U.S. FOOD & DRUG ADMINISTRATION

Public Meeting on Patient-Focused Drug Development for Long COVID

Tuesday, April 25, 2023

FDA will be streaming a live webcast of the meeting in both English and Spanish with the presentation slides, which is open to the public. The webcast recording and presentation slides, along with a meeting transcript and summary report, will also be made publicly available after the meeting.

#PFDD

Welcome

Robyn Bent, RN, MS

Director, Patient-Focused Drug Development Program

Office of Center Director

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

Agenda

- Opening Remarks
- Overview of FDA's Patient-Focused Drug Development Initiative
- Background on Long COVID
- Overview of Discussion Format
- Discussion Topic 1: Health Effects and Daily Impacts
  - Break (30 minutes)
- Discussion Topic 2: Current Approaches to Treatment
  - Break (10 minutes)
- Discussion Topic 3: Clinical Trials
- Closing Remarks

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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

Overview of FDA's Patient-Focused Drug Development Initiative

Theresa Mullin, PhD
Associate Center Director for Strategic Initiatives
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

FDA's role in medical product development and evaluation

FDA's mission is to **protect and promote public health** by evaluating the **safety and effectiveness of new drugs**.

While FDA plays a critical oversight role in drug development, it is just one part of the process. **FDA does not develop drugs nor conduct clinical trials.**

Review divisions at FDA (e.g., Division of Neurology, Division of Psychiatry, etc.) provide **regulatory oversight** during drug development, make decisions regarding **marketing approval for new drugs, and provide guidance** to regulated industry on clinical, scientific and regulatory matters.

What is Patient-Focused Drug Development (PFDD)?

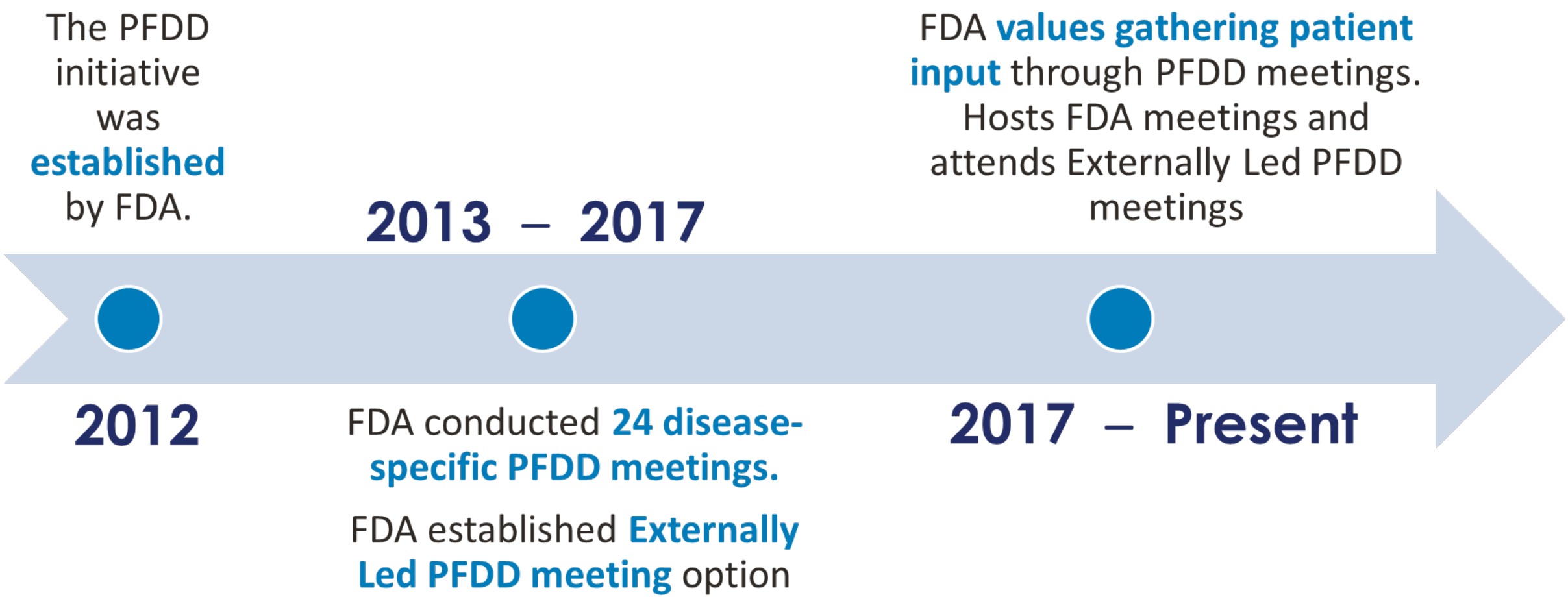
PFDD is a systematic approach to help ensure that **patients' experiences, perspectives, needs, and priorities** are captured and meaningfully incorporated into drug development and evaluation.[1]

[1]https://www.fda.gov/drugs/development-approval-process-drugs/patient-focused-drug-development-glossary

Value of FDA's PFDD Meetings

- Patients are uniquely positioned to inform FDA understanding of the clinical context for drug review and regulatory decision making
- Prior to PFDD, available mechanisms for obtaining patient input were limited to discussions related to specific applications under review, such as Advisory Committee meetings and only a few patient representatives
- PFDD meetings provide a more systematic way to obtain patients' perspectives on severity of a condition, and its impact on daily life, and their assessments of available treatment options

PFDD Meetings Provide Key Stakeholders an Opportunity to Hear the Patient's Voice

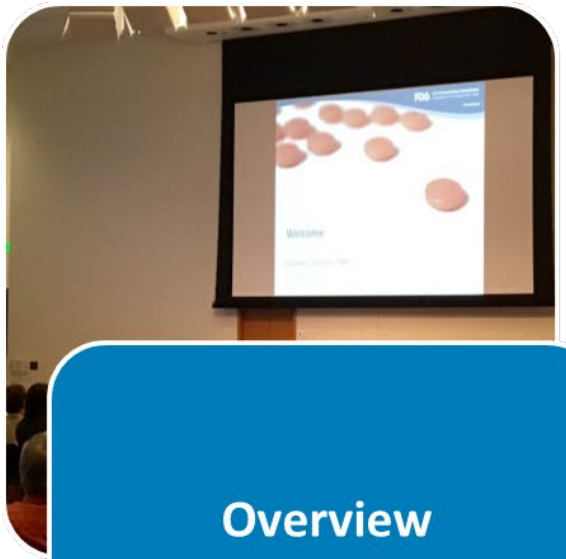


PFDD meetings in a wide range of disease areas providing insights

2013	2014	2015	2016	2017
• Chronic Fatigue Syndrome/ Myalgic Encephalo-myelitis • HIV • Lung Cancer • Narcolepsy	• Sickle Cell Disease • Fibromyalgia • Pulmonary Arterial Hypertension • Inborn Errors of Metabolism • Hemophilia A, B, and other Heritable Bleeding Disorders • Idiopathic Pulmonary Fibrosis	• Female Sexual Dysfunction • Breast Cancer • Chagas Disease • Functional Gastro-intestinal Disorders • Parkinson's Disease and Huntington's Disease • Alpha-1 Antitrypsin Deficiency	• Non-Tuberculous Mycobacterial Lung infections • Psoriasis • Neuropathic pain associated with peripheral neuropathy • Patients who have received an organ transplant	• Sarcopenia • Autism • Alopecia Areata • Hereditary Angioedema
2018	**2020**	**2021**	**2022**	
• Opioid Use Disorder • Chronic Severe Pain	• Stimulant Use Disorder • Systemic Sclerosis	• Vitiligo	• Long COVID	

FDA clinical and statistical review staff have also attended over 80 other *Externally-Led PFDD* meetings 2016-23 conducted by patient advocacy groups

PFDD meetings follow a **town hall style** discussion format



Overview

Clinical Background and Current Available Treatments

Symptoms and Daily Impacts

- Panel of patients and caregivers
- Facilitated group discussion

Current Treatment Options

- Panel of patients and caregivers
- Facilitated group discussion

Each PFDD meeting is tailored to the needs of the specific disease area

- FDA encourages patient advocates, researchers, drug developers, healthcare providers and other government officials to attend PFDD meetings
- However, our focus is on hearing directly from patients and their caregivers, so we ask that others remain silent in listening mode during the discussions since the meetings are a **platform to hear directly from patients, caregivers and patient representatives.**
- After the PFDD meeting, a **Voice of the Patient report** summarizes the input shared by patients and caregivers.

Thank you!

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Clinical Overview of Long COVID

Hilary Marston, M.D., M.P.H
Chief Medical Officer
U.S. Food and Drug Administration

April 25, 2023

Outline

- Terms and Definitions
- Clinical Features
- Potential Causes
- Epidemiology
- Treatment Options
- Regulatory Challenges for Drug Development

Long COVID Terminology

- Long COVID is a patient-created and widely accepted term.
- Many other terms are used to refer to Long COVID including:
  - Post-COVID Conditions
  - Post-acute sequalae of SARS-CoV-2 Infection (PASC)
  - Long-term effects of COVID
  - Post-acute COVID syndrome
  - Chronic COVID
  - Long-haul COVID
  - Late sequelae

Post-COVID Conditions: Information for Healthcare Providers (cdc.gov)

Interim Federal Working Definition

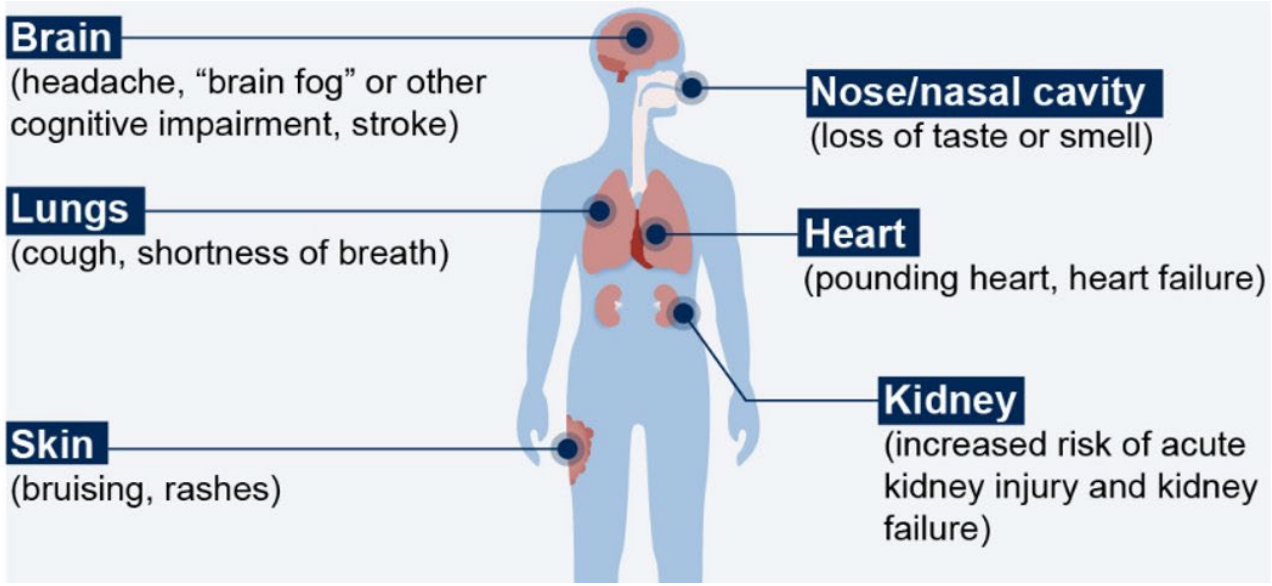
- Long COVID is broadly defined as signs, symptoms, and conditions that continue or develop after initial COVID-19 or SARS-CoV-2 infection.
- The signs, symptoms, and conditions are present four weeks or more after the initial phase of infection; may be multisystemic; and may present with a relapsing–remitting 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.

COVID.gov - Find COVID-19 guidance for your community , National Research Action Plan on Long COVID , Services and Supports for the Longer-term Impacts of COVID-19, Examining the Working Definition for Long COVID | National Academies

HHS Definition March 2023

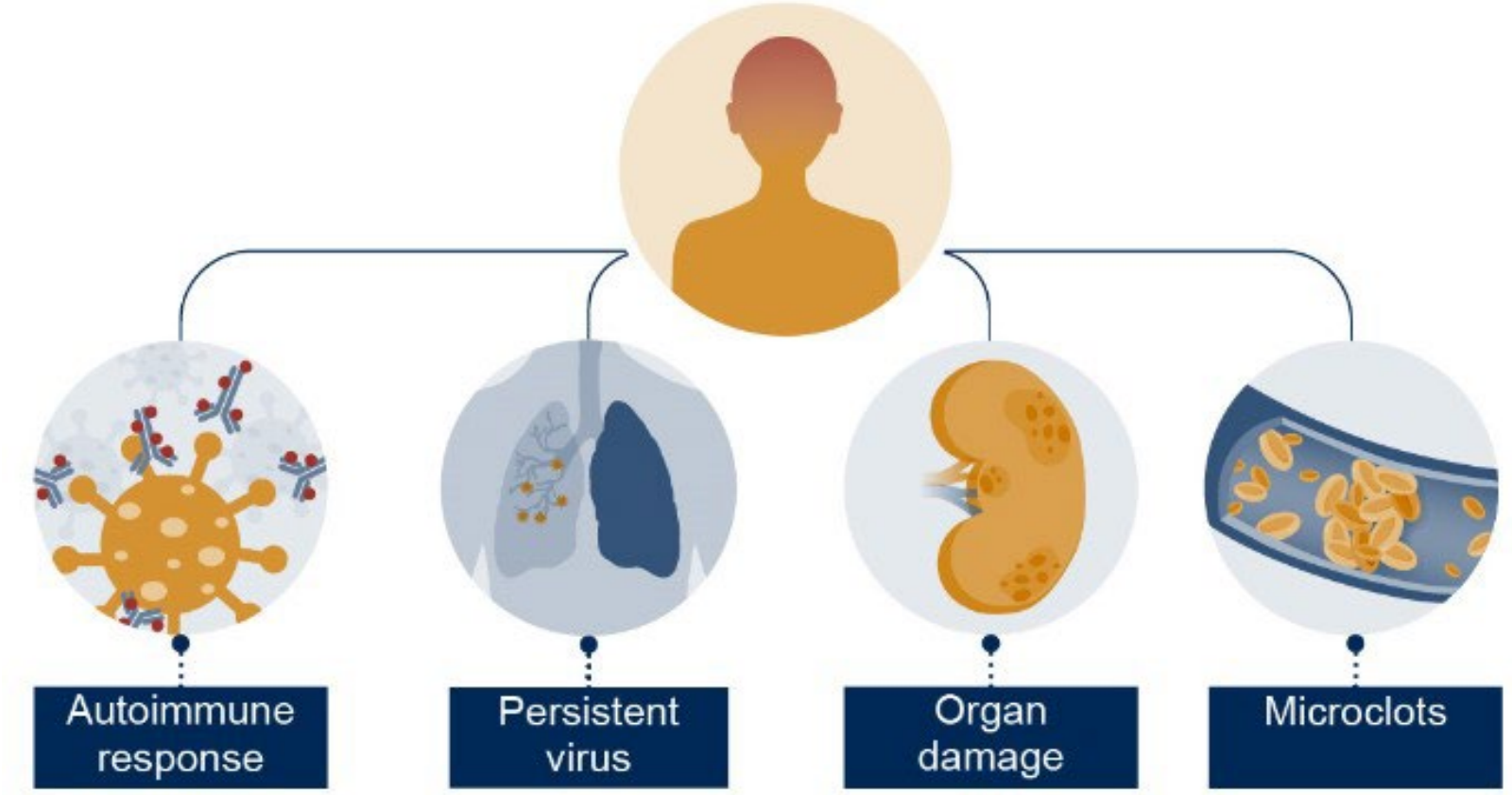
Clinical Features of Long COVID

- Over 200 different Long COVID symptoms have been reported.
- Most common symptoms include fatigue, post exertional malaise, and cognitive impairment ("brain fog").
- Symptoms vary from person to person and can be severe and disabling for some individuals.



Post COVID-19 condition (Long COVID) (who.int), GAO analysis for CDC information and medical literature.

Possible Causes of Long COVID



Source: GAO analysis of medical literature. | GAO-22-105666

Science & Tech Spotlight: Long COVID | U.S. GAO
https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-conditions.html

Prevalence of Long COVID

- The prevalence has been challenging to estimate, with estimates ranging widely (5–30%).
- Based on March 2023 Household Pulse Survey results, the CDC/National Center for Health Statistics estimates that 6% of U.S. adults report currently having Long COVID symptoms.
- An estimated 65 million individuals globally may have Long COVID

Post-COVID Conditions: Information for Healthcare Providers (cdc.gov)
Long COVID - Household Pulse Survey - COVID-19 (cdc.gov)
Persistence of somatic symptoms after COVID-19 in the Netherlands: an observational cohort study

Factors Associated with Long COVID

- Pre-existing health conditions
- More severe initial COVID-19 illness
- Lack of vaccination prior to infection with SARS-CoV-2
- People who experience multisystem inflammatory syndrome during or after COVID-19 illness

Health inequities may affect populations at risk for Long COVID.

Long COVID or Post-COVID Conditions | CDC

Long COVID in Children

- Adolescents and Children may also develop Long COVID
- Symptoms and natural history of Long COVID may be different among children
- Approach to diagnosis and management of Long COVID may differ, especially for younger children

Post–COVID-19 Symptoms and Conditions Among Children and Adolescents — United States, March 1, 2020–January 31, 2022 | MMWR (cdc.gov)
Post-COVID-19 Conditions in Children and Adolescents (aap.org)
Long COVID: An Uncommon Complication in Children | NIH COVID-19 Research
Long-COVID in children and adolescents: a systematic review and meta-analyses | Scientific Reports (nature.com)

Treatment Options

- No drugs are FDA-approved for the treatment of Long COVID.
- For most patients, the goal of medical management is to optimize function and quality of life.
- Symptom management approaches may be helpful.
- Management may change as more evidence becomes available.

Post-COVID Conditions: Information for Healthcare Providers (cdc.gov)

Challenges to Drug Development

- Long COVID is a new entity and COVID-19 epidemiology is evolving.
  - Many knowledge gaps exist and features of Long COVID may change over time.
- Long COVID represents many potentially overlapping entities, with likely different biological causes and different sets of risk factors and outcomes.
  - Different treatment approaches may be needed for patients with different Long COVID symptoms
- Tools to reliably assess how new treatment impact how patients feel, function, or survive have not been established for Long COVID.

Conclusions

- Long COVID is a post-viral condition, which can be severe and disabling, presenting with diverse symptoms and symptom clusters, across body systems, with several proposed biologic causes.
- There are many challenges to drug development for Long COVID.
  - FDA is committed to supporting drug development for Long COVID.
  - Incorporating the Long COVID patient's voice will be essential.
- We appreciate your attendance and look forward to hearing from you today.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Overview of Discussion Format

Robyn Bent, RN, MS

Director, Patient-Focused Drug Development Program

Office of Center Director

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

Discussion Overview

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

- Health effects of Long COVID that have the most significant impact on your daily life
- How your Long COVID has changed over time
- What worries you most about your Long COVID

Topic 2: Current Approaches to Treatment

- Your experience with treating your Long COVID
- What approaches you use to treat your Long COVID
- What you have found to be most effective in helping you treat your Long COVID
- What factors you would consider when considering or seeking treatment

Topic 3: Clinical Trials

- What your experience was like participating in a clinical trial for Long COVID
- What factors would weigh into your decision to participate in a clinical trial
- What outcomes for Long COVID are most important to measure in a trial setting

Discussion Format, continued

You will have a chance to answer polling questions

- Their purpose is to aid our discussion
- Participants can use the mentimeter.com link to answer polling questions
- Individuals or family members only, please

Participants can add comments through the webcast or by telephone

- Although they may not all be read or summarized today, your comments will be incorporated into our summary report

Send us your comments!

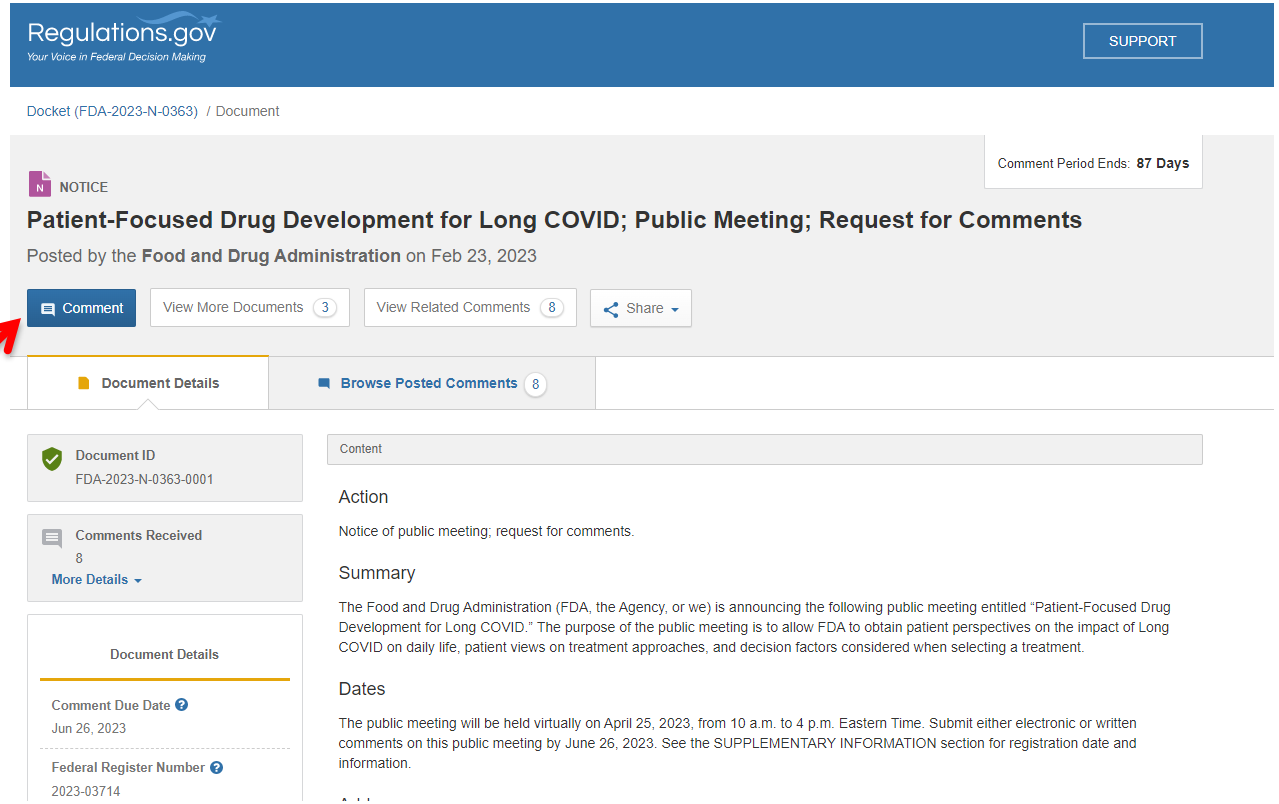
You can send us comments through the “public docket”

- The docket will be open until June 26, 2023
- Comments will be incorporated into our summary report
- Anyone is welcome to comment

Visit:
https://www.regulations.gov/document/FDA-2023-N-0363-0001

Or Search “patient-focused Long COVID” on www.regulations.gov

And **Click Comment!**



Discussion Ground Rules

- We encourage all individuals and family members to contribute to the dialogue
- FDA is here to listen
- Discussion will focus on Long COVID health effects, treatment, and clinical trials
- The views expressed today are personal opinions
- Respect for one another is paramount

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

Participation in the polling questions is voluntary. The results are used as a discussion aid only and should not be considered scientific data.

Are you or a loved one currently experiencing symptoms of Long COVID?

a. Yes
b. No

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We will ask that the remainder of the questions be answered by people who responded "yes" to Question 2. Please answer for the person living with symptoms of Long COVID.

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

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Do you identify as:

a. Female
b. Male
c. Other

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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.)

Participation in the polling questions is voluntary. The results are used as a discussion aid only and should not be considered scientific data.

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

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Discussion Topic 1

Health Effects and Daily Impacts of Long COVID

Topic 1 Discussion Questions

1. Which **symptoms** of Long COVID have the most significant impact on your life? (Examples may include pain, difficulty thinking, 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)?

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

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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

Participation in the polling questions is voluntary. The results are used as a discussion aid only and should not be considered scientific data.

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

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What do you find to be the most disruptive aspects 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

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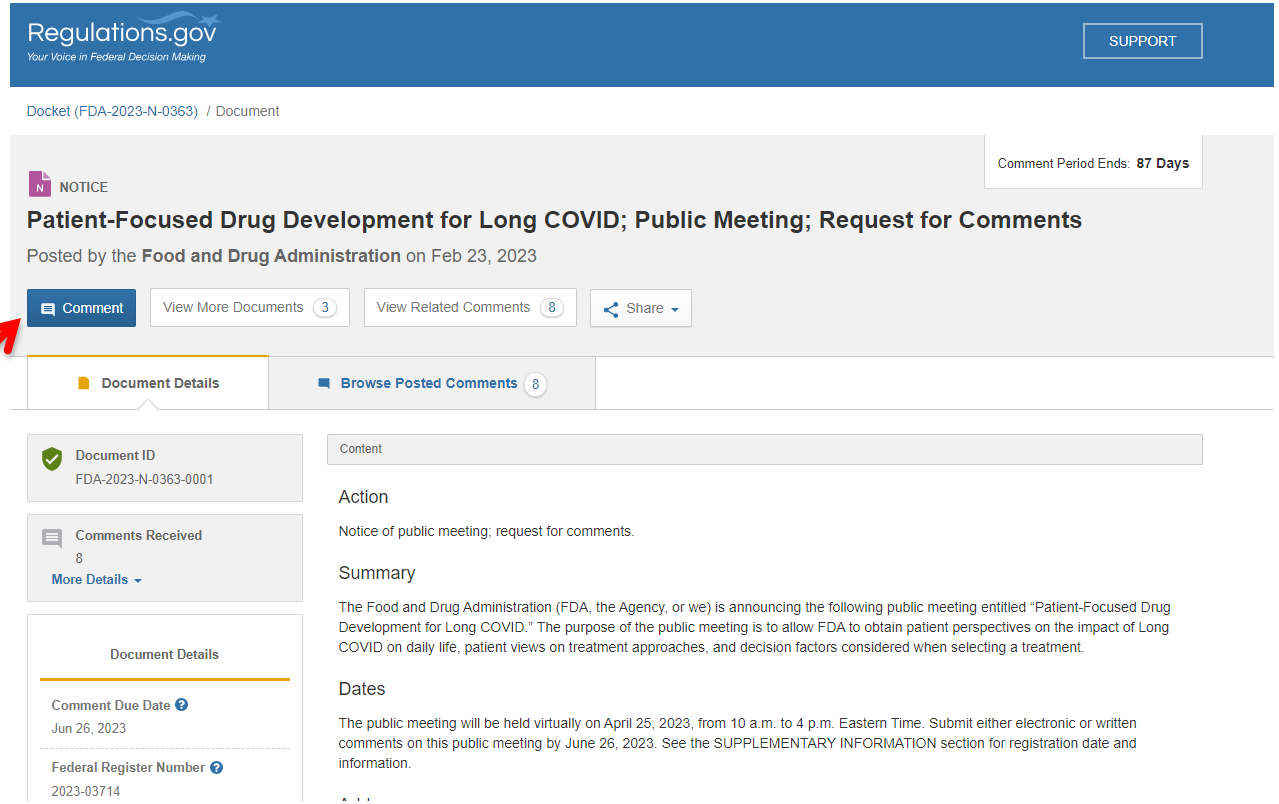

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Discussion Topic 2

Current Approaches to Treatment

Topic 2 Discussion Questions

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?

Currently, there are no medical products approved for treatment of Long COVID. However, some treatments have been 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

Participation in the polling questions is voluntary. The results are used as a discussion aid only and should not be considered scientific data.

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

Participation in the polling questions is voluntary. The results are used as a discussion aid only and should not be considered scientific data.

For the medical products or interventions you use, what do you consider to be the most burdensome aspects of the treatment? **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

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Discussion Topic 3

Clinical Trials

Topic 3 Discussion Questions

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)

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 6 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 2 weeks for the first 3 months then every 3 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 6 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

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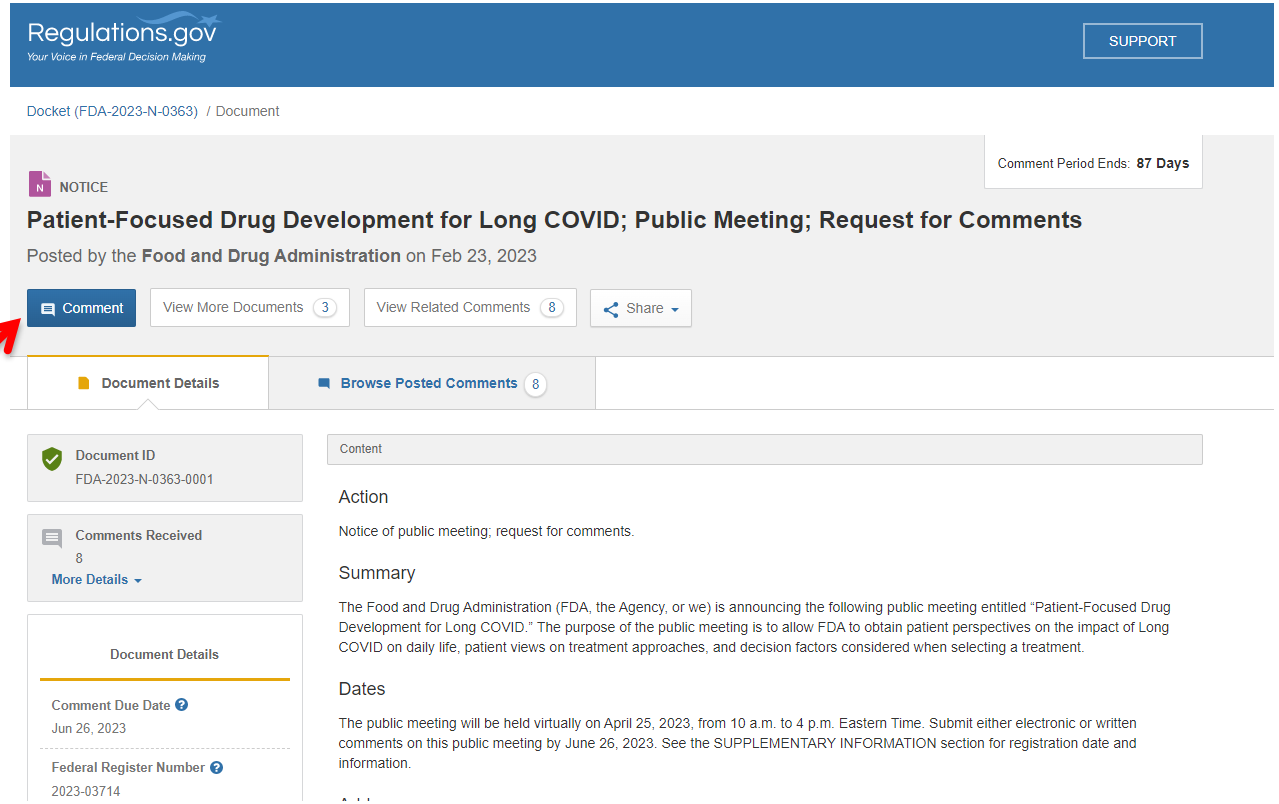

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Closing Remarks

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


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