A targeted literature review to compare COVID-19 symptom diaries and patient-reported concepts

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OBJECTIVE: The aim was to identify relevant patient reported outcome (PRO) instruments used to screen for patients with symptoms of COVID-19 and measure their treatment outcomes in clinical and epidemiological studies.

METHODS: A literature search was conducted to identify PRO symptom instruments developed to screen patients and/or monitor treatment outcomes of COVID-19. The searches were conducted in early May 2021 using ePROVIDE, PubMed Medline, and grey literature search using a generic search engine. The following key words were used: COVID-19, symptom diary, symptom instrument and results were limited to the past two years. 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, MAD-ID 2021) to evaluate conceptual overlap among diaries and patient-reported concepts.

RESULTS: Seven acute COVID-19 diaries and one post COVID-19 symptom/functioning scale were identified from the targeted literature search. Symptoms present across all diaries and reported in the qualitative study included: cough, diarrhea, dyspnea/difficulty breathing, sore throat, myalgia/muscle pain, fever, loss of smell, fatigue, vomiting, headache, loss of taste, loss of appetite/anorexia, nausea, runny nose/stuffy nose. Somewhat frequently reported symptoms captured by at least three diaries and the qualitative study included: abdominal/stomach pain, chills/feeling cold, chest pain, chest discomfort/pressure/tightness, sneezing, sputum, vision disorders/conjunctivitis, constipation, dizziness, epigastric soreness, head congestion, sinus pressure, skin lesions, sweating, tachycardia/heart palpitations and teary or watery eyes. Symptoms that were only reported in the qualitative study included: body ache, back pain, earache, mental fatigue/sleepiness, skin rash, swollen glands, and not feeling like oneself.
CONCLUSION: There are a number of common symptoms similarities across the diaries that were frequently reported in qualitative research. However, there were several discrepancies across diaries for included and excluded symptom concepts. More research is needed to identify symptoms of COVID-19 that matter most to patients.

Table 1: Total number of questionnaires used for COVID-19 SYMP

Article Title	Items and response scale	Recall period	Domains and Subdomains	Description of questionnaire	Citation
Symptom Diary–Based Analysis of Disease Course among Patients with Mild Coronavirus Disease, Germany, 2020	21 items Numeric rating scale 0-10	24-hour	5 Domains • Neurological • Gastrointestinal • Lower Respiratory • Upper Respiratory • Dermatological symptoms	It is an online questionnaire participant were asked for the date when their first COVID-19 symptoms occurred. Where participants were asked to fill symptoms on daily basis. For every day, patient must choose from dropdown menu weather that symptom is present or absent.	Wiegele PN, Kabar I, Kerschke L, Froemmel C, Hüsing-Kabar A, Schmidt H, Vorona E, Vollenberg R, Tepasse PR. Symptom Diary–Based Analysis of Disease Course among Patients with Mild Coronavirus Disease, Germany, 2020. Emerging infectious diseases. 2021 May;27(5):1353.
Rapid COVID-19 Screening Based on Self-Reported Symptoms: Psychometric Assessment and Validation of the EPICOVID19 Short Diagnostic Scale	11 items Dichotomous scale	unknown	4 Domains • Respiratory problems • Chest pain • Loss of taste and smell • Tachycardia (palpitations)	EPICOVID is a self-reported questionnaire where only symptomatic COVID patients where included in the study. For the validation of their tool they have calculated the total score and validated with the help of molecular clinical diagnosis following 4 steps in their study.	Bastiani L, Fortunato L, Pieroni S, Bianchi F, Adorni F, Prinelli F, Giacomelli A, Pagani G, Maggi S, Trevisan C, Noale M. Rapid COVID-19 Screening Based on Self-Reported Symptoms: Psychometric Assessment and Validation of the EPICOVID19 Short Diagnostic Scale. Journal of Medical Internet Research. 2021 Jan 6;23(1):e23897.
Assessing COVID-19-Related Symptoms in Outpatient Adult and Adolescent Subjects in Clinical Trials of Drugs and Biological Products for COVID-19 Prevention or Treatment	14 items Verbal descriptors, Visual Analogue scales and 0–10 numeric rating scales.	12 or 24 hours	Not applicable	FDA issued this guidance to provide sponsors and investigators with considerations for approaches on how common COVID-19-related symptoms can be measured and analyzed in clinical trials evaluating drugs or biological products for the prevention or treatment of COVID19 in outpatient adult and adolescent subjects. This guidance does not address considerations for clinical trial design other than those pertaining to the measurement and analysis of COVID-19-related symptoms among outpatients.	Collins SH, Price D, Johnson LL. The Role of FDA CDER Statisticians in Response Efforts to the COVID-19 Pandemic. Statistics in Biopharmaceutical Research. 2020 Dec 23:1-2.
Self-Assessment Questionnaire for Efficient and Safe Evaluation of Patients with Mild COVID-19	23 items Linear scale- scores from 0 to 10 and Faces Pain Rating Scale	24-hours	Not applicable	It is a self-assessment questionnaire to evaluate the condition of patients with mild COVID-19, and information is shared with experienced healthcare authorities and providers. Patients were asked to rate their worst symptoms on daily basis, and further doctor will decide if the health of patient is showing improvement or deterioration based on the changes in scores.	Jeong H, Lee J, Kim J, Choen S, Sohn KM, Kim YS, Kiem S. Self-Assessment Questionnaire for Efficient and Safe Evaluation of Patients with Mild COVID-19. Infection & chemotherapy. 2020 Jun;52(2):212.
Using eHealth to Support COVID-19 Education, Self-Assessment, and Symptom Monitoring in the Netherlands: Observational Study	Sever symptoms yes/no 6 mild symptoms yes/no Numeric Rating Scale (NRS) (0 to 10)	24-hours	Not applicable	The study demonstrated the successful implementation and use of an app with COVID-19 education, self-assessment, and a 7-day symptom diary. Data was link to COVID-19 screening results from the hospital's microbiology laboratory. This data could be used to support policy makers and health care providers to get valuable insights in the regional distribution of infection load and health care consumption.	Timmers T, Janssen L, Stohr J, Murk JL, Berrevoets MA. Using eHealth to support COVID-19 education, self-assessment, and symptom monitoring in the Netherlands: observational study. JMIR mHealth and uHealth. 2020;8(6):e19822.
Epidemiological Observations on the Association Between Anosmia and COVID-19 Infection: Analysis of Data from a Self-Assessment Web Application	9 items Dichotomous scale	24-hours	Not applicable	It is a self-assessment and participatory surveillance web application for coronavirus disease (COVID-19), which was launched in France in March 2020. This study suggests that anosmia may be highly associated with COVID-19 and its severity. Despite of improper medical assessment and virological confirmation, self-checking instrument could be a relevant tool to monitor outbreak COVID new trends.	Denis F, Galmiche S, Dinh A, Fontanet A, Scherpereel A, Benezit F, Lescure FX. Epidemiological Observations on the Association Between Anosmia and COVID-19 Infection: Analysis of Data From a Self-Assessment Web Application. Journal of medical Internet research. 2020;22(6):e19855.
Post-COVID scales					
Post-COVID-19 Functional Status (PCFS) scale"	6 items Ordinal scales and The post-VTE functional status (PVFS) scale	Unknown	4 domains • COVID symptoms • Psychosocial • Social roles • Daily activities (ADL)	Post-COVID-19 Functional Status (PCFS) scale is developed to identify massive COVID survivors who are suffering from slow/incomplete recovery, would help in directing to use medical resources and standardize research efforts. This scale can also measure the disease outcomes such as mortality.	Klok FA, Boon GJ, Barco S, Endres M, Geelhoed JM, Knauss S, Rezek SA, Spruit MA, Vehreschild J, Siegerink B. The Post-COVID-19 Functional Status scale: a tool to measure functional status over time after COVID-19. European Respiratory Journal. 2020 Jul 1;56(1).

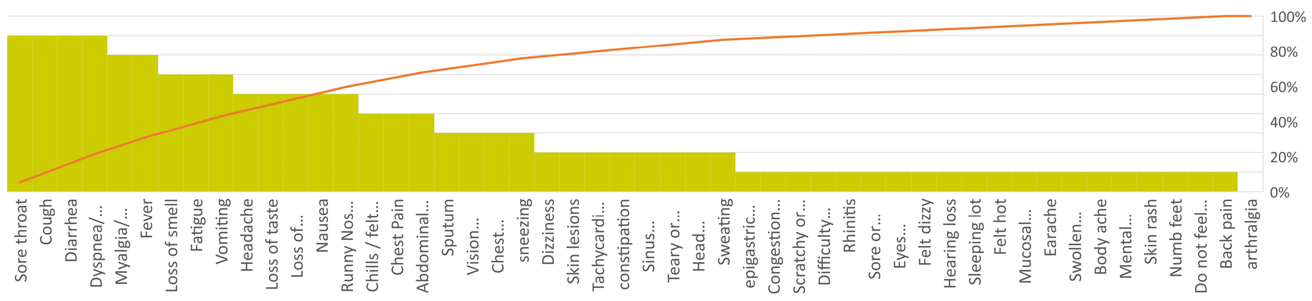
Table 2: Other measures that may be of interest for measuring specific COVID-19 Symptoms.

FLU-PRO Diary	32 Items Patient Global Rating of Flu Severity scale. Patient Global Assessment of Interference In Daily Activities scale. Patient Global Assessment of Physical Health scale. Return to "usual" health and activities scale.	24-hours	7 domains: • Nose • Throat • Eyes • Chest/Respiratory • Gastrointestinal • Body/Systemic. Additional two changes in taste or smell	FLU-PRO was designed to quantify symptom severity in influenza and influenza-like illness. A modification has been made to include two additional items to assess olfactory disturbances to align with COVID-19 symptom experience.	Han A, Poon JL, Powers JH, Leidy NK, Yu R, Memoli MJ. Using the Influenza Patient-reported Outcome (FLU-PRO) diary to evaluate symptoms of influenza viral infection in a healthy human challenge model. BMC infectious diseases. 2018 Dec;18(1):1-9.

Table 3: Item-level comparison from identified symptom diaries and recent qualitative study

Signs/symptoms	Rofail qualitative research study	Symptom Diary–Based Analysis of Disease Course among Patients with Mild Coronavirus Disease	Rapid COVID-19 Screening Based on Self-Reported Symptoms	Assessing COVID-19-Related Symptoms in Outpatient Adult and Adolescent Subjects …	Self-Assessment Questionnaire for Efficient and Safe Evaluation of Patients with Mild COVID-19	Using eHealth to Support COVID-19 Education, Self-Assessment, and Symptom Monitoring in the Netherlands:	Epidemiological Observations on the Association Between Anosmia and COVID-19 Infection	FLU-PRO Diary
Cough	✓	✓	✓	✓	✓	✓	✓	✓
Diarrhea	✓	✓	✓	✓	✓	✓	✓	✓
Dyspnea/ difficulty breathing	✓	✓	✓	✓	✓	✓	✓	✓
Sore throat	✓	✓	✓	✓	✓	✓	✓	✓
Myalgia/ muscle pain	✓	✓	✓	✓	✓		✓	✓
Fever	✓	✓	✓	✓	✓	✓	✓	
Loss of smell	✓	✓	✓	✓	✓		✓	
Fatigue	✓	✓		✓	✓		✓	✓
Vomiting	✓	✓	✓	✓	✓			✓
Headache		✓	✓	✓	✓			✓
Loss of taste	✓	✓	✓	✓	✓			
Loss of Appetite / anorexia	✓	✓			✓		✓	✓
Nausea		✓	✓	✓	✓			✓
Runny Nose/ stuffy nose	✓			✓	✓	✓		✓
Abdominal pain/ stomach pain	✓	✓			✓			✓
Chills / felt cold	✓			✓	✓			✓
Chest Pain	✓		✓		✓			✓
Chest discomfort/ pressure/ tightness	✓				✓			✓
sneezing	✓					✓		✓
Sputum	✓				✓			✓
Vision disorders/ conjunctivitis	✓	✓	✓					
constipation	✓				✓			
Dizziness	✓	✓						

Graph showing most widely captured symptoms and least captured symptoms on various scales



Citations

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 1.

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