resource availability, and any institutional and individual biases that may lead to these inequities. Where potential inequities were identified, modifications intended to address inequities were made to the recommendation statements or expanded upon in the discussion section to draw attention to potential barriers or challenges to implementation.
2. A targeted literature review for known disparities relevant to the symptom or topic area (eg, fatigue) and to identify if special populations may have higher incidence or prevalence of the symptom or condition was conducted to augment collaborative and workgroup input.
3. During collaborative voting and discussion of each recommendation statement, the PASC Collaborative members, with leadership from the health equity workgroup members and patient representatives, again considered and provided input on potential challenges and impact of these inequities on the recommendation statements as presented.
4. Where perceived challenges in achieving equity were identified, writing groups then further considered where additional modifications were necessary in either the recommendation statement or the narrative to mitigate barriers to equitable PASC care.
5. The PASC Collaborative, including the health equity workgroup, was provided a final opportunity for review and discussion during the vote on the recommendation statement sets. Discussion notes were forwarded to the writing group to ensure any remaining concerns about equitable approaches to care in the guidance statements were incorporated prior to publication submission.

“Health equity” means that everyone, no matter race, ethnicity, gender identity, ability status, sexual orientation, education level, socioeconomic status, or any

population characteristic, has the opportunity to be as healthy as possible. Equitable opportunity includes equal access to and distribution of resources, including to social determinants of health, which are health promoting factors in one’s environment - including access to high-quality health care itself. To promote equal access and high quality of care in PASC, we need to ensure resources are equitably available for everyone to maintain physical and mental health. Resources include easy access to information, goods and services, affordable and timely testing and care, and medical and mental health care that are all tailored to meet the individualized needs of people, especially those from historically marginalized communities. When policies, programs, and systems that support health are equitable, poor health outcomes can be reduced, health disparities can be prevented, and the whole of society benefits.

Review and approval of assessment and treatment recommendations and the consensus guidance statements

PASC Collaborative participants have two opportunities to review and vote on the individual recommendation statements and the assessment and treatment recommendation sets for each symptom or focus area. These reviews are done via online survey administered via email. Each vote is followed by an opportunity for discussion during the monthly PASC Collaborative virtual meeting. When areas are identified as needing clarification or expansion of discussion, or when considerable concerns are raised about content, the statements go back to the assigned writing group for further discussion and revisions.

Voting policy

All PASC centers and patient advocate members participating in the AAPM&R Collaborative participate in voting. Centers are asked to submit one designated vote. Patient representatives are considered collaborative participants and also vote on the individual recommendations and the recommendation sets. A minimum of 80% agreement among eligible voters is required to approve the recommendation statements.

LIMITATIONS

The AAPM&R PASC Consensus Guidance Statements are intended to provide clinicians, patients, researchers, policy makers, and other interested individuals with the components of PASC care currently being implemented in established PASC clinics in the United States. The statements are intended to reflect

current practice in patient assessment and workup, treatment referral, reasonable goals, and tools to evaluate the quality of care. These guidance statements are not intended to preclude clinical judgment and must be applied in the context of excellent clinical care, with adjustments for individual preferences, comorbidities, social determinants of health, known disparities and other patient factors. Due to rapidly evolving knowledge on PASC, these guidance statements will be reviewed and potentially revised as new evidence emerges. Each topic area's Consensus Guidance Statement and included assessment and treatment recommendations represents the collaborative's collective analysis, evaluation, and opinion. They are not intended to provide a single correct answer; rather, they encourage clinicians to ask questions and consider a constellation of factors as they define a treatment plan for their patients. Guidance statements may also contain discussions around gaps in evidence and propose areas of future research to address these gaps.

As a rapidly evolving area of clinical practice with very limited evidence, we did not use Grading of Recommendations, Assessment, Development and Evaluations (GRADE) criteria to rate the quality of evidence. Further, the PASC Collaborative did not engage a medical informatics specialist in our initial search given the absence of peer-reviewed data to guide most of this work. Future documents may adopt formal quality-of-evidence criteria as the literature develops in this field and a medical informatics specialist will be used for future literature reviews as the evidence evolves.

Peer review process

The PASC Consensus Guidance Statements undergo independent editorial and peer review via the *PM&R Journal* publication requirements.

Review and maintenance of consensus guidance statements

These PASC Guidance Statements are primarily based on evidence that is limited, reflects what is known about similar conditions and is evolving quickly. AAPM&R intends to continuously assess recommendations to address changes in knowledge and advancing evidence on PASC. The PASC Collaborative will be polled every three months following the release of each guidance statement to determine if revisions are needed to align with current practice.

Target audience

The target audience for the PASC Consensus Guidance Statements is all clinicians, patients, the public, and public health professionals. It should be noted that

although the guidance statements are written primarily for a clinical audience, the collaborative intends to translate guidance for use in training and for targeted consumer resources.

Publication and dissemination

All AAPM&R Consensus Guidance Statements are submitted for publication in *PM&R Journal*. Links to the articles can be found on AAPM&R's website at www.aapmr.org/PASC-guidance.


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 MetroHealth Post-COVID Clinic
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