

Long COVID: Emerging Therapies

Steven Deeks, MD

Professor of Medicine

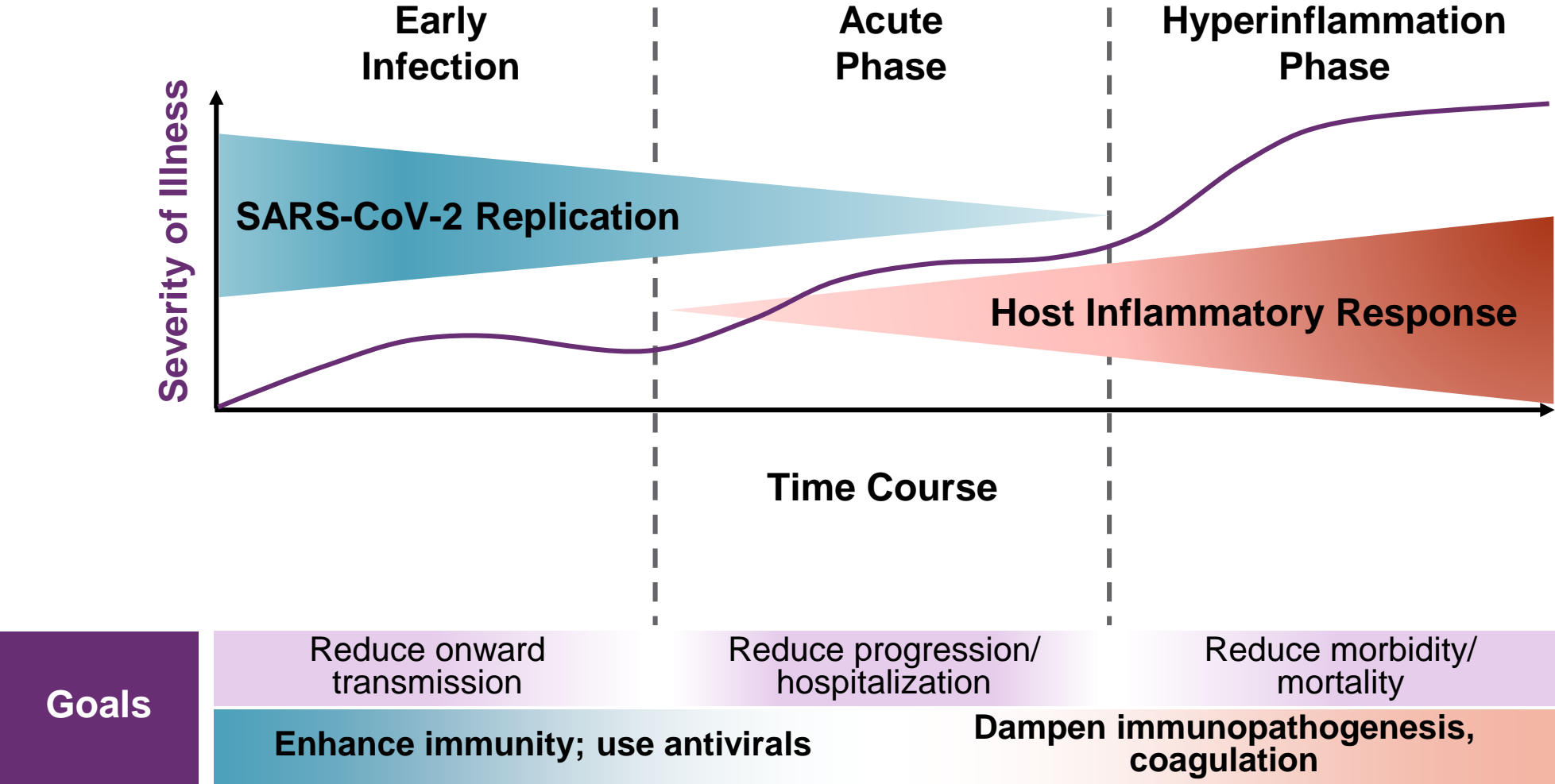
University of California, San Francisco



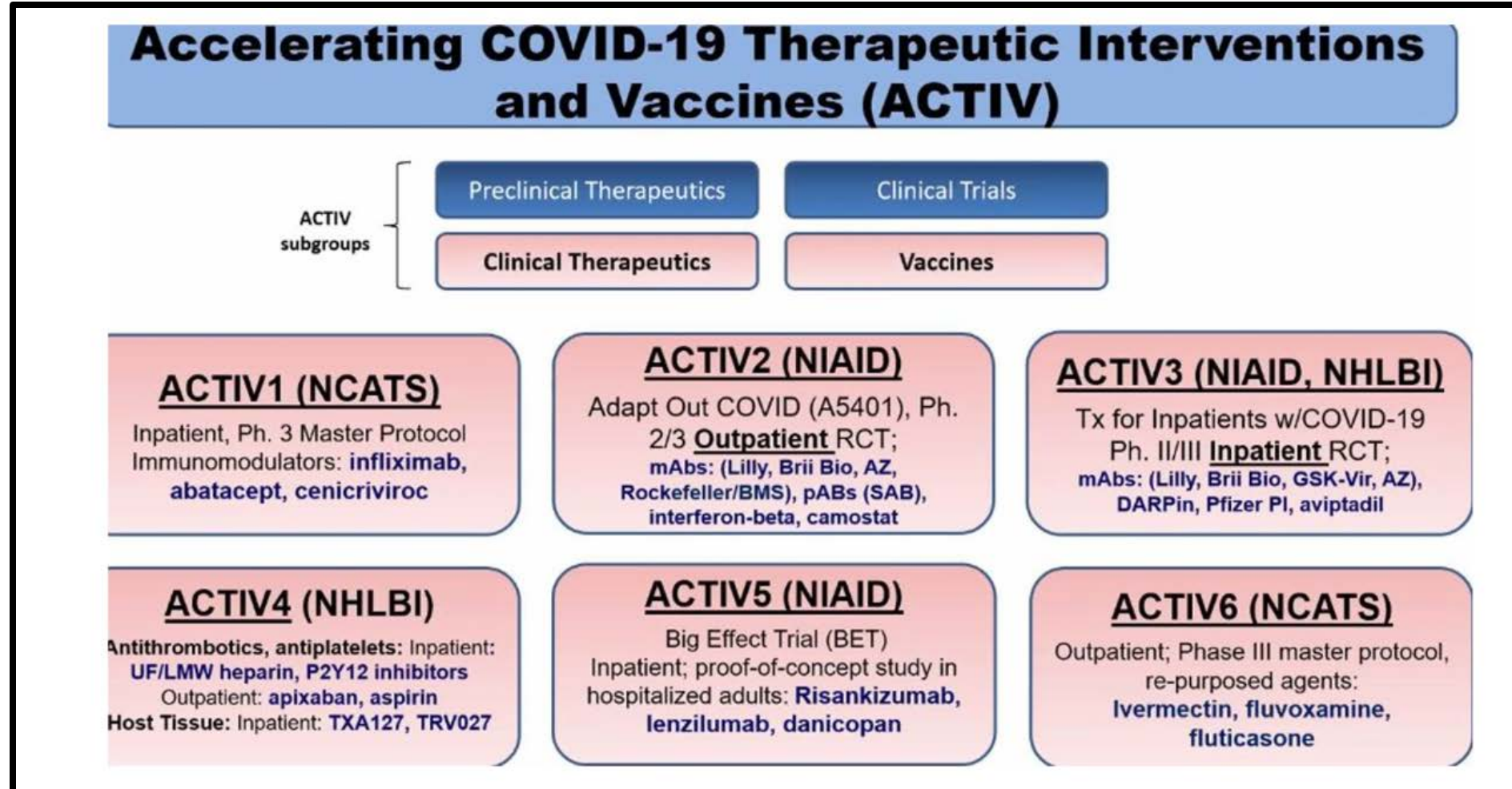
University of California
San Francisco



Management of Acute COVID



Development of acute COVID therapies: Public-private partnerships and adaptive platforms



Key Therapeutic Agents Approved/Authorized or Under Evaluation for Treatment of COVID-19

Antivirals

(Hydroxy)chloroquine
Ivermectin
Lopinavir/ritonavir
Molnupiravir
Nirmatrelvir/ritonavir
Nitazoxanide
Remdesivir

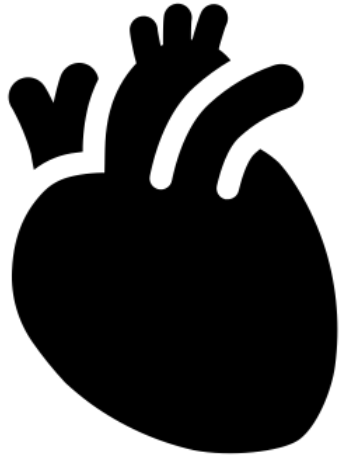
Anti-SARS-CoV-2 mAbs

Bamlanivimab plus etesevimab
Casirivimab plus imdevimab
Sotrovimab

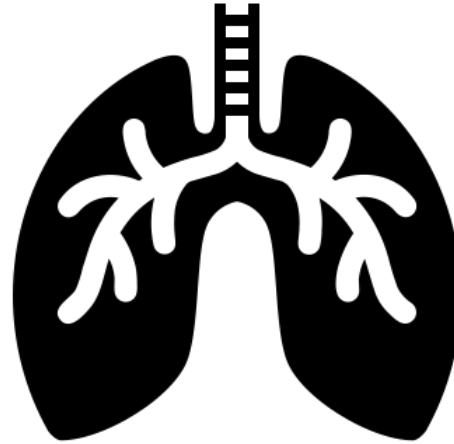
Immunomodulators

Colchicine
Corticosteroids
Fluvoxamine
GM-CSF inhibitors
IL-1 and IL-6 inhibitors
Interferons
Kinase inhibitors
Non-SARS-CoV-2 IVIG

PASC: Several distinct phenotypes



Cardiovascular Syndrome



Pulmonary Syndrome



Neurocognitive Syndrome

- Multiple mechanisms: Direct irreversible tissue injury, inflammation/auto-antibodies, microvascular clotting
- Multiple pathways: Vascular disease (microvascular clotting), nerve damage (dysautonomia), end-organ damage (CNS, CVS)
- Multiple outcomes: CNS, CVD, POTS, ME, MCAS
- Multiple possible treatments: anti-virals, anti-inflammatory drugs

Lessons from the Post-ARDS Literature

The NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

APRIL 7, 2011

VOL. 364 NO. 14

Functional Disability 5 Years after Acute Respiratory Distress Syndrome

Margaret S. Herridge, M.D., M.P.H., Catherine M. Tansey, M.Sc., Andrea Matté, B.Sc., George Tomlinson, Ph.D.,
Natalia Diaz-Granados, M.Sc., Andrew Cooper, M.D., Cameron B. Guest, M.D., C. David Mazer, M.D.,
Sangeeta Mehta, M.D., Thomas E. Stewart, M.D., Paul Kudlow, B.Sc., Deborah Cook, M.D.,
Arthur S. Slutsky, M.D., and Angela M. Cheung, M.D., Ph.D.,
for the Canadian Critical Care Trials Group

Mechanism of PASC

DRIVERS OF INCREASED SUSCEPTIBILITY

Racial and Ethnic Minorities

- Increased risk for exposure & severe manifestation of COVID-19
- Socioeconomic factors prevent proper self-isolation
- Less access to primary and specialty care
- Distrust of medical institutions
- Higher rate of pre-existing conditions
- Multimorbidity

Clinical Complexity

- Pre-existing conditions (obesity, diabetes, heart/lung disease, etc.)
- Multimorbidity
- Severe COVID-19 manifestation
- Prior mental health history
- Women

Older Population

- Increased risk for severe COVID-19
- Higher rate of pre-existing conditions
- Multimorbidity

Rural Residents

- Increased risk for exposure to COVID-19
- Decreased healthcare infrastructure
- Older population
- Higher rate of pre-existing conditions
- Multimorbidity



Basics of clinical management: CDC

- Long COVID can be diagnosed and managed by primary care
 - Conservative approach in the first 4 to 12 weeks
 - Aggressive workup – if indicated – to begin after 12 weeks of symptoms
- Physical examination: Orthostatic vital signs, ambulatory pulse oximetry, exercise capacity (6-minute walk test)
- Laboratory testing
 - Positive COVID test not necessary
 - Tests to rule out common issues and or syndromes that present with similar symptoms (rheumatologic workup, thyroid function, cardiac enzymes) recommended
 - Inflammatory markers may be ordered despite lack of treatment
- Specialized testing: Tilt test (POTS), chest CT, brain MRI
 - Excessive testing can be harmful

Basics of clinical management

- Goal of therapy: Improve quality of life
 - Holistic approach is beneficial (may require referral to Long COVID clinic)
- Orthostasis and dysautonomia: compression stockings, abdominal binder, hydration, physical therapy, medications for POTS
- Post-exertional malaise and similar symptoms: Planning, Pacing, Prioritizing, and Positioning
- Flexibility exercises (yoga and tai chi) and strength exercises
- Off-label therapies: Antivirals, seroids, IVIG, others

"Long covid" in primary care

Assessment and initial management of patients with continuing symptoms

Post-acute covid-19 appears to be a multi-system disease, sometimes occurring after a relatively mild acute illness. Clinical management requires a whole-patient perspective. This graphic summarises the assessment and initial management of patients with delayed recovery from an episode of covid-19 that was managed in the community or in a standard hospital ward.

An uncertain picture



The long term course of covid-19 is unknown. This graphic presents an approach based on evidence available at the time of publication. However, caution is advised, as patients may present atypically, and new treatments are likely to emerge

Managing comorbidities

Many patients have comorbidities including diabetes, hypertension, kidney disease or ischaemic heart disease. These need to be managed in conjunction with covid-19 treatment. Refer to condition specific guidance, available in the associated article by Greenhalgh and colleagues

Safety netting and referral

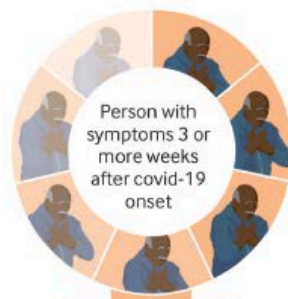
The patient should seek medical advice if concerned, for example:

Worsening breathlessness
 $\text{PaO}_2 < 96\%$ Unexplained chest pain
 New confusion Focal weakness

Specialist referral may be indicated, based on clinical findings, for example:

- ➔ **Respiratory** if suspected pulmonary embolism, severe pneumonia
- ➔ **Cardiology** if suspected myocardial infarction, pericarditis, myocarditis or new heart failure
- ➔ **Neurology** if suspected neurovascular or acute neurological event

Pulmonary rehabilitation may be indicated if patient has persistent breathlessness following review



Person with symptoms 3 or more weeks after covid-19 onset

Clinical assessment

Full history
 From date of first symptom

Current symptoms
 Nature and severity

Examination, for example:

Temperature Heart rate and rhythm Blood pressure Respiratory examination
 Functional status Pulse oximetry Clinical testing *If indicated*

Assess comorbidities

Social and financial circumstances

Investigations

Clinical testing is not always needed, but can help to pinpoint causes of continuing symptoms, and to exclude conditions like pulmonary embolism or myocarditis. Examples are provided below:

Blood tests

Full blood count Electrolytes
 Liver and renal function Troponin
 C reactive protein Creatine kinase
 D-dimer Brain natriuretic peptides
 Ferritin – to assess inflammatory and prothrombotic states

Other investigations

Chest x ray Urine tests
 12 lead electrocardiogram

Social, financial, and cultural support

Prolonged covid-19 may limit the ability to engage in work and family activities. Patients may have experienced family bereavements as well as job losses and consequent financial stress and food poverty. See the associated article by Greenhalgh and colleagues for a list of external resources to help with these problems

Medical management

Symptomatic, such as treating fever with paracetamol
 Optimise control of long term conditions
 Listening and empathy
 Consider antibiotics for secondary infection
 Treat specific complications as indicated

Self management

Daily pulse oximetry
 Attention to general health
 Rest and relaxation
 Self pacing and gradual increase in exercise **if tolerated**
 Set achievable targets

Diet
 Sleep
 Quitting smoking
 Limiting alcohol
 Limiting caffeine

Mental health

In the consultation:
 Continuity of care
 Avoid inappropriate medicalisation
 Longer appointments for patients with complex needs (face to face if needed)

In the community:
 Community linkworker
 Patient peer support groups
 Attached mental health support service
 Cross-sector partnerships with social care, community services, faith groups

PRACTICE POINTER

Management of post-acute covid-19 in primary care

Trisha Greenhalgh,¹ Matthew Knight,² Christine A'Court,¹ Maria Buxton,³ Laiba Husain¹

Long COVID clinics

- Validate experience
- Discuss uncertainty
- Rule out PASC mimickers: Usual diagnostic tests may be normal
- Rehabilitation and physical therapy
- Mental health
- Financial support
- Multidisciplinary approach is critical

Emerging clinical trials networks

- Drugs
- Biologics
- Rehabilitation
- Behavioral
- Medical devices
- Complementary and alternative therapies



Eligibility: Unique phenotypes

Outcomes: QOL, functional status

Adaptive platform trials likely to emerge as they did for
management of acute infection

Pharmaceutical trials for PASC

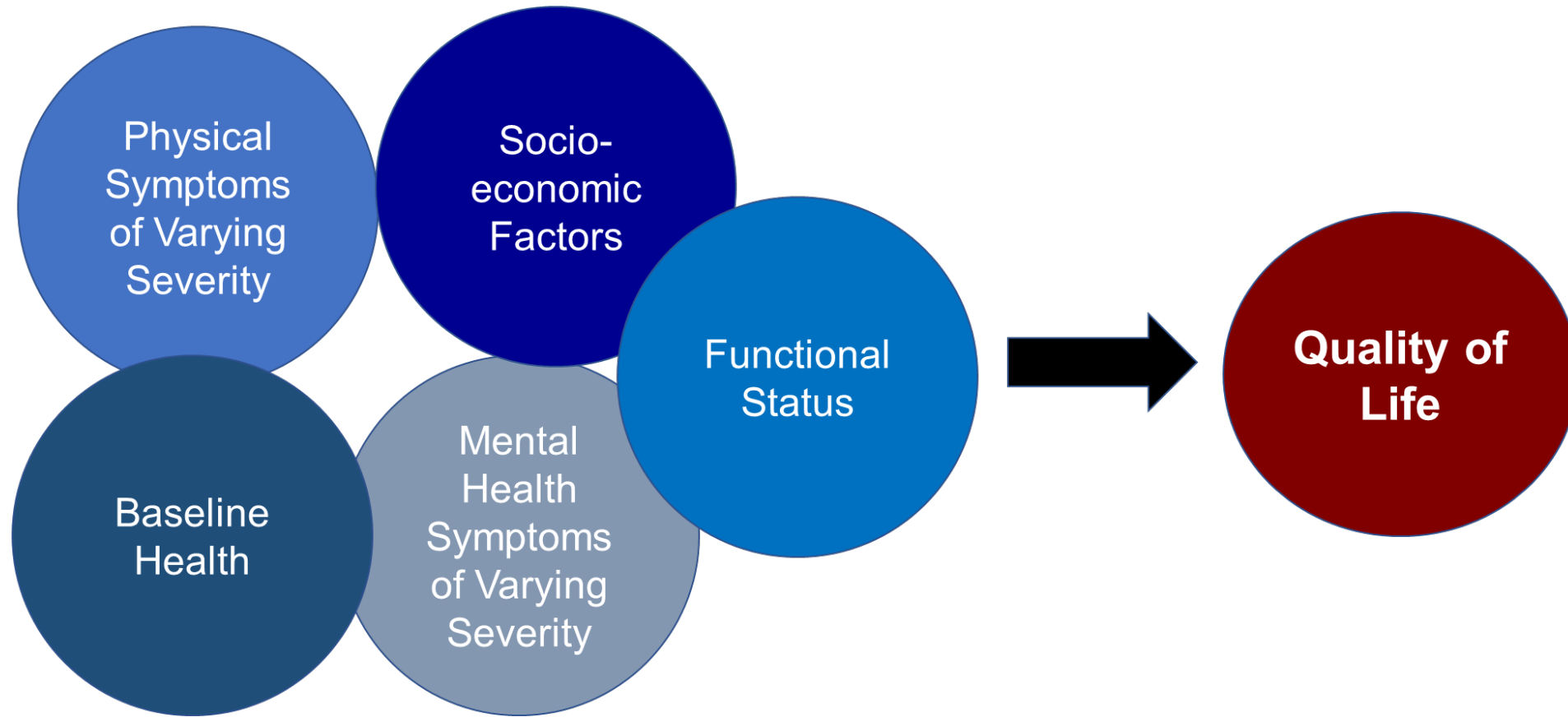
Company	Intervention	Target
Amgen	Ivabradine (HCN channel blocker)	POTS
Ampio Pharmaceuticals	Cyclized peptide derived from aspartyl-alanyl diketopiperazine	DAMPs
CytoDyn	Leronlimab (CCR5 inhibitor)	Inflammation
GioCOV, Sorrento	Allogeneic mesenchymal stem cells	Inflammation
AIM ImmunoTech	Rintatolimod (poly(I):poly(C12U))	Virus
PureTech	Pirfenidone	Pulmonary fibrosis
Synaigen	Inhaled interferon beta-1a	COPD
Resolve Therapeutics	RSLV-132 (ribonuclease to digest autoantibodies and immune complexes)	Autoantibodies
AgelessRx	Naltrexone and nicotinamide adenine dinucleotide	Fatigue
n/a	Montelukast	Respiratory Symptoms
SolAeroMed	S-1226 (inhaled surfactant)	Surfactant function
n/a	Sirolimus	Pulmonary fibrosis
n/a	Atorvastatin	Neurocognitive function
n/a	Metoprolol	POTS, dyspnea
n/a	Clopidogrel/aspirin, apixban	Amyloid microclots

Adapted from Schmidt, Nature Biotechnology (2021); updated via ClinicalTrials.gov

Phase II studies now maturing

- LYT-100: deuterated form of pirfenidone (PureTech, NCT04652518)
 - Post-hospitalization with long-term respiratory complications stemming from a prior hospitalisation due to Covid-19 (N=168)
 - Outcome: 6-minute walk test
- AXZ1125: amino acids that can improve mitochondrial function (Axcella, NCT05152849)
 - Population: Long COVID (=40)
 - Outcome: Mitochondrial tests (phosphocreatine recovery rate following moderate exercise)
- AT1001: larazotide acetate, CD163 antagonist/zonulin antagonist (Mass General Hospital, NCT05022303)
 - Population: MIS-C (n=20)
 - Outcome: GI symptoms
- RSLV-132: RNase fused to a human IgG1 Fc domain (RESOLVE, NCT04944121)
 - Population: PASC (n=70)
 - Outcome: Symptoms

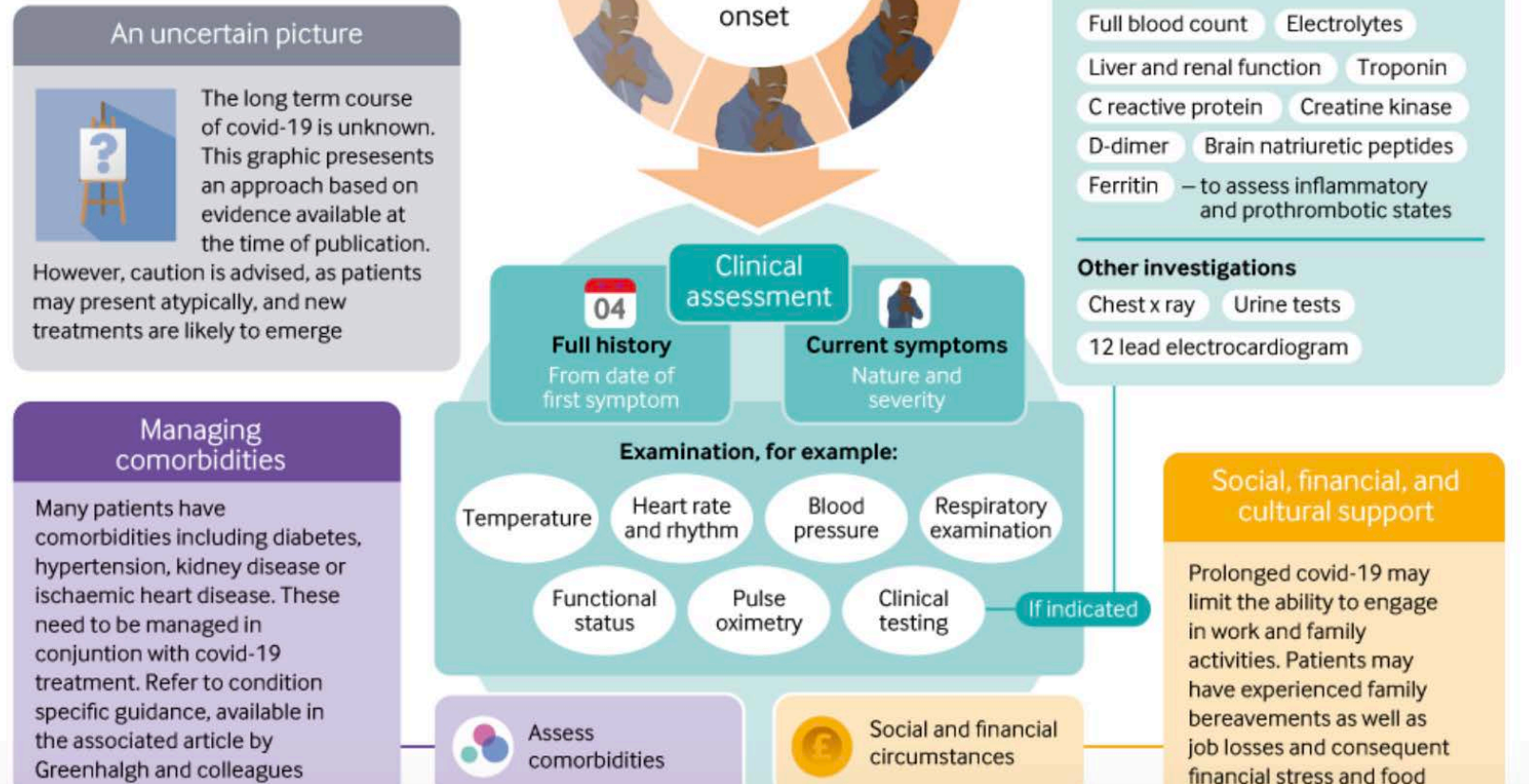
Quality of life and functional status are the outcomes that will shape drug development, which poses regulatory challenges



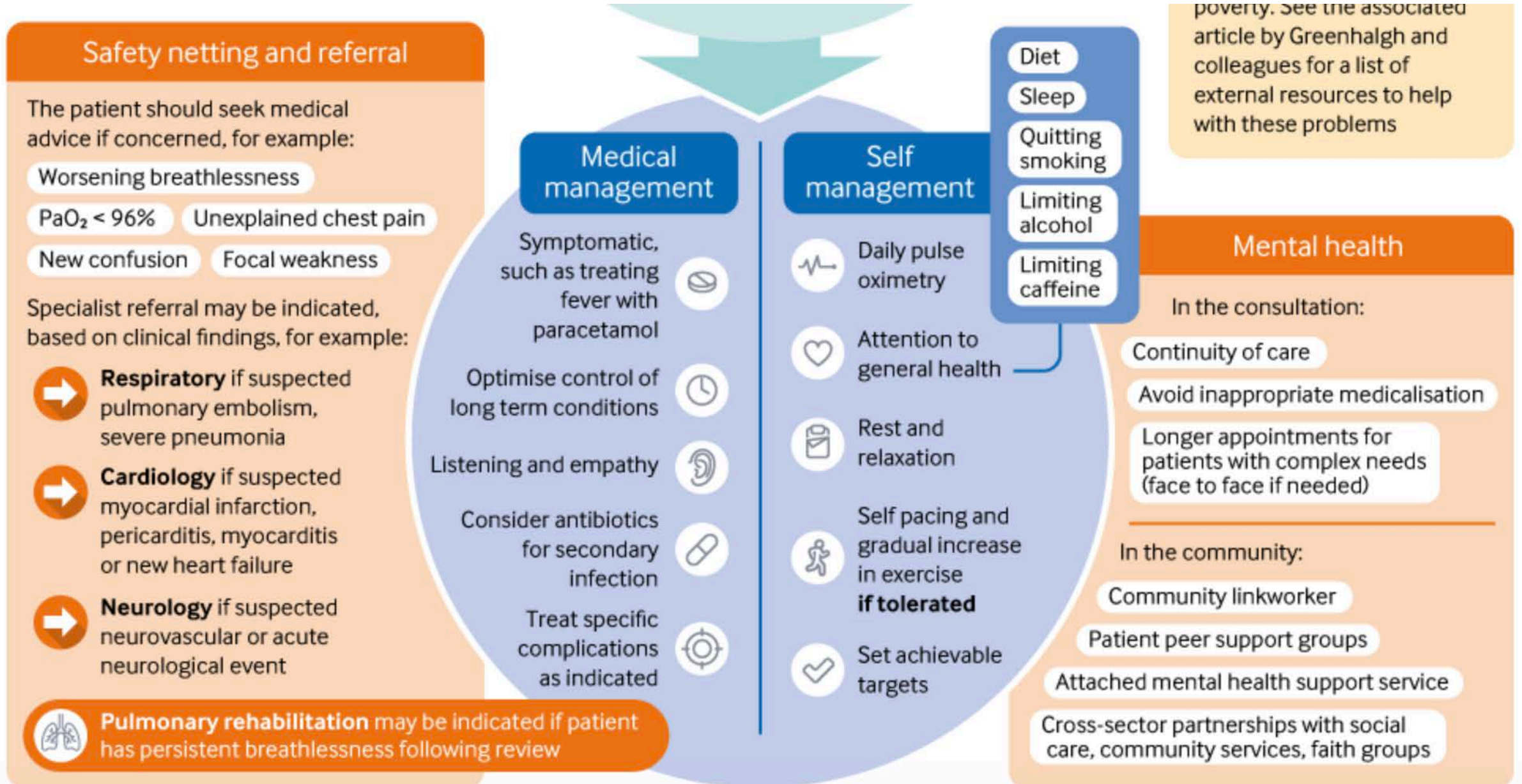
- Multiple biologic mechanisms and hard-to-define clinical outcomes that wax and wane will make drug development challenging
- Limited industry engagement remains a major barrier

UK Guidelines

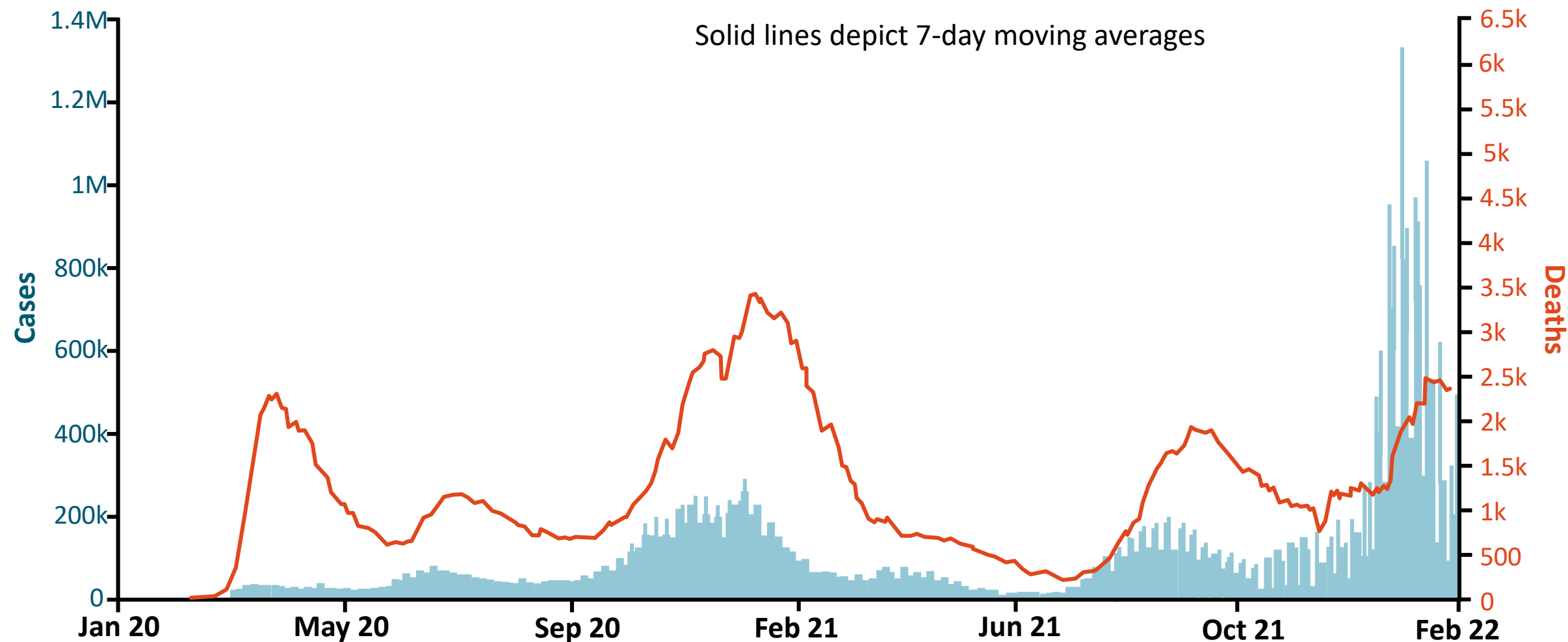
Post-acute covid-19 appears to be a multi-system disease, sometimes occurring after a relatively mild acute illness. Clinical management requires a whole-patient perspective. This graphic summarises the assessment and initial management of patients with delayed recovery from an episode of covid-19 that was managed in the community or in a standard hospital ward.



UK Guidelines



CDC: COVID-19 Reported Cases and Mortality



UCSF OPTIMAL Approach to Diagnostics

- Pulmonary Function Tests
 - I like to include 6MWT
- If DLCO is low, consider CT chest
- Also consider TTE
- Labs:
 - CBC diff, ESR/CRP, Thyroid, +/- CPK

