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A Minimal Common Outcome Measure Set for COVID-19 Clinical Research

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Abstract

Clinical research is vital to an effective response to an emerging infectious disease outbreak. However research efforts are often hastily organized and conducted using a variety of research tools, with the result that pooling data across studies is challenging.

In response to the needs of the rapidly evolving COVID-19 outbreak, the Clinical Characterization and Management Working Group of the World Health Organization R&D Blueprint program, leveraging international research collaborations through the International Forum for Acute Care Trialists (InFACT) and the International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC), developed a minimal common- outcome measure set for studies of COVID-19 infection. The set includes three elements – a measure of viral burden (qPCR or Ct), a measure of patient survival (mortality at hospital discharge or 60 days), and a measure of patient progression through the health care system, the WHO Clinical Progression Scale that reflects patient trajectory and resource use over the course of clinical illness

We urge investigators to include these key data elements in ongoing and future studies to expedite the pooling of data during this immediate threat, and to hone a tool for future needs.

Clinical research is vitally important to an effective public health response during an emerging infectious outbreak [1-3]. It enables early description of the nature, extent, epidemiology, and prognosis of the outbreak, and guides the selection of management strategies that benefit the largest number of patients.

But pandemic research is challenging because a new outbreak represents an unknown threat. Data must be accumulated rapidly to guide a response whose priorities are uncertain and whose geographic reach is unknown. This information informs patient management, but is also critical for resource planning to ensure benefit for the greatest number of people, and for public health measures to limit spread and protect those who are directly involved in the response.

Reliable management conclusions require reproducible and widely accepted metrics to describe the emerging threat – to define natural history, including infectivity and clinical course, to understand spread and consequences for the health care system, and to evaluate the impact of interventions that could modify the clinical course. Because these metrics are chosen rapidly, and defined and measured differently from one study to the next, data sharing across studies could be facilitated if investigators agree to collect data for a common outcome measure set.

The concept of a core outcomes set or COS has been championed by the Core Outcome Measures in Effectiveness Trials (COMET) initiative [4]. A core outcome set is defined as "an agreed standardised collection of outcomes that should be measured and reported for a specific area of health" [5]. It comprises a minimal set of outcomes that will be routinely recorded, whether or not it includes primary or secondary outcomes in a specific study, so that the results of clinical trials in a particular disease can be reliably synthesized and compared. Collecting data for a COS does not restrict the selection of primary or secondary outcome measures for a study. Rather it ensures that certain data elements that are deemed essential to the study of the disease of interest are routinely collected and available. The development of a COS presupposes prior experience with the disease, and so while the rationale is relevant to studies of a new disease, them methodology differs. In the unfolding research response to an emerging pandemic, where data are collected quickly, and coordination of activities is difficult, a common minimal outcomes set could be invaluable in understanding epidemiology, evaluating therapies, and guiding a public health response.

As part of a WHO-led international collaborative response to the COVID-19 outbreak, a working group on clinical characterization and management undertook the task of developing a common minimal outcome measure set for studies of the emerging outbreak. We describe a rapid consensus process used to create this COS drawing on input from researchers, clinicians, patients, funders, and policy-makers.

Development of the Common Minimal Outcomes Set The initiative was led by the Clinical Characterization and Management Working Group established by the World Health Organization

as a component of its R&D RoadMap process in the response to COVID-19. The members of this group comprised an international panel having expertise in clinical trials, epidemiology, virology, infectious diseases, critical care, and public health; it also included funders and policy makers.

The working group met by videoconference and at a face-to-face meeting in Geneva, February 11th and 12, 2020 to discuss multiple issues relevant to research into the clinical management of patients during the evolving outbreak. We agreed that a minimal but comprehensively collected outcome set could facilitate study design and data sharing, and that this set should include information on viral burden, clinical course, and survival measured at a more distant time point.

Our goal was that the final product should meet a minimum set of key criteria. Its variables should be simple, objective, and readily measured across a range of health care systems from low to high income countries. It should capture the full spectrum of illness, from asymptomatic viremia to complete recovery or death. Its variables should be readily obtained and rapidly recorded. It should measure patient benefit, but also viral burden; in addition, it should reflect demands on the healthcare system, since a healthcare response during a pandemic must consider not only individual patient benefit but the capacity of the system to provide maximal benefit to the population. Finally the outcomes selected should be acceptable to clinicians and researchers, and reliably reflect the key clinical features of the disease.

We aggregated data from all trials or cohort studies targeting patients with Covid-19 infection included in the) WHO International Clinical Trials Registry Platform (ICTRP; https://www.who.int/ictrp/search/en/; updated April 21, 2020) - to understand the spectrum of outcomes being collected. We further analyzed clinical characteristics as reported in published series describing the outbreak in China [6-8] and elsewhere [9,10], as well as data from the clinical data platform of the International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC; https://media.tghn.org/medialibrary/2020/04/ISARIC_Data_Platform_COVID-19_Report_8APR20.pdf)

We then developed a candidate set of key outcome measures that was disseminated by email (MailChimp®) to members of WHO expert panels and to members of clinical trials groups in critical care medicine (the International Forum for Acute Care Trialists – InFACT) and infectious diseases (ISARIC) to seek their input on the proposed model – its elements and their calibration. Responses were compiled and incorporated into a revised core outcome set. Differences were resolved by majority vote of members of the Clinical Characterization group.

Review of clinical research databases

As ofApril 21, 2020, there are 1135 planned or ongoing observational studies or clinical trials studying patients with COVID-19 infection in in the WHO International Clinical Trials Registry Platform (ICTRP; https://www.who.int/ictrp/search/en/). Most (792; 69.8%) of these were based in China, however 41 different countries had registered clinical studies. The interventions varied, and included antiviral agents, mesenchymal stem cells, a variety of immunomodulatory agents, corticosteroids, convalescent plasma, and traditional Chinese medicines. The majority of these studies used viral burden, mortality or length of hospitalization and progression or resolution of clinical symptoms as trial endpoints (Table 1); measures of lung function were the primary endpoint in 101 studies.

Response to Questionnaire

We received input from 67 individuals in response to the first mailing of the outcomes questionnaire. These people represented 43 different research or professional networks and 25 different countries. Fully 63 respondents indicated an ability to recruit patients to clinical trials of COVID-19 disease.

Our review of the extant literature, combined with input from the questionnaires, identified three core domains to be included in a minimal common outcome set: mortality, viral load, and clinical course (progression and recovery). We sought input on how each of these should be best measured.

Additional outcome measures that might be considered for a core outcomes set are listed in Table 2, reflecting the spectrum of variables reported, rather than recommending their incorporation , or the cutoffs that might be used

Mortality

Contemporary estimates place the mortality of COVID-19 infection at 1.4 to 5.7% [11,12]. All respondents agreed that mortality was important to include in a minimal outcome measures set, and 50/67 (74.6%) respondents agreed that hospital discharge was the appropriate time point for evaluation of mortality status. Twenty-three replies indicated a preference for one or more landmark time points for ascertainment of mortality status, ranging from 28 days to one year. Potential limitations of the use of hospital discharge as a mortality endpoint included that in low and middle income countries patients may leave hospital against medical advice when the prognosis is poor in order to avoid costs of hospitalization; that in a pandemic, need for care might exceed hospital resources with the result that patients would be managed at home; and that such an endpoint might miss hospital readmission and subsequent death. Moreover mortality

rates are dependent upon the availability of resources, and so may vary from one geographic area to another, particularly when need overwhelms available capacity [13].

Mortality is an intuitively sensible outcome for any disease that carries a significant attributable mortality risk. The magnitude of this risk for COVID-19 infection is currently unknown, but appears to be approximately 5% for infected patients [14] (https://coronavirus.jhu.edu/data/mortality; accessed April 24, 2020). Emerging clinical data suggest that acute sudden death from pulmonary embolism, rather than failure of resolution of organ dysfunction, may be responsible for death in some cases [15]. For this reason, we recommend that survival status be routinely collected in all studies, and that the time horizon for mortality ascertainment be sufficiently long to capture delayed deaths, ideally at hospital discharge or 60 days. . Such a time point may miss patients who are discharged home in anticipation that they will die at home, and patients who are discharged, only to return with progressive illness, although the latter cohort can be evaluated by recording mortality at the last hospital discharge for COVID-19 infection.

Viral Burden

The majority (49/67) of respondents agreed that a measure of viral burden was an appropriate core outcome; real-time PCR (qPCR) to quantify viral copies was considered to be the best measure, with Ct (the threshold cycle during PCR) an alternative. The respiratory tract was deemed the optimal site for obtaining specimens from nasopharyngeal swabs, throat swabs, sputum, and upper or lower respiratory secretions.

qPCR is currently the most reliable method for detection of the coronavirus responsible for COVID-19, although there are reports that radiographic evidence may be present in the face of negative viral qPCR [16]. qPCR quantifies viral transcripts in the selected sample relative to a standard control RNA, using the ratio of the number of amplification cycles needed to detect the virus. Thus an alternate measure of viral load is the amplification cycle – Ct – at which viral transcripts can be detected. Since COVID-19 is predominantly (at least initially) a respiratory pathogen, we recommend its assay in specimens obtained from the upper or lower respiratory tree, recognizing that the virus may also be present in the feces of infected patients [17]. Quantification of viral burden provides no insight into the clinical status of the patient, but does confirm the presence of the pathogen, and can be used to measure pathogen burden in response to treatment.

Non-mortal Clinical Outcomes

Adapted from a previously used measure [18], and a scale used in a Chinese trial of the efficacy of lopinavir and ritonavir in combination with interferon-alpha 2B [19], we modified an ordinal scale to measure clinical progression and recovery, based on location and supportive measures used within the health care system. Our modifications sought to capture the entire spectrum of clinical illness from an asymptomatic carrier state to death, and to provide greater discrimination at the more severe end of the spectrum. The scale ranged from 0 (virus-free) to 10 (dead), with increasing numbers reflecting severity of symptoms in ambulatory patients, hospitalized patients, and patients admitted to an intensive care unit (ICU) or high-dependency unit (HDU).

We sought input into the structure of the planned scale, and used these comments to revise the measure. In particular, respondents noted that it may be difficult to separate patients at the lower, less severe end of the scale, and conversely, that greater granularity might be provided at the upper, more severe end of the scale. Particular note was made of the limitations of the construct – it is largely untested, and it is unknown how gradations of the scale correlate with mortality risk. The scale is ordinal, rather than numeric, and likely should be analyzed using appropriate ordinal approaches – non-parametric tests or enumeration of transitions between classes on the scale – although the issue is controversial [20,21].

Data for the clinical response score would ideally be collected daily while the patient is being studied. Since the variables measure symptoms or location and support within the health care system, recording this daily value should be rapidly accomplished.

Respondents were asked about their perspectives on the scale as an aggregate outcome measure: "To what extent does the concept appeal to you as a simple generic measure of illness progression?". They expressed support for the use of the scale as a core outcome rating it as 7.5±1.3 (range 3 – 9) on a 9 point Likert scale where 1 was "Not at all" and 9, "Very much".

Additional outcome measures that might be considered for a core outcomes set are listed in **Table 2**, reflecting the spectrum of variables reported, rather than recommending their incorporation , or the cutoffs that might be used.

The final proposed minimal outcome set is presented in **Table 3**, and **Figure 1**.

Uses of the WHO Clinical Progression Scale

Drawing on work done by others in measuring the therapeutic response to viral infection [18], and further, using approaches generally accepted for measuring outcomes in neurology [22], rheumatology [23], and psychiatry [24], we have proposed a modified rating scale – the WHO Clinical Progression Scale (WHO-CPS) – that measures patient illness by tracking progress through the healthcare system. The WHO-CPS incorporates a number of explicit features that are advantageous for its use in in emerging infectious disease epidemic. It provides a measure of

illness severity across a range from 0 (not infected) to 10 (dead), using data elements that are rapidly obtainable from clinical records. Modeling in other disease states has shown that discrimination is greater when seven or more classes are used, particularly at the lower range of disease severity [25].

This spectrum – from the absence of infection to death - enables its use across a broad range of studies. Clinical and virological absence of infection is suggestive of a cure for patients initially infected, or a misdiagnosis for those included in a trial; equally it can be the entry criterion for patients in a vaccine trial. At the other end of the severity spectrum, the scale recognizes that mechanical ventilation provides support that is survivable, although that probability is impacted by both the severity of respiratory failure and the development of additional physiologic organ dysfunction.

Tracking progress through the healthcare system is potentially confounded by variability in the structure and capacity of those systems. Despite this variability, the health care system is where infected patients receive their care, and the burden of an emerging pandemic is felt both by the patient as acute illness and the health care system as strained resources. Systems with abundant or even excess capacity may care for patients in hospital or within the ICU, whereas systems in resource-limited settings must rely on improvisation using available services; this creates a potential bias for studies which report locale in the healthcare system as an outcome. We have tried to minimize this bias. First, we recognize that patients may be hospitalized for isolation, and so accommodate this in the outcome scale. Second, we do not require admission to an ICU, but rather focus on the support that is typically provided there, and so a patient who is ventilated outside the hospital would achieve a high score; intensive care is a process, rather than a geographic location.

The scale has challenges. At the lower end of the scale, the measures are subjective; differentiation between hospitalization for quarantine versus hospitalization for clinical support may be difficult. Quantification of subjective symptoms is similarly challenging. At the upper end of the scale, the use of life support measures is variable not only on the basis of patient baseline co-morbidities, but also on the basis of regional practice preferences. Although the scale has inherent face validity based on its elements, it must be tested and validated in independent data sets. A need for validation as a trial outcome does not preclude its utility as a measure of treatment intensity within clinical trials of COVID-19.

The scale is intentionally presented as a simple minimal data set, focusing on variables relevant to most or all of patients included in cohort studies or clinical trials. Special populations such as pregnant women are not included, but pregnancy outcomes would be important to monitor in women of child-bearing age.

There are a number of ways that the WHO-CPS might be used to identify a population for study, and to track the progress of COVID-19 patients within clinical trials. At the time of

trial randomization, the scale can serve to identify an appropriate cohort for study. Vaccine studies would recruit patients with a score of 0, and use as endpoints, any progression across the scale. Large studies of patients with mild disease could recruit patients with a score of 3 or less, and use progression to the need for hospitalization or ICU admission as a study endpoint. Similarly, studies of patients with severe disease could restrict recruitment to patients with a score of 5 or greater, and measure efficacy as either survival time or successful recovery to a lower score, for example a value of less than 4 indicating discharge from hospital.

The scale can be modeled in a number of different ways, including median values at a fixed time point, time to a defined state, aggregate values over time, or change from baseline.

Integration into Clinical Research

COVID-19 research is fluid – rapidly changing, globally collaborative, and critically dependent upon new and unproven models of data aggregation. We urge those who care for COVID-19 patients, and those who study the clinical characteristics of the illness, to contribute data, and to recruit patients to trials across a spectrum of platforms (Table 4).

In summary, we present a novel model of a minimal common outcome measures set for ongoing and future studies responding to this outbreak. Further testing and validation of the measure is needed, and this process may result in further modifications to its structure.

The WHO Clinical Progression Scale has been developed to facilitate data pooling across cohort studies and clinical trials, with the objective of expediting the exchange of knowledge to benefit infected patients and to inform optimal resource planning. To this end, and independent of the design and reporting of individual studies, we urge researchers to record these data elements, and to share them with the international community. Platforms and agreements for doing so are under development.

Table 1 Endpoints used in Clinical Studies Planned or Conducted during the COVID-19 Outbreak (N=1135 registered studies)

Domain	Number of Studies	Specific Metrics
Viral burden	148	qPCR
Mortality	118	
Duration of Hospital/ICU Stay	32	
Symptoms	45	Fever, vital signs, cough
Progression/Resolution	175	Multiple measures, scales
Lung injury/function	101	SpO2, Murray score, Oxygenation index
Other measures	117	
Imaging findings	76	CT Scan, chest xray, ECHO
Biomarkers	73	CRP, Cardiac enzymes, CRP, cytokines
Depression, anxiety, long term quality of life	63	
Co-infection, acute kidney injury, myocardial injury	15	

Table 2 Outcomes Considered Important for a Core Outcome Set

Domain	Outcome
Organ dysfunction	Murray score Sequential Organ Failure Assessment, Multiple Organ Dysfunction Score Acute coronary syndrome; arrhythmias Delirium
Biochemical parameters	C-Reactive protein, d-dimers, IL-6, ferritin, leukocyte counts
Radiologic findings	CT scan chest; chest xray
Secondary infection	Bacterial, viral
Duration of intervention	Hospital stay Ventilation Organ support or hospital-free days
Quality of Life	Longer term survival (3 – 12 months) EQ5D, a measure of generic health status Discharge venue
Pregnancy outcomes	Pre-term delivery, miscarriage Fetal status
Resource utilization	

Table 3 A Proposed Core Outcome Measure Set for Clinical Studies of COVID-19 Infection

Domain	Measure
Viral burden	COVID-19 semiquantitative viral RNA measured by qPCR cycle threshold (Ct) in nasopharyngeal or throat swab, sputum, or upper or lower respiratory tract secretions
Survival	All-cause mortality at hospital discharge or 60 days
Clinical progression	WHO Clinical Progression Scale, measured daily over course of study

Table 4 International Clinical Research Studies of COVID-19 Infection

Research Platform	Study Model	Access
Cohort studies of COVID-19 infection		
WHO Clinical Characterization Study	Abbreviated case report form	https://www.who.int/publications-detail/global-covid-19-clinical-platform-novel-coronavius-(-covid-19)-rapid-version
ISARIC Clinical Characterization Study	Abbreviated ISARIC case report form	ncov@isaric.org
Clinical Trials		
WHO SOLIDARITY trial	Global trial of COVID-19 therapeutics	https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments
REMAP-CAP	Platform trial of COVID-19 therapeutics in the most seriously ill patients	https://www.remapcap.org/

Figure Legend

Figure 1 The WHO Clinical Progression Scale

Notes.

1. If hospitalized for isolation only, record status as for ambulatory patient
2. If pO_2 not available, use SpO_2/FIO_2 ratio with a cutoff of 200 [26]

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