Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Outcomes assessed in therapeutic randomized controlled trials in hospitalized patients with COVID-19: is the meta Core Outcome Set (meta-COS) adopted?

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To the editor

We have recently reported that outcomes evaluated in interventional randomized controlled trials (RCTs) for coronavirus disease 2019 (COVID-19) vary significantly [1]. This complicates the interpretation of results, their synthesis in meta-analyses (MAs), and the development of solid treatment recommendations [2,3].

To homogenize RCT outcomes, Core Outcome Sets (COSs) have previously been developed for many diseases. A COS is a minimum set of outcomes to be measured in all trials in a specific healthcare area [4]. A research collaboration that focused on COS methodology throughout the past decade is the Core Outcome Measures in Effectiveness Trials (COMET) Initiative. Following a distinct methodology, the COS development comprises: (a) a systematic review to identify outcomes measured in previous trials, (b) qualitative studies to identify outcomes considered important by patients and caregivers, (c) Delphi surveys distributed to patients, care-givers, and other stakeholders, aiming to prioritize the outcomes, and (d) consensus meetings involving patients, caregivers, and other stakeholders to finalize the COS [4].

From February to March 2020, four COSs for trials in patients with COVID-19 were registered in the COMET database and subsequently published. As each of these sets had different scopes, the COMET initiative sought to define a meta-COS covering the most crucial outcome variables across the COS. The overlapping outcomes all authors of the COS agreed upon were mortality and respiratory support, and the meta-COS was published in its final version on 15th April 2020 (https://www.comet-initiative.org/assets/downloads/COVID-19%20meta%20COS_Table%201_15th%20March%202021.pdf).

In early COVID-19 RCTs (January to April 2020), the uptake of the meta-COS was 49% [1]. In the present review, we investigated the uptake of the meta-COS in the scientific community by reviewing the protocols for ongoing or planned RCTs registered on clinicaltrials.gov between January and August 2021. We searched the database on 2nd September 2021 and selected interventional trials, excluding phase I and II trials.

We identified 839 studies which were screened independently for eligibility by three authors. Of these studies, 137 (16%) were eligible for this review. Altogether, 702 studies were excluded: 104 due to being diagnostic/not interventional, 103 due to targeting outpatients, one due to targeting children, and 494 due to not targeting COVID-19 (160 not targeting COVID-19 at all, 212 prevention studies, 28 studies on COVID-19 complications, 94 studies on post/long-COVID-19).

Of the eligible 137 studies, 98 (72%) report on the full meta-COS (mortality and respiratory support), nine (7%) report only on mortality, and seven studies (5%) only on respiratory support. Twenty-three (17%) studies report neither mortality nor respiratory support. Of the 98 studies reporting both outcomes, 70 report respiratory support in a complete manner (i.e. all types of support ranging from oxygen by mask/nasal cannula to extracorporeal

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Table 1
The use of ordinal scales as measurement instruments and timepoints for measuring the meta-COS outcomes (mortality and respiratory support) in the included randomized controlled trials (RCTs) studying interventions for patients hospitalized with coronavirus disease 2019 (COVID-19)

The use of ordinal scales as measurement instruments in the included studies	
Ordinal scale	Number of studies that use the scale
5-point scale	1/137
6-point scale	4/137
7-point scale	11/137
8-point scale	28/137
9-point scale	3/137
10-point scale	3/137
11-point scale	1/137
An ordinal scale not further specified	6/137

Timepoints for measuring the meta-COS outcomes (mortality and respiratory support)		
	Timepoints for measuring mortality, *n*	Timepoints for measuring respiratory support, *n*
Day 0–6	14	19
Day 7–14	34	53
Day 15–28	69	61
Day 29–45	28	23
Day 60–100	25	10
Day 150–365	9	8
NA	1	2

membrane oxygenation) and 28 report only selected, often site-specific aspects of respiratory support.

Fifty-seven of the 137 eligible studies use an ordinal scale of clinical status to measure the outcomes, ranging from 5-point scales to 11-point scales (Table 1). Thirty-one studies refer specifically to one of the World Health Organization (WHO) scales, four studies use scales published by other societies, and 22 use a scale of unspecific origin.

Compared to earlier COVID-19 trials, considerably more studies report on the meta-COS outcomes in general. However, there is considerable variation regarding timepoints of outcomes measurement (range 0–365 days, Table 1) and the used measurement instruments. This can potentially jeopardize future attempts to perform MAs in a reasonable fashion, as both outcomes may vary significantly over time in lower respiratory tract infection, and because the often-used ordinal scales show some variation as well. As MAs are often the foundation for solid treatment recommendations, these issues will have impacts on clinical practice guidelines and, ultimately, patient outcomes.

The found heterogeneity probably originates in: (a) the quantity of research published for COVID-19, making it difficult for researchers to keep up with the latest recommendations, (b) the unawareness of the existence of COS/meta-COS, and (c) and the lack of validated instruments for outcome measurement. Mortality and respiratory support are vague terms if not explained further. Right now, only one of the COSs clearly defined mortality to be measured at discharge or day 60 [5]. This was also the COS that ultimately defined the latest ten-point ordinal score of disease progression [5].

We interpreted the recorded data on clinicaltrials.gov to be the full study protocol. This is probably the main limitation of our review, as it has been shown previously that not all protocol data are registered in this database. Furthermore, we did not incorporate RCTs registered on other platforms. While these studies are missing in our analyses, we still believe that we have captured a globally representative sample of studies.

To make it easier to perform MAs and systematic reviews for interventions in patients hospitalized with COVID-19 in the future, we strongly recommend using the suggested meta-COS in all planned RCTs. Given the results of our review, we believe that further recommendations are needed on specific timepoints for measuring the prioritized outcomes as well as appropriate, consensus-based measurement instruments.

Research ethics statement

The present work is a methodological systematic review accessing, processing and analysing data from the publicly accessible database clinicaltrials.gov. Hence, no patient data were processed. Patient consent and/or registration via human research ethics committees were, therefore, not relevant.

Transparency declaration

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