

Long COVID symptom diary:

Development of a pro instrument to support drug development and regulatory submissions in Europe

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Background

.A targeted literature search was conducted to assess the availability of Long COVID symptom diaries. In consultation with the EMA, one was needed to

support outcome evaluation for inclusion as a secondary endpoint in a clinical trial of a product’s efficacy in Long-COVID.

The objective of this review was to identify and potentially re-purpose an existing symptom diary for a trial start for 2022.

Methods

A search of both PubMed and ePROVIDE was conducted in January 2021 covering a period of approximately 1 year from the onset of the SARS-CoV-2 pandemic in the US. PubMed is a search engine accessing primarily the MEDLINE database of references and is maintained by the US National Library of Medicine.

ePROVIDE is a proprietary commercially-available database that references over 5,600 validated and published Clinical Outcomes Assessments.

The following key words were used: LONG COVID-19, symptom diary, symptom instrument and searches were limited to the past two years.

Results

- Only 2 published Long COVID symptom diaries were identified.
- Subsequent applications for licensing submitted to both copyright holders were denied for various reasons; therefore, a new instrument needed to be rapidly developed.
- The only publicly available instrument for COVID was the CDC’s acute COVID symptom questionnaire. We therefore conceptually extended and supplemented that instrument with additional symptoms of Long COVID as published in peer-reviewed epidemiological cohort studies.
- Thematic qualitative analyses were utilized to develop the new content for Long COVID symptoms and response scales were amended to better fit the disease.
- Results from the literature review were combined and compared against a recently published qualitative interview study with patients recovering from COVID-19 (Rofail et al, 2021) to evaluate conceptual overlap among diaries and patient-reported concepts.

Figure 1 – Daily Symptom Severity

	For items 1–20: “What was the severity of your [insert symptom] at its worst over the last 24 hours?”	0 = Not at All 1 = A little bit 2 = Moderate 3 = Severe 4 = Extremely Severe	Over the last 24 hours, has your symptom been present all of the (3), more than half the time (2); less than half the time (1)?
1.	Chest pain or tightness	0 1 2 3 4	
2.	Problems with memory or concentration (brain fog)	0 1 2 3 4	
3.	Shortness of breath (difficulty breathing)	0 1 2 3 4	
4.	Cough	0 1 2 3 4	
5.	Low energy or tiredness (fatigue)	0 1 2 3 4	
6.	Muscle or body aches and pain	0 1 2 3 4	
7.	Difficulty Sleeping (insomnia)	0 1 2 3 4	
8.	Dizziness	0 1 2 3 4	
9.	Feeling hot or feverish	0 1 2 3 4	
10.	Nausea (feeling sick)	0 1 2 3 4	
11.	Depression	0 1 2 3 4	
12.	Pins and needles	0 1 2 3 4	
13.	Loss of smell	0 1 2 3 4	
14.	Loss of Taste	0 1 2 3 4	
15.	Anxiety	0 1 2 3 4	
16.	Earache	0 1 2 3 4	
17.	Headache	0 1 2 3 4	
18.	Sore throat	0 1 2 3 4	
19.	Rashes	0 1 2 3 4	
20.	Diarrhoea	0 1 2 3 4	

Figure 2 – Sleep and ADL impact

ASK DAILY

• How many hours did you sleep in the past 24 hours? _____ Hours

• How tired were you in the past 24 hours, whilst being awake, on a scale from 0-10 (0 not at all – 10 Extremely tired)? _____

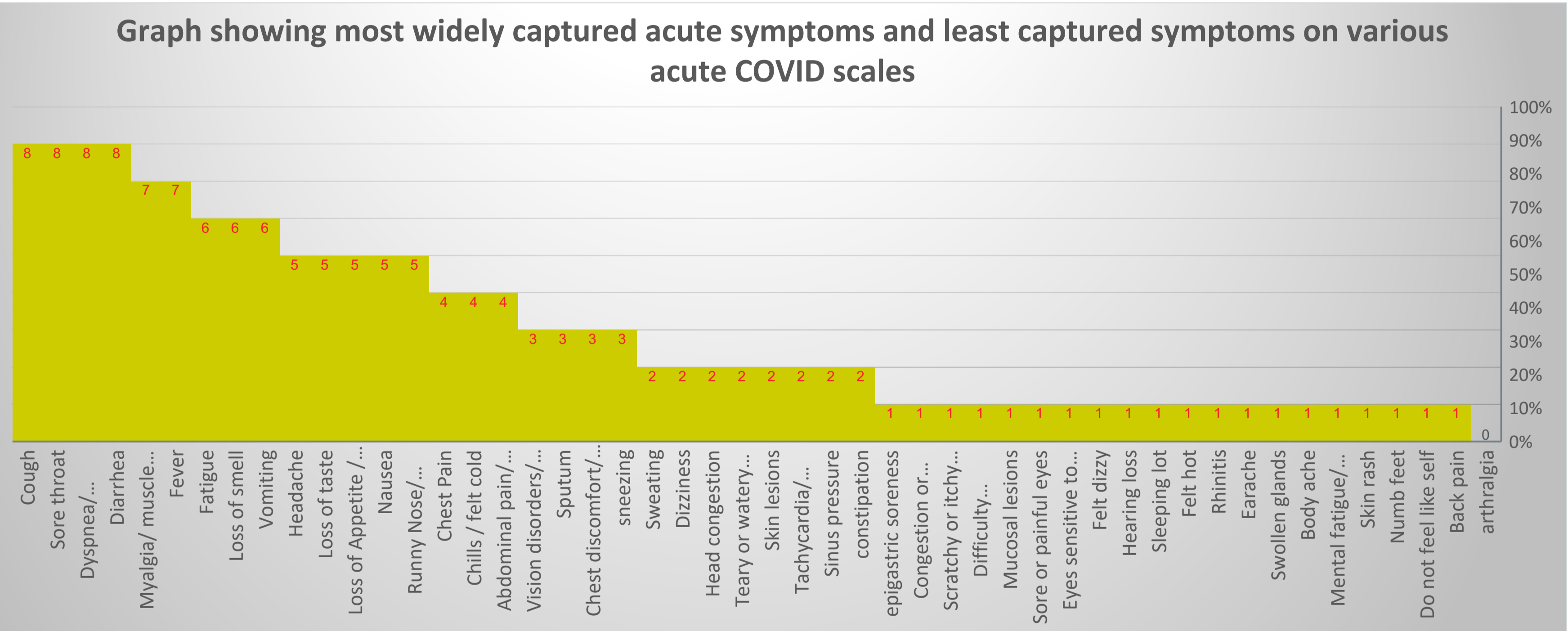
• How would you rate the quality of your sleep in the past 24 hours on a scale from 0-10 (0 Extremely bad – Extremely good)? _____

• Have you seen your doctor yesterday? YES NO
If yes?
How do you feel today?
Same as yesterday Better than yesterday Worse than yesterday

• Were your daily symptoms influenced by the activity?
No they remained the same Yes they improved Yes they worsened

➤ In bold are the items of the acute COVID diary these were supplemented with findings of prevalence of symptoms in other studies from our own systematic review in 2021 for ACUTE Covid Diaries below. Items such as runny nose or long time fever were not reported in Long Covid and were hence eliminated and replaced with long term effects such as depressive feelings, problem with concentration and brain fog.

Original Draft available in 2021	Original Copyright holder	Final Validated Term
Long COVID Rehabilitation Scale (3)	Manoj Sivan at University of Leeds	C19-Yorkshire Rehabilitation Scale (C19-YRS)
Symptom Burden Questionnaire for Long COVID (SBQ-LC) (4)	Sarah Hughes at University of Birmingham	SBQ-LC



Conclusions

- The literature review, thematic analyses and pragmatic extension of the CDC’s acute COVID symptomatology instrument resulted in the rapid design of a novel Long COVID symptomology patient diary.
- Initial results of efficacy from the trial are expected in 2024, including results for the novel patient diary of a pragmatic size of 20 symptoms per day plus 5 questions regarding sleep and impact on ADL
- In the emergence of unmet need, COA researchers may need to work creatively to repurpose existing instruments for use in clinical trials of emerging infectious diseases, particularly in the setting of a pandemic.
- Such methods are acceptable for secondary endpoints in phase II, which can then be used to further validate the symptom diary.

REFERENCES

1) Rofail D, McGale N, Podolanczuk A, Rams A, Przydzial K, Sivapalasingam S, Mastey V, Marquis P. The patient experience of COVID-19: A qualitative investigation with symptomatic outpatients. medRxiv. 2021 Jan

2) CDC’s COVID-19 Symptoms of Coronavirus web page available at https://www.cdc.gov/coronavirus/2019-ncov/symptomtesting/symptoms.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fabout%2Fsymptoms.html.

3) Creating a gold standard of care for long COVID | University of Leeds <https://www.leeds.ac.uk/news-health/news/article/4871/creating-a-gold-standard-of-care-for-long-covid>

4) Symptom Burden Questionnaire - University of Birmingham <https://www.birmingham.ac.uk/research/applied-health/research/symptom-burden-questionnaire/index.aspx>

