The Voice of the Patient

A series of reports from the U.S. Food and Drug Administration's (FDA's)
Patient-Focused Drug Development Initiative

Long COVID

Public Meeting: April 25, 2023
Report Date: March 2024

Center for Drug Evaluation and Research (CDER)
U.S. Food and Drug Administration (FDA)

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Introduction

On April 25, 2023, FDA held a public meeting to hear perspectives from people with Long COVID, their loved ones/caregivers, and other patient representatives regarding the symptoms of Long COVID that matter most to patients, and patients' current approaches to treating this condition. In 2012, FDA established the Patient-Focused Drug Development (PFDD) initiative to more systematically obtain patient perspectives on specific diseases and their currently available treatments. The Long COVID public meeting was the Agency's 31st Patient-Focused Drug Development meeting.

Overview of Long COVID

The long-term effects of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome 2 coronavirus (SARS-CoV-2), is known as Long COVID, post-COVID syndrome, post-acute sequalae of SARS-CoV-2 (PASC), long-haul COVID, or post-acute COVID-19 syndrome. [1,2] The persistence of COVID-19 symptoms four weeks beyond SARS-CoV-2 infection has been referred to as post-acute COVID-19 syndrome. Based on the working definition developed by the U.S. Department of Health and Human Services including the Office of the Secretary (OS), the Center for Disease Control (CDC), and the National Institutes of Health (NIH), in collaboration with patient groups, medical societies, and experts inside and outside the government, Long COVID is "broadly defined as signs, symptoms, and conditions that continue or develop after an initial SARS-CoV-2 infection. The signs, symptoms, and conditions are present four weeks or more after the initial phase of infection; may be multisystemic; and may be present with a relapsing-remitting pattern and progression or worsening over time, with the possibility of severe and life-threatening events even months or years after infection. Long COVID is not one condition. It represents many potentially overlapping entities, likely with different biological causes and different sets of risk factors and outcomes."[3]

Long COVID symptoms may vary widely from one individual to another and depend on the organ(s) that are affected by SARS-CoV-2. Organs that are prone to damage from SARS-CoV-2 infection include the heart (cardiovascular system), lungs (respiratory system), nervous system, liver, and kidneys.

Depending on the affected area[4,5], symptoms, signs, and conditions may present as follows:

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[1] https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html#:~:text=Some%20people%20who%20have%20been,after%20acute%20COVID%2D19%20infection

[2] https://covid19.nih.gov/covid-19-topics/long-covid

[3] https://www.covid.gov/longcovid/definitions

[4] https://covid19.nih.gov/covid-19-topics/long-covid

[5] https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html

- **Neurological:** Including but not limited to headaches, migraines, brain fog/cognitive dysfunction, fatigue, dizziness, seizures, paresthesia, loss of smell and/or taste.[6]

- **Cardiovascular:** May include chest pain, heart palpitations, inflammation, increased resting heart rate, and postural orthostatic tachycardia syndrome (POTS).[7,8,9]

- **Pulmonary:** May include, shortness of breath, cough, decreased total lung capacity, and decreased diffusion capacity of carbon monoxide.[10]

- **Digestive:** May include diarrhea, bloating, constipation, nausea, abdominal pain, and vomiting.[11]

- **Psychological:** May include post-traumatic stress disorder (PTSD), depression, anxiety, insomnia, and obsessive-compulsive disorder (OCD).[12]

- **Other:** Other general symptoms reported by individuals living with Long COVID include muscle or joint pain, post-exertional malaise (PEM), changes in menstrual cycle, and erectile dysfunction.[9, 13]

There are no FDA-approved treatments for Long COVID. However, some treatments have been used off-label to manage symptoms. These treatments include prescription and over the counter products such as antivirals, antihistamines, anticoagulants (blood thinners), analgesics (pain medicine), and corticosteroids, among others. Other interventions used to manage symptoms of Long COVID include pulmonary rehabilitation, physical or occupational therapy, activity pacing, diet modifications, vitamins, herbal or dietary supplements, meditation, acupuncture, and other therapies.

Meeting overview

This virtual (online only) public meeting was conducted in English and Spanish with live translation and closed-captioning. The meeting provided FDA, NIH, CDC, the HHS Office of the Assistant Secretary for Health (OASH), medical product developers, researchers, patients/advocates, and other interested parties the opportunity to hear directly from patients, caregivers, and other patient representatives

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[6] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7550857/
[7] https://jamanetwork.com/journals/jamacardiology/fullarticle/2768916
[8] https://www.nature.com/articles/s41591-022-02000-0
[9] https://pubmed.ncbi.nlm.nih.gov/32979574/
[10] https://erj.ersjournals.com/content/55/6/2001217?ijkey=ce9e35c642c7414e8c315e5583ac082cba2b7c33&keytype2=tf_ipsecsha
[11] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8236920/
[12] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7390748/
[13] https://wjmh.org/DOIx.php?id=10.5534/wjmh.210055

about their experiences with Long COVID. Patients, caregivers, and other patient representatives were encouraged to participate in the facilitated discussion by submitting comments online during the meeting or by calling in via phone to share their experiences. The discussion focused on three key topics:

1) health effects and daily impacts of Long COVID,
2) patients' perspectives on current approaches to treating Long COVID, and
3) patients' considerations for determining whether or not to participate in a clinical trial.

For each topic, a panel of patients and caregivers (Appendix 2) shared comments to begin the session. Panel comments were followed by a large group-facilitated discussion inviting other patients, caregivers, and patient representatives to call in or submit written comments through the webcast platform. An FDA facilitator led the discussion, and members of a listening panel from across HHS, including FDA, OASH, NIH, and CDC (Appendix 2) asked follow-up questions. Throughout the meeting patient and caregiver participants were invited to respond to polling questions (Appendix 3), which provided a sense of the demographic makeup of participants and how many participants shared a particular perspective on a given topic.

Approximately 3,200 people attended the virtual meeting through the live webcast, with around 76% of the participants identifying as patients with Long COVID or patient representatives. According to responses to polling questions, participants ranged in age from 10 years to over 70 years of age, with 73% of participants between the ages of 30 and 59. 76% of participants identified as female (Appendix 3 Q2-4).

Participants reported experiencing a range of symptoms from Long COVID, with the most burdensome reported as multi-organ/system dysfunction, PEM, weakness or fatigue, orthostatic intolerance, and cognitive impairment (brain fog) (Appendix 3 Q8-10).

Participants indicated that they had tried a variety of treatment options to manage Long COVID, such as prescription and non-prescription drugs, physical rehabilitation, vitamins, supplements, dietary modifications, and other therapies (Appendix 3 Q11-12).

Participants also expressed interest in contributing to clinical trials and identified hurdles for participation, as well as the types of clinical trials and meaningful outcomes they would prefer. Although participants in this meeting may not fully represent the diverse population living with Long COVID, the perspectives they shared reflected a diverse set of experiences with Long COVID symptoms and treatments (Appendix 3 Q13).

To supplement the input gathered at the meeting, individuals with Long COVID and others were encouraged to submit comments on the topic to a public docket,[14] which was open from February 23, 2023 to June 26, 2023. In total, 421 comments were submitted to the public docket. Overall, the

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[14] A *docket* is a repository through which the public can submit electronic and written comments on specific topics to U.S. federal agencies such as FDA. More information can be found at www.regulations.gov.

comments received from the public docket reflected the experiences and perspectives shared during the public meeting and are summarized and incorporated throughout the report. The docket comments reiterated the significant and incapacitating health effects of Long COVID on every aspect of individuals' lives. Most comments were submitted by individuals with Long COVID or their caregivers, patient advocates, healthcare providers, professional organizations, and Long COVID researchers.

Some comments received through the public docket discussed possible vaccine-induced injuries or urged the approval of certain vaccine or drug products. Individual drug products, vaccines, and other biological products must undergo the agency's existing review process for assessing the quality, safety, and effectiveness, in accordance with rigorous scientific and regulatory standards. Patients, caregivers, parents, health care providers, pharmacists, vaccine manufacturers, and other concerned individuals are encouraged to report any adverse events associated with vaccines via the Vaccine Adverse Event Reporting System (VAERS), which is a national vaccine safety surveillance program co-sponsored by FDA and CDC. There were also comments on the removal of masking requirements, with some calling for the return of mask mandates, especially on mass transit and in healthcare settings. Individuals and institutions should refer to relevant CDC or other appropriate and applicable guidelines, recommendations, and practices on infection prevention and control.

More information, including the archived webcast, meeting transcript, and docket comments, is publicly available on the meeting website.

Report overview and key themes

This report summarizes the input shared by patients and patient representatives during the public meeting as well as written comments submitted after the public meeting to the public docket. To the extent possible, the terms used in this report to describe specific Long COVID symptoms, impacts, and treatment experiences reflect the words used by the patient and caregiver participants and commenters to the docket. It is recognized that the views and experiences shared in this report may not be representative of the broader population of patients with Long COVID, and that there may be other patient experiences, such as symptoms, impacts, treatments, or other aspects of Long COVID, that are not included in this report.

The input from the meeting and docket comments provided rich detail on the impact of Long COVID on patients. The physical, emotional, and social toll Long COVID takes on daily life, along with the need for new treatment options, emerged within the key themes:

- Many participants described a range of symptoms such as learning difficulties, brain fog/cognitive dysfunction, weakness/fatigue, and diagnoses such as PEM and orthostatic intolerance/postural orthostatic tachycardia syndrome (POTS). Participants also experienced underlying dysfunction and damage to multiple organs and systems, including to the heart, lung, blood, skin, brain, as well as the digestive and sensory systems. Some participants who had mild symptoms during the acute phase of their COVID infection reported developing debilitating Long COVID afterwards.

- Participants stressed the profound impact of their Long COVID on their physical abilities, emotional well-being, social interactions, and financial stability. They described limitations in mobility, decreased endurance, and reliance on caregivers for daily needs. Emotional distress and feelings of loss were common among participants, with many having to give up activities they once enjoyed, leading to isolation, anxiety, and depression. They noted that social interactions, relationships, education, and employment were negatively affected, with financial strain due to high treatment costs and inability to work.

- Participants shared their experiences with a range of medical products and therapies. They discussed prescription and nonprescription medications, physical rehabilitation, vitamins, supplements, dietary restrictions, and other therapies. Participants expressed that they have tried a variety of treatment options but that overall, their Long COVID was not well managed. Participants noted the need for treatment options that could go beyond managing their most debilitating symptoms and address the root causes of Long COVID. They indicated that their ideal treatment would allow them to return back to their levels of health prior to having Long COVID.

- Participants expressed interest in participating in clinical trials for Long COVID treatments but highlighted several hurdles, including limited trial availability, accessibility challenges, physical limitations, eligibility criteria, financial barriers, and concerns about toxicities and side effects. Participants commented on what they consider meaningful treatment outcomes, emphasized the need for broadened inclusion criteria, and wanted researchers and medical product developers to look for treatments that treated the underlying causes of Long COVID as well as addressing its symptoms. Many preferred virtual or remote trial options due to limited energy. They also called for better dissemination of trial results to healthcare providers. They shared their opinions about participating in placebo-controlled trials and discussed their willingness to tolerate toxicities. Opinions varied among participants.

The patient input generated through this PFDD meeting and the public docket comments strengthens FDA’s understanding of the burden of Long COVID on patients, the challenges with approaches currently used to manage Long COVID and its symptoms, and the barriers to participation in clinical trials for Long COVID. FDA staff will carefully consider this input during the regulatory review process, including when advising sponsors on their drug development programs and when assessing products under review for marketing approval. The information from these meetings can also help support the assessment of clinical trial questionnaires.

This input may also be of value to drug developers and researchers. For example, it could help drug developers identify better endpoints for clinical trials to measure those aspects of Long COVID that are important to patients. It may help drug developers select or develop questionnaires that measure important concepts and engage with the FDA as they develop treatments.

Topic 1: Health Effects and Daily Impacts That Matter Most to Patients

The first discussion topic focused on patients' experiences with Long COVID and its impact on their daily lives. FDA was particularly interested in hearing participants describe specific health effects and impacts in their own words. FDA was also interested in learning about how Long COVID affects people's ability to live normally and perform activities as fully as they would like.

Six panelists (Appendix 2) shared their Long COVID experiences to start the dialogue:

- A White female participant shared her experience battling Long COVID since November 2022 after becoming acutely ill with COVID-19. Her symptoms and diagnoses include vertigo, brain fog, fatigue, dizziness, muscle weakness, irritable bowel syndrome (IBS), and POTS. She had to adjust her lifestyle and seek medical support to manage her condition. She fears that her ongoing symptoms could jeopardize her job.

- A Black female participant discussed experiencing Long COVID symptoms ever since a severe case of COVID-19 in April 2020. Long COVID has affected every major system in her body, from the nervous system to the reproductive, digestive, lymphatic, and endocrine systems. She deals with extreme fatigue, brain fog, and residual emotional challenges, including PTSD. She also reported having developed diabetes, high blood pressure, blood clotting issues leading to a stroke and other complications following a COVID-19 infection, all of which have taken a significant toll on her daily life and employment.

- A White female caregiver and a pediatric Long COVID advocate shared her 14-year-old son's experience with Long COVID, including severe and centralized pain in his lower right back which can spread throughout his body and lead to nonepileptic seizures. He also has reported difficulty thinking, decreased executive function, fatigue, heart palpitations, blood flow problems, intermittent loss of speech, and trouble sleeping. These symptoms have a significant impact on his quality of life. She highlighted that the lack of public awareness, insufficient understanding and compassion from the medical community, limited access to quality care, and the financial burdens are all challenges faced by families.

- A Hispanic White female participant's Long COVID experience began in January 2021. She described experiences of fatigue, brain fog, body aches, shortness of breath, heart palpitations, chest pain, gastrointestinal issues, and recurring headaches. These symptoms have made it difficult to engage in physical activities and maintain a normal routine, which have greatly affected her daily life and work schedule.

- A White female participant contracted the SARS-CoV-2 virus twice and has been living with Long COVID for over a year and a half. She described suffering from fatigue, brain fog, muscle weakness, respiratory issues, autonomic nervous system dysfunction, and depression. Long COVID also worsened her pre-existing conditions including endometriosis, asthma, and allergies. These symptoms have significantly impacted her daily life, employment, and personal relationships.

- An Asian American female participant shared that she contracted COVID-19 in June 2022 and has been experiencing Long COVID symptoms. Her symptoms and signs include abnormal heart rate, sore throat, shortness of breath, and chest tightness. These symptoms have given her tremendous physical and emotional stress, affecting her work and overall quality of life.

Panelists discussed the difficulties they experienced navigating the healthcare system and the interaction between primary care and specialty care. One panelist mentioned having to wait months to access Long COVID clinics and specialists, often experiencing a combination of rushing and waiting. She mentioned being dismissed or put down due to her age. Another panelist shared that she was fortunate to have access to comprehensive health insurance through her employer, which covered expensive medications. She emphasized the importance of continuity of care with providers who had treated her during her initial hospitalization for COVID-19. However, she also faced challenges, including long wait times for admission to a Long COVID clinic and the need for self-advocacy as a patient. Another panelist highlighted the difficulties her family faced when initially seeking care for her son's Long COVID symptoms. They were told that his severe pain and other symptoms were psychiatric in origin and were directed to mental health services. After a great deal of trial and error they were able to find quality care through familial advocacy and crowdsourcing.

The panelists' statements provided a detailed account of the physical and emotional burden of living with Long COVID daily. Their perspectives were further reflected in the subsequent large-group discussion, where meeting participants shared comments via phone and internet.

Perspectives on most significant symptoms

Participants shared their perspectives on the aspects of Long COVID that impact their daily life. Through input received at the meeting and from the public docket, participants described a wide range of symptoms that emphasized that Long COVID is a disorder associated with dysfunction and damage to multiple organs and systems, including the brain, heart, lungs, blood, skin, as well as the digestive, sensory, and immune functions. Participants were asked to identify which aspects of their Long COVID were most bothersome (Appendix 3, Q9). In addition to multi-organ or system dysfunction, the most bothersome symptoms of Long COVID also include weakness or fatigue, post-exertional malaise (PEM), exercise intolerance, orthostatic intolerance/POTS, and cognitive impairment (e.g., brain fog). Some participants reported varying degrees of improvement for certain symptoms over time or with treatment, while others experienced lingering symptoms lasting for years. Many participants noted experiencing worsened or “flare-ups” of Long COVID symptoms after varying degrees of physical activity and emotional stress.

Organ/System Dysfunction

Many individuals reported tachycardia and heart-related symptoms, including increased heart rate, heart palpitations, and abnormal electrocardiogram (ECG), often in connection with POTS. For example, one participant described that “my heart rate will suddenly shoot up to like 190 or 200 and typically deep breathing will bring it down.” Another commenter wrote, “Any time I would stand up I would have a massive increase in heart rate and blood pressure and start flushing and heating up.” An additional commenter stated: “My heart rate while doing the dishes matches what it used to be while deadlifting my body weight; walking to the subway now spikes my heart rate as much as my former bike commute would."

A number of individuals discussed having persistent vascular blood clotting issues after COVID, including in the lung or brain, resulting in strokes. One participant who was hospitalized multiple times due to stroke events reported that several conditions were discovered as part of the evaluation: “four brain aneurysms were found. Scans found lesions throughout my brain and brain stem, progressive encephalomalacia of the right parietal lobe, a brain mass on my pineal gland, worsening Chiari malformation, aneurysm of the left carotid artery, aneurysm of the right carotid artery, aneurysm of the vertebral [sic] artery, aneurysm of the basilar artery…” She continued: “I've now received a potential terminal diagnosis because my brain aneurysms are inoperable, and I have clots surrounding them.”

Some participants described experiencing prolonged lung and respiratory issues, including shortness of breath, cough, chest pain, lung damage, and the need for respiratory therapy. One participant stated: “I developed asthma, post-viral-induced asthma. I am now on six inhaler treatments and four breathing treatments a day from my asthma that I got from COVID.” Lung damage was also discussed by some patients, with one noting “I still have noncalcified nodules in my lungs.”

Other participants noted sensory issues such as heightened sensitivity to stimuli including light, sound, and temperature. Some also reported having vision problems, tinnitus, and hyperacusis. A few mentioned having small fiber neuropathy due to COVID-19, with one describing “It has felt like every nerve ending in my body is raw and exposed, resulting in frequent unpleasant electrical sensations.”

Patients described gastrointestinal symptoms and problems such as nausea, stomach pain, reflux, gastroparesis, and IBS. One commenter wrote that a family member with Long COVID “cannot keep food down” and “is constantly nauseated.” One reported developing “many food intolerances and allergy-like reactions to food, drink and temperature." Another commenter reported being severely underweight due to what they described as gastrointestinal distress.

Many with Long COVID also reported developing immune system dysfunction, including mast cell activation and autoimmune inflammation, noting the presence of abnormal autoantibodies and deficient lymphocyte subsets. For example, one commenter reported developing psoriatic arthritis, an autoimmune disease.

Some individuals reported dermatological issues, including developing skin rashes or burning sensations on their skin. One participant described suffering from granuloma annulare, while another mentioned a new onset of eczema due to Long COVID.

Fatigue

Almost all participants described experiences with significant debilitating fatigue that limited their ability to perform daily activities, including brushing teeth, washing hair, showering, walking short distances, changing clothes, or even standing up for extended periods. Participants shared examples of how they struggled with profound exhaustion while completing basic tasks. One participant explained, “It’s as if your inner dialogue becomes full of static, making it difficult to sort through your thoughts without further exhausting yourself or fatigue is like a phone that has been charged all night long only to drop to 10 percent after one call…” One commenter wrote: “I can't shampoo my hair or my child, cook as I'd like as often as I'd like, tie shoes, brush hair, and find fine motor movement difficult and painful.” A caregiver shared that Long COVID significantly decreased his partner’s stamina, noting: “She sits upright for less than 30 minutes per day and stands for less than 10 minutes, never consecutively. Sometimes she doesn't have enough energy to speak.”

Many participants reported becoming bed ridden due to Long COVID. One illustrated her typical day as “…in bed about 18 to 20 hours a day and lying down was the only thing that made me feel any sort of any better.” Another stated: "It's debating if I should just deal with the pain from laying in one position for too long because the idea of getting enough energy to roll over is unbearable."

Post-Exertional Malaise (PEM)

Participants described suffering from PEM, where even small amounts of physical or mental exertion could result in a severe worsening of symptoms. These episodes were typically referred to as *crashes* or *flare-ups* by meeting participants. One participant described that after mental or physical exertion, she might experience, “a two-week migraine or a two-week IBS flare, or I'll be too dizzy to leave my couch for days.” Another described the symptom they developed after exertion as, “post-exertion neuroimmune dysregulation… composed of my worst symptoms like insomnia, cognitive dysfunction and confusion, sleep apnea, heart palpitations, fevers and chills, severe migraines, joint and muscle pain, invisible tremors and muscle jerks.” While symptoms of malaise were described differently, many participants felt that their PEM was the most limiting symptom. One participant shared how PEM may cause a worsening of symptoms following even minor physical or mental exertion: “Sometimes I can do an activity in the moment or exercise in the moment, but then hours or a day or two days later, I'm left with a severe flare-up of my symptoms." Another participant shared that after a recent re-infection with COVID-19, her conditions flared quite extensively for several weeks, and her PEM was much more prominent.

Many participants described how, prior to Long COVID, they had been very active. They now find themselves exhausted from simple physical activities and unable to exercise due to energy crashes throughout the day. One commenter wrote: “Prior to getting acute Covid and Long Covid, I was biking 25 miles twice a week and enjoying my best life. Now, I cannot walk slowly for more than 30 minutes without getting Post Exertion Malaise (PEM) that lasts two to five days which totally fatigues me.”

Orthostatic Intolerance/POTS

Many participants discussed being diagnosed with POTS and dysautonomia as part of their Long COVID experience. One participant described it as heart palpitations, increased heart rate and painful blood pooling upon standing. Another commenter described POTS as causing several symptoms when transitioning from lying down to standing up, such as a fast heart rate, dizziness, and fatigue. A third commenter emphasized that POTS is not driven by anxiety but by a more primary dysfunction of the autonomic system. One commenter described that his blood pressure and heart rate fluctuate wildly at times. Still another stated, “If I had been able to obtain healthcare to regulate my new high blood pressure, Postural Orthostatic Tachycardia Syndrome, & Dysautonomia, I probably wouldn't have had the stroke or developed the aneurysms.”

Patients noted that POTS made simple activities like taking a shower or walking short distances challenging. One commenter described the inability to stand for long periods of time because of POTS and commented on the difficulty of getting a POTS diagnosis, saying it “took me 2.5 years to find a doctor that would diagnose my POTS.” Another commenter suggested that “We need to implement basic screenings for POTS in clinics instead of trying to make everyone do a tilt table (which isn't very accessible).”

Cognitive Impairment (Brain Fog)

Many participants reported experiencing cognitive difficulties, such as memory problems, difficulty finding words, and overall mental fatigue. Patients described brain fog as affecting their ability to think clearly and perform tasks that required focus and concentration, leading to challenges with memory, word retrieval, and overall mental clarity. These challenges impaired patients’ ability to effectively perform daily tasks and work-related activities. One participant described her brain fog as feeling like she was thinking through mud, and described her difficulty with language and speaking: “I often find myself messing up words, unable to find words, unable to write or swapping in different words when I write…” One participant summed up her experience as “a conscious coma, like the world is going by around you. You can hear everything, you can see what's going on, but you can't move or speak or even really form thoughts. And it's extremely disabling.” Another commenter described having “odd brain pressures, sensations like my brain is screaming and needs help.”

Other Symptoms

Pain and headaches: Several participants described random and unpredictable migraines with varying degrees of severity. Others also reported pain of the ear, throat, muscles, joints, and abdomen.

Menstrual symptoms: Some participants mentioned experiencing abnormal menstrual cycles and severe menstrual pain.

Sleep problems: Some participants reported having difficulty sleeping or staying asleep, which led to further exhaustion. One commenter reported being diagnosed with hypersomnia after COVID-19.

Mental health: Participants mentioned experiencing depression, anxiety, and post-traumatic stress disorder (PTSD) as a result of Long COVID. One participant at the meeting said: "My friends would tell you that prior to Long COVID…I was a person fueled by hope…The Long COVID fueled depression dissolved my hope…I could no longer feel joy, purpose, or motivation. I would have very excessive crying spells out of nowhere, sleep issues and suicidal ideation."

Pre-Existing Conditions

Some participants reported having existing chronic asthma conditions worsened as a result of Long COVID. One commenter reported that Long COVID substantially worsened their preexisting chronic pain and fatigue, which was manageable before their COVID-19 infection.

Overall impact of Long COVID on daily life

Through the meeting and docket comments, participants described the impact that Long COVID has had on their daily lives, including:

- **Physical/mobility:** All participants emphasized the profound impact Long COVID has on their physical abilities in their daily lives, including limitations in mobility and decreased endurance. One participant said: "We are shells of the people we were before COVID and lead a very limited life now... watching my once active teenager crawl up the stairs to get to bed." A written commenter noted: "I am not able to prepare my own meals. I eat cereal and milk twice a day. I cannot clean."

  Many individuals had to give up activities they previously enjoyed, such as hiking, running, or working full-time. One commenter who identified as an active 30-year-old prior to getting COVID wrote: "…after my…infection, I went on a relatively easy hike. Less than a week later, I ended up in the hospital…I felt paralyzed, like I could barely move…" One participant said: "I used to cook all the dinners, I used to clean up downstairs, I used to take the kids to the park and I can't do any of that physical stuff anymore." Another participant described the need for assistive devices: "I now use a wheelchair to leave my house, to go shopping...I just don't have the ability to be upright, to cook, to shower upright, to walk, to socialize with friends, or work in any capacity without creating post-exertional malaise." One participant illustrated the significant limitation PEM placed on his activities and the need to carefully manage the energy expenditure to avoid energy crashes: “I call it giving up everything you love. So not walking, not trying to hike.” Another stated: "Because I have that payback with the PEM, I have to really limit my activities."

Many Long COVID patients relied on assistance from caregivers to manage their daily needs. One shared, “I had to give up my house and move in with my parents as well.” Another noted that his symptoms resulted in him being almost entirely bedbound and his partner being his full-time caretaker.

- **Emotional impacts:** Almost all participants expressed feelings of frustration, loss, and emotional distress due to the dramatic changes in their lives caused by prolonged and intractable Long COVID symptoms. One participant captured the sentiment shared by many, saying that Long COVID, “…really has stolen almost the entirety of my life.” Another participant shared, “…I really have a lot of… internalized shame around not being able to provide for my family by working and doing those tasks anymore.”

  Many participants discussed their inability to engage in previously enjoyed activities, leading to a loss of independence, sense of isolation, anxiety, depression, and PTSD. For example, one participant said, “The Long COVID fueled depression dissolved my hope. It furthered the negative impact on my personal relationships. I could no longer feel joy, purpose, or motivation. I would have very excessive crying spells out of nowhere, sleep issues and suicidal ideation.” Another participant described that on his worst days, “suicidal ideation is constant, and the immense grief I've experienced from the full life I can no longer live is crushing.” One caregiver noted that her 17-year-old son with Long COVID “…is not living. he is only surviving. He is extremely depressed and has had to drop out of school.” Another participant shared that he saw a psychologist for help dealing with anxiety and depression “because it was hard to know that I was not the same person I was before COVID.”

- **Social impacts:** Many participants and caregivers noted how Long COVID negatively affected their social interactions, relationships, education, and employment. One participant mentioned missing out on family gatherings and travel due to limited energy and PEM: "We had to cancel our family vacation... we don't even have the ability to be upright long enough to have dinner at a restaurant, let alone take a big trip like that." Another participant said: “Previously, right before COVID, I…volunteered for six different organizations…played ukulele and sang. All of those things had to be given up.”

  One participant shared how her condition prevented her from working: “Since my COVID infections, I am no longer able to work any job, even part-time. I am primarily housebound…” Another shared concerns about remaining employed, saying, “if I'm unable to meet my job expectations due to my cognitive deficits, fatigue, ongoing migraines and GI issues, continued need for remote work, continued crashes, that I could be moved to a different position or lose my job.” A participant who was previously a dancer said that after COVID, “dancing pushed me into fatigue spells that lasted for days, shelving my art career.” One caregiver shared that her son can no longer attend school, noting that “the mental fatigue, academic requirements and attendance laws have been huge hurdles for someone with medical documentation of symptoms that ebb and flow. Even with accommodations and parents who genuinely care about his education and future, he is struggling.” Another caregiver shared that her daughter, once “an honors student who was going to graduate high school at least a year early with a goal of becoming a doctor…is unable to start college.”

One participant summed his life after Long COVID up as: “…I am missing weddings and bat mitzvahs and holidays. I am missing time with my family, friends, and community. I am missing my chance to get married and start a family.” Another participant said: “Long COVID has not only affected my life, but the lives of my family, my friends, my elderly parents and my brother who have had to sacrifice so much to continue to support me during the seemingly never-ending journey.”

Financial burden: Many patients and caregivers discussed that Long COVID required them to reduce their work hours or stop working entirely, resulting in a loss of income and financial strain. One couple living with Long COVID wrote: “We cannot work full time normal jobs. We are on the verge of losing our apartment. I've had to cash out all my retirements I've built and more. We're having to sell our belongings to make rent.” One parent of a patient with Long COVID noted: “Parents like me are having to quit their jobs to be full-time caregivers and do not have caregiver or supplemental financial support.” Many commented that the cost of medical treatments, therapies, and accommodations all add to their financial burden. Another caregiver shared that her daughter’s hospitalizations and medications due to Long COVID cost their insurance tens of thousands of dollars each month. A different participant described her experience of “dealing with different types of disability, private and SSDI [Social Security Disability Insurance], Medicare and transitioning from independent living to dependent living.” Another participant talked about experiencing food insecurity for the first time due to her inability to work.

Topic 2: Patient Perspectives on Treatments for Long COVID

The second discussion topic focused on patients’ experiences with therapies used to treat their Long COVID. Five panelists (Appendix 2) provided comments to start the dialogue:

- A Black female participant, diagnosed with Long COVID in February 2021, shared her experience as part of a post-COVID recovery program that assessed how Long COVID impacted her physically. She was referred to a physical medicine department and was prescribed medications for brain fog, however, discontinued them. She was also referred to the pulmonary rehabilitation department, which was focused on exercise endurance via treadmill, bike, arm ergometer, free weights, and standing and sitting exercises. After her insurance stopped paying for pulmonary rehabilitation, she decided to continue with pulmonary maintenance to manage her symptoms.

- An Asian American female, diagnosed with Long COVID in January 2022, shared her experiences using different approaches to manage her dysautonomia and POTS. She discussed being prescribed daily exercise which caused PEM and taking medications that caused adverse reactions. She found support in the online community which helped her learn about and explore various interventions. She described treatments she found beneficial, such as acupuncture, avoiding dairy and gluten, and vagus nerve stimulation. She expressed a desire for individualized treatment plans that address the root physiological causes of symptoms, and that focus on improving one's health to the level they had prior to Long COVID.

- A White male, diagnosed with Long COVID, spoke about the lack of safe and effective treatment options. He discussed how his medications were focused on symptom management and how it has not fundamentally improved his condition, especially in regard to his most disabling symptoms which are related to exertion. He experienced a slight benefit from taking a beta blocker and midodrine for POTS and bupropion for fatigue.

- A White female, diagnosed with Long COVID as a result of a March 2020 SARS-CoV-2 infection, discussed her challenges accessing and receiving care in a rural setting. The participant noted that it took almost 18 months to find care and described her treatment as a continually evolving plan. She initially had the most success with physical therapy but as more exercises were added, she had to discontinue the program due to exercise intolerance. Due to endocrine and gastrointestinal issues, she follows an anti-inflammatory and low carbohydrate diet. She also makes sure to eat every three hours to keep her blood sugar stable. She shared that she would prioritize treatments that focus on pain relief and fatigue.

- A Hispanic/Latinx non-binary participant, diagnosed with Long COVID as a result of a March 2020 SARS-CoV-2 infection, discussed their experience having unaddressed symptoms from 2020. The participant noted their biggest barrier to treatment was lack of a coherent treatment plan due to lack of provider familiarity with infection-associated chronic conditions. Their treatment plan includes a variety of medications, supplements, pacing, and other therapies. However, they noted that their treatments do not address the underlying causes of Long COVID. They would like treatments to focus on addressing PEM.

In the following large group facilitated discussion, patients and patient representatives discussed their experiences with a range of medical products and therapies. Many participants discussed difficulties in accessing treatments due to clinic locations, cost, insurance, and lack of provider familiarity with Long

COVID. Participants acknowledged the online community as a valuable support network that has helped them understand and explore various treatment options. Participants further discussed how treatments are primarily focused on managing symptoms and emphasized the need for individualized treatment plans that could address the root causes of Long COVID. Perspectives on treatments and therapies, as well as factors that participants would look for in an ideal treatment, are summarized below.

Perspectives on current treatments

Participants described using a combination of treatment approaches when managing their Long COVID. They reported (Appendix 3, Q11) use of prescription and nonprescription products, such as antihistamines, analgesics, and sleep aids. Many also reported the use of dietary and herbal supplements, vitamins, diet modifications, and physical activity. A large number of participants described using other therapies to manage their symptoms.

Participants noted that even with a range of treatments, their Long COVID was not sufficiently managed. Many patients mentioned having to switch their treatment regimens, with one panelist describing the process as trial and error. Some patients noted that their treatments only served to manage their Long COVID symptoms rather than remedy them. For the patients who felt their Long COVID was well managed, some expressed concerns that they were still not back to their pre-COVID health status and that they feared regressing.

Prescription and non-prescription medications

While there are no FDA-approved treatments for Long COVID, participants reported using a variety of prescription and nonprescription drug options, including:

- **Antihistamines** – Antihistamines were reported as the most commonly used class of drugs by the participants, and users often described experiencing a partial resolution of their symptoms. Participants reported using primarily H1 antihistamines such as fexofenadine, loratadine, cetirizine, and ketotifen as well as H2 antihistamines like famotidine to manage various symptoms like nausea, brain fog, respiratory issues, and Mast cell activation syndrome. One patient noted that, “With the help of antihistamines and antioxidants, I have plateaued at a livable place but not fully recovered. If I were to stop antihistamines, my symptoms would come back at full force.”

- **Analgesics** – Many patients used analgesics to manage their pain, migraines, and cardiac symptoms, improve their energy levels, and avoid malaise. For some, prescription analgesics like Nurtec and low-dose naltrexone were the most beneficial medications in their path to recovery. One commenter described how analgesics improved their symptoms, “It isn't perfect but I have seen a dramatic improvement in energy levels and less malaise/fewer crashes/less severe crashes.” Other patients noted using over the counter pain relievers such as acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDS) like ibuprofen to manage their pain, however, one participant shared that those products didn't relieve her of pain.

- **Antidepressants** – Several participants used antidepressants, mainly selective serotonin reuptake inhibitors (SSRIs) such as fluvoxamine, escitalopram, and fluoxetine, to improve fatigue and mood. One commenter stated "They [antidepressants] have slightly helped with my energy levels and certainly with the depression…" While some patients found symptom relief, others mentioned that their antidepressants were ineffective, with one noting that their antidepressants worsened their brain fog.

- **Antivirals** – Several patients described taking antivirals like Paxlovid, Ampligen, and HIV medications to treat an array of symptoms, typically related to PEM and fatigue. A small number of patients mentioned that their medications only provided temporary relief and that some of their symptoms returned later. One patient wrote how they have seen others benefit from taking antivirals and noted that antiviral therapy was the only treatment that had improved their health.

- **Other medications** – Other medications included but were not limited to beta blockers, sleep aids, corticosteroids, and guanfacine.

Physical rehabilitation

Many patients participated in physical activity and rehabilitation therapies as part of their treatment plan. Patients reported attempting physical therapy but many expressed frustrations and mentioned quitting or modifying their routines due to adverse effects like exercise intolerance and PEM. One patient explained that "it's hard to rehabilitate something that automatically gets worse when you engage in physical activity." Another participant shared that once she modified her physical therapy to not cause PEM and setbacks, it helped improve her physical fatigue and POTS symptoms.

Participants discussed how they felt they benefitted from less exertional interventions like pacing and resting. One patient wrote: "With ME/CFS it is necessary that I pace and rest…I have to be aware of everything I do, think, and feel during a day and take all of it into consideration when I do anything." Another commenter described that their most manageable day-to-day regimen has involved "[scaling] back my daily tasks, work, and physical exertion and to sleep or rest whenever I am tired." Additionally, some patients emphasized the contrast between the effects of pacing and resting with their physician's recommendations. One patient expressed that "With fatigue… the biggest thing has been pacing and not pushing myself to crash (which was in direct violation of everything my first doctor suggested: trying harder, pushing myself, forcing myself to exercise… all of which I believe contributed to my Long COVID to begin with)."

Patients additionally discussed other less strenuous interventions like meditation, yoga, Pilates, breathing exercises, and practicing mindfulness. One commenter noted that "My yoga and meditation practices have been the biggest contributor to my recovery… Initially, I was unable to do any of them due to shortness of breath, but over time was able to meditate and slowly work in my yoga practices." Some patients engaged in pulmonary therapy which focused on enhancing exercise endurance and capacity rather than speed and intensity. One participant shared how their pulmonary wellness program helped them with their symptoms, but the effect disappeared after they stopped participating in their program. Another participant mentioned that they had to do a modified pulmonary therapy at home since they could not reach the goals of their rehabilitation program. To reduce symptoms like pain and fatigue, some patients utilized mobility aids and compression garments.

Vitamins and supplements

Many participants discussed their experiences with a variety of vitamins and supplements. Antioxidants, amino acids, vitamins B, C, and D, and minerals like magnesium and zinc were frequently mentioned for improving symptoms related to fatigue, PEM, and brain fog. Patients also incorporated other dietary supplements like probiotics, nattokinase, curcumin, and reishi mushrooms to improve their symptoms. Some participants noted the limitations of these methods. One participant said that "[these supplements] markedly improved my energy and helped against fatigue but seemed to have an upper limit of effectiveness." This was echoed by another commenter, who wrote "The diet and supplements can only take you so far."

Dietary modifications

Participants described their experiences adopting a variety of diets when looking to manage their Long COVID. Others mentioned needing to restrict their diet due to their gastrointestinal symptoms. Some participants mentioned limiting complex carbohydrates, sugar, gluten, and dairy to manage symptoms like gastrointestinal issues, POTS, energy levels, and brain fog. Many participants reported increasing their electrolyte and fluid intake to stay hydrated and address the low blood volume induced by POTS. Patients also mentioned raising their salt intake to increase blood volume. Several commented on the benefits of consuming an anti-inflammatory diet by incorporating foods like ginger, turmeric, black pepper, and herbal teas. One participant discussing their diet said, "controlling inflammation with fresh ginger has further improved my energy level and has helped with residual brain fog." Other patients mentioned trying a low-histamine diet to help improve symptoms, with one commenter stating that low histamine foods along with other drug treatments, were one of "the few things that have taken me from a bed bound state."

Other therapies and products

In response to a polling question (Appendix 3, Q12), some participants indicated engaging in various other therapies to manage their Long COVID. Participants discussed using acupuncture to improve their circulation and manage pain but felt that its effectiveness varied. Some patients noted the benefits of treatments like Hyperbaric Oxygen Therapy and discussed using medical devices like inhalers, continuous positive airway pressure (CPAP) machines, and nebulizers to improve their respiratory symptoms. One patient describing the impact of their device in their day-to-day stated, “I carry a purse sized nebulizer due to not knowing if I’ll get incredibly winded and need a treatment to help with my breathing.” Patients further mentioned other therapies such as vagus nerve stimulation, intravenous immunoglobulin (IVIG), saline infusions, and speech therapy. Additionally, participants mentioned the benefits of seeing a therapist to handle the mental health impacts of Long COVID.

Perspectives on ideal treatments for Long COVID

Participants provided a range of perspectives on attributes that they would like to see in an ideal treatment that would manage or address Long COVID and improve the quality of patients’ lives. Many patients expressed a desire for treatments focused on alleviating the neurological symptoms of Long COVID such as fatigue, PEM, brain fog, cognitive dysfunction, headaches, and migraines. Additionally, some participants expressed a desire for treatments focused on cardiovascular symptoms like POTS, microclots, and respiratory symptoms like shortness of breath. When asked to name the symptom they would prioritize for treatment, fatigue was most frequently mentioned. One patient said that an acceptable treatment outcome would be, “not having to spend every waking moment treating my body like a laptop with a dying battery, obsessing over whether I’ll be able to find a power outlet and whether I can save my document before it shuts down. Knowing that I have enough energy to do something and being able to do spur of the moment activities again.”

Overall, participants expressed that their ideal treatment, in addition to being accessible and affordable, would not inhibit their day-to-day activities, would allow them to be independent, and would help them return to the level of health they had prior to experiencing Long COVID. As one patient stated, “I just want to be ‘me’ again.” Another defined successful treatment as “one that enables me to exert physically and mentally without worsening my ability level and sickness symptoms. If a treatment were successful, I would be able to work again and support myself financially, spend more than a few minutes at a time every couple of months with friends and family, be able to speak on the phone at length, and be able to walk around the city rather than needing a wheelchair… I would be able to dance when a good song comes on guilt-free, without the likelihood that I will be bedbound the next day because of it. I’d be able to travel the world again. I would be able to do all these things with confidence that they would not adversely affect my health, ability level, or independence.” Some patients noted that even a slight reduction in symptoms would improve their quality of life. One commenter wrote, “if I could reduce my headaches and symptoms to a few days a month and get back to exercising, working full-time, and being a present father, that would be a great outcome.” Another patient defined success as, “standing, walking, talking, and being able to handle sitting up for longer than five minutes.”

Many participants also stressed the importance of further research into and developing treatments that address the underlying pathology of Long COVID. Patients emphasized the need for treatments that could address their symptoms rather than manage them. One commenter wrote that “[Long COVID patients] want to address and treat the root cause of our illness. We do not want to repurpose drugs that are meant to mask our symptoms… For instance, I can tell that my brain is inflamed. If my brain inflammation is treated, many of my symptoms improve – memory, mood, sleep. Treating symptom by symptom seems like an easy answer but is not the long-term solution. The fatigue, brain inflammation, and PEM are all connected – all three need to be addressed, treated, and researched together." Participants noted that recovery cannot be a one-size-fits all approach and needs to be tailored to meet each individual's needs. Additionally, some patients noted that treatments should prevent risk of reinfection and that future interventions should consider preventative measures.

Topic 3: Patient Perspectives on Clinical Trials for Long COVID

The third discussion topic focused on patients' perspectives on clinical trial participation. Participants shared factors they consider when deciding whether or not to participate in clinical trials, their desired outcomes, and what experiences have made it easier or harder for them to participate in the clinical trial.

Five panelists (Appendix 2) provided comments to start the dialogue:

- A White female, who is a caregiver to two children with Long COVID, shared her belief that research and clinical trials are essential for understanding disease causes and finding treatments. She enrolled her daughter in the NIH-funded RECOVER trial because it addresses her daughter's key impairments. She considers eligibility criteria, side effects, treatment interruptions, study visits, location, and compensation when assessing whether to participate in a trial. To her and her children, the most meaningful outcome is addressing the cognitive dysfunction and fatigue.

- A White male with Long COVID emphasized the importance of impact, practicality, and compassion in clinical trials. He joined a clinical trial for Paxlovid, considering the broad impact and potential positive effects on his health. Practicality is crucial for him, including accessibility, virtual visits, and tracking outcomes that matter most to him, such as fatigue and cognitive symptoms. He values compassionate interactions and genuine collaboration with trial staff.

- A Black and White mixed-race female discussed challenges participating in clinical trials. The lack of availability, access, and strict exclusion criteria prevented her from being eligible for a clinical trial. Financial barriers, lack of virtual options, and side effects of interventions also impacted her decision to participate. She emphasized the importance of measuring outcomes such as energy levels, fatigue, cognitive symptoms, autonomic dysfunction, and performance of activities of daily life.

- A White male discussed the need for well-controlled trials that are able to assess whether any improvements are due to the intervention being studied or if they are due to the passage of time. He highlighted the importance of identifying biomarkers that change as patient's symptoms improve. He also emphasized the need to use patient-reported outcome measures to assess symptoms related to PEM and brain fog because laboratory tests or vital signs alone may not adequately capture the patient's experience. He suggested considering interventions that have existing evidence and that test multiple medications simultaneously. Limited energy, lack of accessibility, and difficulty finding trials were challenges for him when considering participating in a trial.

- A White female panelist emphasized the need for well-designed and accessible trials. She prioritizes interventions with promising evidence and those that address important symptoms for patients. She values decentralized trials, stratification by phenotype, meaningful outcome measures (e.g., quality of life, symptom severity), and allows concomitant use of other medications.

During a discussion about meaningful improvements to brain fog, one panelist shared that she measures her daughter's brain fog through cognitive exercises. Sometimes her daughter will exhibit cognitive symptoms, including paraphasia, which she described as "she might want to tell me to close the door one day, and instead she said, can you please close the bananas." She also mentioned that a meaningful improvement for her daughter would be the ability to return to school. Several panelists discussed that it is difficult to measure brain fog objectively and suggested the importance of subjective measures of daily activities as a metric. Another panelist mentioned cognitive assessments such as Cogstate and CNS Vital Signs, emphasizing the need to include quality of life measures.

On the topic of tolerating toxicities in a clinical trial, one panelist responded that she takes a nuanced approach by asking the types of questions that assess the impact trial participation will have on her quality of life: "Is my GI [gastrointestinal] symptom going to be upset by this medication 15 percent more five days a week or 10 percent more three days a week?" Another panelist looks at the risk and benefit ratio and is more willing to accept the risk "…if a treatment is working, the risks are much more palatable, as well as knowing that there is treatment or there's something we can do or after the study, the chances are very high that any side effects will be reversed." One other panelist shared that she was willing to tolerate side effects unless they were irreversible or life-threatening, such as microclots potentially caused by some anticoagulants. The panelists highlighted the need to consider risk-benefit tradeoffs and the importance of evidence-based treatments.

Perspectives on Factors to Consider in Long COVID Clinical Trials

In the subsequent facilitated large-group discussion and through comments to the public docket, many people expressed interest in participating in clinical trials for Long COVID treatments. However, they also shared concerns about trial availability, accessibility, physical limitations, overly stringent eligibility criteria, toxicities/side effects, and financial barriers to participation. Patients also provided input on what outcomes they would like to see assessed as part of clinical trials, the therapeutic regimens they would like to see studied, and how they would like results of trials to be shared back to them and disseminated more broadly.

- **Availability of trials:** Some participants discussed the limited availability of clinical trials for Long COVID. One participant commented that "there's just not enough happening right now, particularly given the scale and severity of Long COVID" and that despite being heavily involved in Long COVID research herself, "it takes significant effort to even find clinical trials." One commenter suggested that "Clinical trial researchers should coordinate with disability/long covid experts to design trials more people can participate in." Others expressed a need for clinical trials that test new and repurposed drug treatments specifically with regards to viral persistence and reproductive health in females with Long COVID.

- **Accessibility, location, and physical hurdles:** One caregiver shared her daughter's experience in the NIH RECOVER trial and noted that, "The RECOVER trial has made it easy for us to participate. We are lucky to have a site only 20 minutes away from our home." Other participants living in rural areas or far from trial centers expressed difficulties accessing trials. Commenters cited reasons including a "lack of access to Long Covid clinics (no options to partake in trials)" and "cannot travel to places doing trials due to symptoms." One participant suggested that "researchers need to better promote their studies to the patient population and not focus solely on recruiting through Long COVID clinics, which have many barriers to entry." Another participant suggested "there can be coordinated locations to help reach people who want to participate in these trials, but they're not near a main center…" One commenter from a rural area wrote that there "should be a way for people who live far away to send in samples (ex. urine, stool, blood)." Another one suggested that "Studies organized with plenty of rest periods during study and a place to lay/rest horizontally is a must, as many of us have orthostatic intolerance or POTS."

  Many participants shared that they had been able to participate in clinical trials because there was a remote or virtual option. Others also expressed a desire for virtual trials or fewer clinic visits due to limited energy capacity and risk of re-infection. One participant said: "Just researching and applying for participation in clinical trials on my own through the .gov website is extremely difficult cognitively." A caregiver shared that her daughter had started to participate in a computer-based cognitive rehab program, "but unfortunately, she had to stop due to a significant increase in her symptoms due to the cognitive exertion required." Another participant who had forgone a cardiac rehabilitation trial commented "there's no way I would participate in that because it would have required significant physical activity." One participant summarized: "most of us with Long COVID are operating at just a fraction of the energy capacity of the patient you might be used to. That means we need you to respect our time and focus on and track the things that matter most to us."

- **Eligibility criteria:** Some participants shared that they were excluded from Long COVID clinical trials because they did not have a positive PCR test, and called for clinical trials to "at minimum, have an arm that allows for clinical diagnoses of COVID so that the millions of people…can participate." Some emphasized the need for trials to include diverse populations, considering participants' preexisting conditions and complex medical histories. One participant commented that “it's really important the clinical trials look at the effect of treatment on people who represent the full complexity and the full diversity of the large Long COVID community. Lots of us have preexisting chronic illness or disability, looking at the frequency of people with autoimmune and complex chronic conditions.” Another one called for “inclusion of patients with acceptable degrees of documented or suspected organ damage. This would include patients who've been sick for a number of years, who may be more likely to display it as organ damage seems to appear over time.”

Some participants described how they were excluded from clinical trials due to their need for certain routine medications. One participant shared that she doesn’t meet inclusion criteria due to the off-label treatments she is on, such as steroids. The same participant also noted that “there's other problematic exclusion criteria in clinical trials that involves the activity ranges for vitals. They're just not sensitive for this nuance of patient population.” Another said she was disqualified from many trials “due to any one or combination of the ten prescription medications I am on from my neurologist, cardiologist, psychologist, pulmonologist, GP or pain management doctor, all necessary due to COVID.” Others chose not to enroll in clinical trials due to requirements for stopping all other medication. One caregiver stated: “We recently chose to not participate in a study for one diagnosis that she has because it required stopping a very effective medication that took many months to find the correct dose for her.”

- **Outcomes that are meaningful to patients:** Participants expressed interest in tracking a range of symptoms, including fatigue, brain fog, PEM, POTS, neurocognitive function, pain, vision problems, chest pain, breathing problems, and immunological dysfunction. While some participants indicated that just an improvement in pain relief and fatigue would be significant, others stressed the importance of outcomes beyond just safety and efficacy, including quality of life and the ability to function independently. For example, a commenter wrote, “The most important outcome is to perform daily activities like school, work, exercise.” One caregiver mentioned, “our most meaningful outcome at this point would be finding a treatment for the cognitive dysfunction and cognitive fatigue that is preventing her from returning to her baseline function and from being able to go to school and move forward with her life.” One participant said, “I wish there was more about post-exertional malaise, but I'll take what I can get.” Another participant commented, “I want to be able to sit up and stand and move again, it would vastly improve my quality of life.”

  One participant commented on the specific outcome measures to use: “Ways to measure this include quality of life measures, standardized tools for symptoms and conditions like the DSQ-PEM and COMPASS-31 and the severity of our most impactful symptoms.” A commenter noted that “If something ends up being only 5% impact, that is a huge improvement for some.” Another participant suggested measuring biomarkers in medication trials, in particular, "involving things like microclotting or endothelial dysfunction, immunological biomarkers like T cell disturbances or cytokines that are associated with perhaps chronic infection or just immune dysfunction in general as well as neurological markers like imaging tests or neuroinflammatory markers, indicators of blood-brain barrier dysfunction, things like that, as well as metabolic markers like disruptions to lipid metabolism, oxidative stress, increases in anaerobic respiration." The same participant also commented, "I do think it's also important to try testing multiple medications at once in the same trial, because, again, this is probably a complicated multisystem disorder." One other participant would like to see trial endpoints include improvements in organ dysfunction as well as prevention of organ dysfunction in the future.

- **Therapeutic regimens:** Participants discussed various treatment options for Long COVID. Some urged trials to focus on cures rather than symptomatic treatments, saying, "the treatments that have been mentioned today are Band-Aids, and I hope that trials will focus on cures." Another participant suggested, "I'd like the FDA to address not only palliative therapies for symptoms, but also definitive ones targeting underlying causes." One commenter added that such preference is because "they're much more likely to address a wide range of symptoms rather than just one at a time." One participant who took part in a trial testing the drug Paxlovid commented, "we need a variety of extended trial and titration times. Fifteen days of Paxlovid isn't going to cure people."

  Participants discussed a wide range of drugs and therapeutic regimens they would like tested in clinical trials. Some participants desired trials testing specific drugs or class of drugs, such as antivirals for COVID, antivirals against reactivated viruses, vaccines, anticoagulants, antiplatelets, antihistamines, monoclonal antibodies, and immunomodulators, while others called for trials addressing specific symptoms or issues of Long COVID, such as ME/CFS, PEM, cognitive deficit, POTS, microclotting, migraines, and gastrointestinal problems. A few participants noted the negative impact of trials involving exercise and physical exertion, with one emphasizing that "There is little to no interest/motivation surrounding trials of lifestyle interventions, habits, exercise, cognitive retraining, etc. as these are all things that have been accessible throughout the duration of illness and have not improved the condition of myself or most others." One commenter wrote, "exercise trials and physical therapy have exacerbated my malaise and fatigue, and these approaches are many times harmful to Long COVID patients." Another commenter suggested, "Behavioral treatments including exercise, graded exercise therapy (GET), and cognitive behavioral therapy (CBT) should not be trialed, let alone prioritized, for Long COVID."

- **Control arms:** On the topic of participation in a clinical trial if it included a placebo-control arm some patients expressed willingness to participate "as long as I can continue taking other medications and supplements that currently help me somewhat manage my symptoms" or "if I knew that the advantageous results would be provided after the trial." Many patients preferred not being assigned to a placebo arm, though they understood its importance for certain trials.

One participant shared that he felt, “controls are one of the most important parts of clinical trials…Sometimes I'll see a study that's been trialing a medication for six months and they've seen moderate improvement, but that's my experience without medication.” Some patients stated that they would be unwilling to participate in a trial with a placebo-control arm. One participant commented, “placebo studies seem like a waste of time given the urgency of this crisis.” A different participant stated: “Ideally, studies that don't include a placebo are better for patients, in my opinion, because everyone who has Long COVID right now wants a chance to get better as soon as possible,” but also felt that “Any studies are better than no studies.” Another stated that “The only morally and ethically acceptable means of trialing treatments at this point is to trial them against one another, or in an observational fashion with the control group being the overall patient population not in the trial.”

- **Toxicities and side effects:** Participants discussed their willingness to tolerate toxicities and side effects that may occur. Opinions varied among participants. Some were willing to take risks, stating, “While I wouldn't want permanent or irreversible damage, my symptom threshold is high, and I'm comfortable taking risks given my desperation." One participant commented that although “the side effects aren't necessarily as prohibitive. But when you go into a patient community and you find other people who have been trying it, you see something that could possibly trigger an increase, it may cause you to refrain.” Another participant agreed that “I would also consider the side effects of the intervention, particularly if there is a high likelihood my symptoms could be permanently made worse on the intervention. But I would be willing to risk some side effects for drugs that are showing promise from patient anecdotes and that test a promising hypothesis.” Another participant discussed the factors she usually takes into consideration when making decisions, saying, “could those toxicities cause permanent damage because that would be something that might turn me away, or if those toxicities would just be short-term damage or would get better once the drug was stopped, I would still consider trialing a drug.”

  Some commented that they are not willing to accept any side effects that would make them sicker than they already are, or that might take away any of their remaining function. One participant said, “I cannot participate in any trial that includes graded exercise or the likelihood of worsening my symptoms and putting at high risk of stroke, heart attack and increased seizure-like activity I got from COVID.” One commenter wrote that “Lots of pain, headache, nausea or organ damage would be a definite no for me.” Another one shared an experience she had with a medication that caused “bruising around my knees and achilles tendons in my ankles. I immediately discontinued that med because losing ability to stand and walk, in addition to everything else that I have already lost, would be an intolerable risk. We should not lose more of our limited functionality because of a treatment med.” Another commenter noted that she is “willing to tolerate: mild symptoms that I can find OTC [over the counter] symptom relief such as indigestion, nausea, mild pain, low level headaches” but “not willing to risk: worsening brain fog to where I would not be able to communicate…”

- **Financial barriers:** Some patients mentioned economic burden as a barrier to participating in trials due to Long COVID's impact on their income status. One participant noted, “Anything that is in-person is extensively more difficult…and it also continues to add to the cost associated with participating in trials, as you've already experienced a loss of either employment and income or healthcare coverage.” Another one described her experience participating in one clinical trial, which was “at significant personal financial cost, requiring personal loans from friends to cover travel and accommodations, as it was in Southern California, and I am based in Brooklyn.” A different participant mentioned, “There was one clinical trial that sounded great. I would effectively be subsidizing it because the small stipend didn't even cover the cost of gas.” Another participant commented that “I would consider more in-person clinic visits with additional travel that is reimbursed.” This was echoed by a commenter who wrote that the factors enabling participation would include “reimbursement for transportation costs.”

- **Reporting results:** A few participants shared their experiences with receiving results from the clinical trials in which they participated. One participant noted that “another part of the study that I like is that you do get your results back, which is also useful just for my own personal medical -- I can provide it to medical providers and make further treatment options based on that.” One caregiver whose child participated in a trial mentioned that “Results from standard lab tests are forwarded to us so we can submit them to our doctors to avoid duplicate testing.” Another participant urged for “a different flavor of outreach, one that's more rapid and more thorough once clinical trial results are out so that more and more medical professionals can be aware of the news of the developing field.”

Conclusion

This PFDD meeting for Long COVID provided FDA, NIH, CDC, others within HHS, medical product developers, researchers, and other interested parties the opportunity to hear directly from individuals living with Long COVID and their loved ones. The meeting discussions covered important topics about the health effects that matter most, the impact that Long COVID has on daily life, the factors individuals consider when selecting a treatment, and the factors individuals consider when determining whether to participate in a clinical trial for Long COVID. Long COVID is a debilitating condition, with serious physical, emotional, and social impacts for individuals living with it. FDA recognizes the unique perspective patients contribute to the understanding of their condition and treatment management, and patient perspectives can play a critical role in informing both drug development and regulatory decision making.

Participants shared perspectives at this public meeting that illustrated the daily challenges and burdens of living with Long COVID. These perspectives emphasized the severe physical, emotional, social, and financial impacts of Long COVID and the need for more effective therapeutic options to treat the debilitating symptoms including fatigue, PEM, brain fog, POTS, as well as underlying multi-organ/system dysfunctions across all age groups and racial/ethnic groups.

FDA is grateful to the individuals living with Long COVID, as well as their loved ones and representatives, for courageously sharing their personal experiences and perspectives. As Dr. Hilary Marston shared during the clinical overview presentation, “FDA is committed to supporting drug development for Long COVID along with our federal partners. And in this, it is essential that we have the patient’s voice front and center. So, to that end, thank you so much for your attendance here today. We really appreciate it, and we look forward to engaging in the discussion today.” FDA shares the Long COVID community’s desire and commitment to advancing the development of safe and effective treatment options.

Appendix 1: Meeting Agenda

Public Meeting on Patient-Focused Drug Development for Long COVID

April 25, 2023

10:00 – 10:05 am	**Welcome** Robyn Bent, R.N., M.S. *Director of Patient-Focused Drug Development, Office of the Center Director (OCD), Center for Drug Evaluation and Research (CDER), FDA*
10:05 – 10:10 am	**Opening Remarks** Rachel L. Levine, M.D. *Admiral, U.S. Public Health Service* *Assistant Secretary for Health, U.S. Department of Health and Human Services*
10:10 – 10:20 am	**Overview of FDA's Patient-Focused Drug Development Initiative** Theresa Mullin, Ph.D. *Associate Center Director for Strategic Initiatives, FDA*
10:20 – 10:30 am	**Background on Long COVID** Hilary Marston, M.D., M.P.H. *Chief Medical Officer, FDA*
10:30 – 10:40 am	**Overview of Discussion Format** Robyn Bent, R.N., M.S. *OCD, CDER, FDA*
10:40 – 11:10 am	**Topic 1: Health Effects and Daily Impacts** A panel of patients and patient representatives will provide comments to start the discussion on health effects and daily impacts of Long COVID.

11:10 am – 12:15 pm	**Large-Group Facilitated Discussion on Topic 1** Patients and patient representatives in the audience are invited to add to the dialogue.
12:15 – 12:45 pm	**Break**
12:45 – 1:15 pm	**Topic 2: Current Approaches to Treatment** A panel of patients and patient representatives will provide comments to start the discussion on current approaches to treatment for Long COVID.
1:15 – 2:20 pm	**Large-Group Facilitated Discussion on Topic 2** Patients and patient representatives in the audience are invited to add to the dialogue.
2:20 – 2:30 pm	**Break**
2:30 – 3:00 pm	**Topic 3: Clinical Trials** A panel of patients and patient representatives will provide comments to start the discussion on clinical trials related to Long COVID.
3:00 – 3:55 pm	**Large-Group Facilitated Discussion on Topic 3** Patients and patient representatives in the audience are invited to add to the dialogue.
3:55 – 4:00 pm	**Closing Remarks** Michael Iademarco, M.D., M.P.H. *Rear Admiral and Assistant Surgeon General, U.S. Public Health Service* *Deputy Assistant Secretary for Science and Medicine, U.S. Department of Health and Human Services*

DISCUSSION QUESTIONS

Topic 1: Health effects and daily impacts that matter most to patients

1. Which **symptoms** of Long COVID have the most significant impact on your life? (Examples may include pain, brain fog, fatigue, heart palpitations, recurring blood clots, depression, or anxiety).
2. Are there **specific activities** that are important to you that you cannot do at all or as fully as you would like because of your Long COVID? (Examples may include reading, sleeping, or exercising).
    a. Is there a particular impact of Long COVID (such as need to work a reduced work schedule, inability to complete daily tasks, anxiety, or depression) that worries you? If so, what worries you most?
3. How has your Long COVID changed from original diagnosis to now (have you noticed differences in severity, change in symptoms)?

Topic 2: Patients' perspectives on current approaches to treatment

1. **What are you currently doing** to treat or manage your Long COVID? (Examples may include prescription medicines, over-the-counter products, nutritional supplements, and other therapies including non-drug therapies such as pulmonary rehabilitation, aerobic exercises, or diet modifications).
    a. Has your treatment regimen changed over time, and why?
    b. What factors went into your decision making when it came to selecting a course of management for your Long COVID?
2. Would you say your Long COVID today is well-managed? Please explain.
3. Assuming there is no complete cure for your Long COVID, what specific things would you look for in an **ideal treatment** for your Long COVID?
    a. Is there a particular symptom of Long COVID (such as fatigue, brain fog, or loss of sense of smell/taste) that you would prioritize for treatment? If so, which symptom would you prioritize?
    b. What would you consider a successful treatment outcome?

Topic 3: Patients' perspectives on clinical trials for Long COVID

1. If you considered participating or have participated in a clinical trial for Long COVID, please tell us about your experience.

   a. What factors (if any) of the clinical trial **enabled** you to participate?
   b. What factors (if any) of the clinical trial made it **more difficult** for you to participate?

2. How would the following factors weigh into your decision if you were considering participating in a clinical trial?
   a. **The clinical trial intervention** (Examples may include side effects of the medical intervention, how the intervention is administered etc.).
   b. **The logistics of the clinical trial** (Examples may include the duration of the trial, whether the trial is fully remote or requires clinic visits, the number of in-person clinic visits required, distance from home to clinic site, or whether you might receive a placebo or not).
3. What **outcomes** for Long COVID are most important to measure in a trial setting? (Examples may include reduction in pain, brain fog, fatigue, or other aspects; or improvement in your ability to perform daily activities such as reading, sleeping, or exercising)

Appendix 2: Patient and FDA/HHS Panel Participants

Patient Panel, Topic 1

- Jill Anderson
- Heather-Elizabeth Brown
- Lynda Varno
- Estefania Fernández Otero
- Katie Drackert
- Sudeepti K.

Patient Panel, Topic 2

- Stephanie Hughes
- Jacqueline Luciano
- Daniel Lewis
- Tammy Wilshire
- Angela Vazquez

Patient Panel, Topic 3

- Michelle W.
- Ezra Spier
- Liza Fisher
- Ryan
- Lisa McCorkell

FDA/HHS Panel

- Banu Karimi-Shah (Division of Pulmonology, Allergy and Critical Care (DPACC), Office of New Drugs (OND), Center for Drug Evaluation and Research (CDER))
- Fortunato Senatore (Division of Cardiology and Nephrology (DCN), OND, CDER)
- Nadia Habal (Division of Rheumatology and Transplant Medicine (DRTM), OND, CDER)
- Shannon Sullivan (Division of General Endocrinology (DGE), OND, CDER)
- Larissa Stabinski (Division of Antivirals (DAV), OND, CDER)
- Mark Connelly (Office of Vaccines Research and Review (OVRR), Center for Biologics Evaluation and Research (CBER))
- Adam Weltz (Office of Product Evaluation and Quality (OPEQ), Center for Devices and Radiological Health (CDRH))
- Theresa Mullin (Office of the Center Director (OCD), CDER)
- RADM Michael Iademarco (Office of the Assistant Secretary for Health (OASH), U.S. Department of Health and Human Services (HHS))
- Lumy Sawaki-Adams (Division of Clinical Research (DCR), National Institutes of Health (NIH))
- Priti Patel (Centers for Disease Control and Prevention (CDC))

Appendix 3: Meeting Polling and Scenario Questions

The following questions were posed to participants at various points throughout the April 25, 2023 public meeting on Patient-Focused Drug Development for Long COVID. Participation in the polling questions was voluntary. The results were used as a discussion aid only and should not be considered scientific data.

Demographic Questions

1. Where do you live?
    a. Within Washington, D.C. metropolitan area (including the Virginia and Maryland suburbs)
    b. Outside of the Washington, D.C. metropolitan area

2. Are you or a loved one currently experiencing symptoms of Long COVID?
    a. Yes
    b. No

We will ask that the remainder of the questions be answered by people who responded "yes" to Question 2.

3. What is your age?
    a. 0 – 10 years old
    b. 10—17 years old
    c. 18 – 29 years old
    d. 30 – 39 years old
    e. 40 – 49 years old
    f. 50 – 59 years old
    g. 60 – 69 years old
    h. 70 years old or older

4. Do you identify as:
    a. Female
    b. Male
    c. Other

5. What part of your body is affected by Long COVID? **Select all that apply.**
    a. Muscles and joints
    b. Heart
    c. Lungs
    d. Brain/nervous system
    e. Kidneys
    f. Liver
    g. Digestive System (stomach and intestines)
    h. Blood
    i. Other (such as mouth, nose, hair, etc.)

6. Which type of health care provider are you seeing for your Long COVID symptoms? **Check all that apply.**
    a. Primary care physician
    b. Long COVID specialist/clinic
    c. Medical specialist (specialty care outside of a Long COVID clinic)
    d. Chiropractor or complementary health care provider
    e. Other
    f. None of the above

Questions for Topic 1: Health Effects and Daily Impacts

7. How long after your COVID-19 illness did you begin having symptoms of Long COVID? **Select one.**
    a. 0-1 months
    b. 1-2 months
    c. 2-3 months
    d. 3-6 months
    e. 6-12 months
    f. 12-24 months
    g. 24-36 months
    h. Other

8. Which of these symptoms have you experienced because of your Long COVID? **Select all that apply.**
    a. Pain (including headaches)
    b. Learning, attention, or memory difficulty (for example brain fog)
    c. Weakness or fatigue
    d. Shortness of breath, cough
    e. Racing heartbeat/dizziness, postural tachycardia syndrome (POTS)
    f. Post-exertional Malaise (PEM) or exercise intolerance
    g. Depression and/or anxiety
    h. Difficulty falling asleep or staying asleep (Insomnia)
    i. Other

9. What symptoms of your Long COVID are most bothersome to you? **Please choose up to three answers.**
    a. Pain (including headaches)
    b. Learning, attention, or memory difficulty (for example brain fog)
    c. Weakness or fatigue
    d. Shortness of breath, cough
    e. Racing heartbeat/dizziness, postural tachycardia syndrome (POTS)
    f. Post-exertional Malaise (PEM) or exercise intolerance
    g. Depression and/or anxiety
    h. Difficulty falling asleep or staying asleep (Insomnia)
    i. Other

10. What do you find to be the <u>most disruptive aspects</u> of Long COVID on your daily life? **Please choose up to three answers.**
    a. Lost productivity (such as employment, education)
    b. Loss of physical function
    c. Loss of job
    d. Impact on relationships with family and friends
    e. Emotional or psychological impacts
    f. Cognitive effects (thinking and remembering)
    g. Other
    h. None of the above

Questions for Topic 2: Current Treatment Approaches

11. Currently, there are no medical products approved for treatment of Long COVID. However, some treatments may be used off-label. Which of the following medical products (drug therapies or medical devices) or interventions have you ever used to treat the symptoms related to your Long COVID? **Check all that apply.**
    a. Antidepressants (such as amitriptyline, vortioxetine, doxepin)
    b. Sleep Aids (such as melatonin, quazepam, temazepam)
    c. Antivirals (such as Paxlovid, molnupiravir, remdesivir)
    d. Antihistamines (such as diphenhydramine HCl, Benadryl)
    e. Anticoagulants (blood thinners such as warfarin, aspirin)
    f. Analgesics (pain medicine such as acetaminophen, NSAIDs)
    g. Corticosteroids (such as dexamethasone, prednisone, cortisone)
    h. Medical Devices or other procedures
    i. Other

12. Which of the following interventions have you ever used to manage the symptoms related to your Long COVID? **Check all that apply.**
    a. Pulmonary rehabilitation or aerobic exercises
    b. Vitamins, herbal supplements, or dietary supplements
    c. Diet modifications
    d. Meditation
    e. Acupuncture
    f. Physical or occupational therapy/rehabilitation
    g. Psychological/cognitive behavioral therapy
    h. Other
    i. None of the above

13. For the medical products or interventions you use, what do you consider to be the <u>most burdensome aspects of the treatment</u>? **Please choose up to three answers.**
    a. How the treatment is administered
    b. The time it takes to receive or administer the treatment
    c. The treatment only provides minimal benefit
    d. The treatment is effective only for a short-term
    e. Bothersome side effects of the treatment
    f. Concern about serious risks of the treatment

g. Uncertainty about long-terms effects of treatment
h. Difficulty in accessing treatment
i. Other

HYPOTHETICAL SCENARIO: CLINICAL TRIAL FOR A NEW DRUG

Imagine that you have been invited to participate in a clinical trial to study an experimental treatment for Long COVID. Your doctor believes that you may be a good candidate for this clinical trial.

This experimental treatment is an ***oral antiviral****. A small study in people suggests that this treatment* ***may improve some Long COVID symptoms by up to 30%*** *of people when taken* ***once a day for six months.*** *The purpose of this study is to better understand how well this treatment works and its safety.*

More ***common side effects of this therapy may include rash, diarrhea, and muscle aches.*** *Rare but more serious side effects may include* ***trouble breathing or swelling in feet and legs.***

Participants in this clinical trial will receive either the study drug or a placebo for six months and will be followed for a ***total of 12 months. Clinic visits will occur every two weeks for the first three months then every three months after that.*** *Clinical visits will involve* ***routine blood work. Participants will also be expected to complete Long COVID symptom questionnaires online every week for the first six months of the study,*** *as well as other questionnaires that are designed to measure changes in quality of life, function, and symptoms over the trial period.*

Based only on the information presented in the scenario, how likely are you to participate in this clinical trial? **Please choose one response.**

a. Highly likely
b. Somewhat likely
c. Somewhat unlikely
d. Highly unlikely
e. I’m not sure