Core outcome set developers' response to COVID-19 (March 2021)

Background

Many clinical trials and systematic reviews are already underway, or will begin shortly, to strengthen the evidence base for the COVID-19 response. Core outcome sets (COS), showing the outcomes that should be measured and reported in these studies, will ensure that this evidence base will contain, as a minimum, the key information needed by decision makers about the effects of interventions. This briefing paper has been prepared by COMET to summarise work to date on COS for COVID-19 and the COMET team will try to respond to any queries you have about it. COMET will also facilitate contact with COS developers to help determine which COS may be most relevant to your particular research study. A summary of all this work is available in the COMET database - http://www.comet-initiative.org/Studies/Details/1538 and will be updated as further evidence becomes available.

(1) COS for studies for the prevention of COVID-19 transmission

COVID-19 has significant morbidity and mortality, and so recent attention and research has focussed on preventing the transmission of COVID-19. Evidence is accumulating to describe the effectiveness of various interventions (including public health measures and primary and secondary care practices), however, there are challenges with evidence synthesis due to inconsistent selection, measurement and reporting of outcomes. A 'core' COS has recently been developed for studies evaluating public health, primary and secondary care interventions to prevent COVID-19, identifying SARS-CoV-2 infection and intervention-specific harms as critical outcomes to measure in all COVID-19 prevention studies [1]. This work is being used to inform the development of supplementary specific 'modules' that may be required for key areas of relevance. One such 'module' is the prevention of COVID-19 transmission in care homes [2].

[1] http://www.comet-initiative.org/Studies/Details/1594
Lead(s): Paula R Williamson, University of Liverpool; Jane Blazeby, University of Bristol
Summary: This 'core' COS was published as a short report in the Cochrane COVID-19 Supplement (pages 15-18)
https://www.cochranelibrary.com/documents/20182/0/2020+Cochrane+COVID-19+Supplement+V2/3ada04e7-d95a-10c4-645c-15dbe7bba9f4
Work is now underway to identify how best to measure SARS-CoV-2 infection.

[2] http://www.comet-initiative.org/Studies/Details/1810
Lead: Kerry Hood, Cardiff University
Summary: The aim of this study is to build on the 'core' COS that includes a minimum set of outcomes relevant to all studies of COVID-19 disease prevention [1] and to develop a supplementary specific module for COVID-19 prevention in care homes.

(2) COS for studies of any intervention in hospitalised patients with confirmed or suspected COVID-19

Table 1 shows a 'meta-COS' resulting from four COS projects conducted in parallel, and agreed by the leads of the projects.

History: In February 2020, three COVID-19 COS projects were registered in the COMET database [3-5]. A fourth was registered in March [6], with the aim of engaging patients in the COS development process, and is therefore complementary to the existing initiatives. Each COS is slightly different in its scope or methods, including the range of stakeholders involved, and they are complementary to one another.

Earlier work by ISARIC sought to standardize outcome data collected by research networks conducting clinical and epidemiological research in preparation for and during epidemics and pandemics [7]. In addition, existing COS projects for specific interventions used in and after critical care may be relevant [8-11].

Teleconferences were convened with representatives of the four COVID-19 COS for studies of in hospital patients (Junhua Zhang, John Marshall, Ruijin Qiu, Allison Tong) and the COMET Initiative (Paula Williamson, Liz Gargon, Mike Clarke). These discussions will continue, in order to maintain awareness of work on this topic, determine what information to disseminate more widely, and promote the uptake of COS in relevant research.

The three completed COS [3-5] overlapped, and a 'meta-COS' for research in adult hospitalised patients (Table 1) was agreed by the leads of the COS development projects [3-5] during a teleconference on 2nd April 2020. The results of the fourth COS [6] also agreed with the meta-COS, and Table 1 has been updated accordingly.

Adverse events: Adverse events, relevant to the particular research question, should also be measured and reported.

Paediatric studies: During the COVID-19 pandemic, children have generally presented with mild disease. The rates of clinical infection, hospitalisation, need for respiratory support, and mortality, are low. Current and future clinical trials are focussed on adults with COVID-19 who are acutely or critically ill, and hospitalised or on intensive care. From a paediatric perspective it is reasonable to utilise the adult meta-COS for COVID-19 in studies of children, or those in which children are included with adults. As clinical trials are developed to evaluate vaccines and prophylactic medications, the studies may be more focussed on children and relevant efficacy and safety outcomes for this age group may need to be reconsidered.

Each of the COS include other core outcome domains for hospitalised patients, and also core outcome domains for those patients with asymptomatic or mild disease who are not hospitalised. These other outcomes deemed core but not in all COS are described in Table 2.

Table 1: The 'meta-COS' for research in COVID-19 hospitalised patients

Scope of the meta COS: Patients being treated in hospital for confirmed or suspected COVID-19				
Outcome domain	**WHO COS [3]**	**Jin et al [4]**	**Qiu et al [5]**	**Tong et al [6]**
Key stakeholder groups included; geographical location				
	Health professionals, funders, policymakers; International	Health professionals; China	Health professionals, patients, public; China	Health professionals, patients, public; International
Mortality	✓	✓	✓	✓
	Agreed*: All-cause mortality at hospital discharge Researchers should also consider 'time to death', clearly defined as appropriate for their research question.	Agreed*: All-cause mortality at hospital discharge Researchers should also consider 'time to death', clearly defined as appropriate for their research question.	Agreed*: All-cause mortality at hospital discharge Researchers should also consider 'time to death', clearly defined as appropriate for their research question.	Agreed*: All-cause mortality
Respiratory support	✓	✓	✓	✓
	Agreed*: Type of respiratory support, as appropriate to the research question: - oxygen by mask or nasal prongs; - oxygen by NIV or high flow; - intubation & mechanical ventilation; - ECMO.	Agreed*: Type of respiratory support, as appropriate to the research question: - oxygen by mask or nasal prongs; - oxygen by NIV or high flow; - intubation & mechanical ventilation; - ECMO.	Agreed*: Type of respiratory support, as appropriate to the research question: - oxygen by mask or nasal prongs; - oxygen by NIV or high flow; - intubation & mechanical ventilation; - ECMO.	Agreed*: Respiratory failure

* This table was agreed on the 2nd April 2020, and updated on the 15th April, by the following:

COS developers - John Marshall (WHO), Junhua Zhang (*Tianjin* University of Traditional Chinese Medicine), Ruijin Qiu (Beijing University of Chinese Medicine), Bronagh Blackwood (Queen's University Belfast), Ian Sinha (Alder Hey Children's Hospital), Allison Tong (University of Sydney)

COMET Management Group - Paula Williamson (University of Liverpool), Liz Gargon (University of Liverpool)

Table 2: Other outcomes deemed core but not in all COS

Scope of the meta COS: Patients being treated in hospital for confirmed or suspected COVID-19				
Outcome domain	**WHO COS [3]**	**Jin et al [4]**	**Qiu et al [5]**	**Tong et al [6]**
	Key stakeholder groups included; geographical location			
	Health professionals, funders, policymakers; International	Health professionals; China	Health professionals, patients, public; China	Health professionals, patients, public; International
Viral burden *- text describes additional information in each COS*		✓	✓	
	In a study of hospitalised patients with COVID-19 confirmed, the time to viral load negativity would not be a core outcome since molecular testing capacity would be limited and serial assay not possible in many situations.	Time to 2019-nCoV RR-PCR negativity	Time taken by SARS-CoV-2-RNA to become negative Proportion of patients negative for SARS-CoV-2 Declining speed of SARS-CoV-2 Viral load	
Respiratory rate *- text describes additional information in each COS*		✓	✓	
		Respiratory rate	Improvement in respiratory rate Time to achieve a normal respiratory rate	

Oxygen saturation *- text describes additional information in each COS*		✓	✓	
		Oxygen saturation	Blood oxygen saturation or prevalence of improvement	
Oxygen intake *- text describes additional information in each COS*			✓	
			Oxygen intake: -Duration of supplemental oxygenation -Frequency of requirement for supplemental oxygen -Prevalence of supplemental-oxygen requirement -Oxygen-intake method	
Mechanical ventilation *- text describes additional information in each COS*		✓	✓	
		PaO2/FiO2 Respiratory failure occurred and mechanical ventilation required Duration of mechanical ventilation	PaO2/FiO2 Mechanical ventilation: -Duration of mechanical ventilation -Frequency of requirement for mechanical ventilation -Prevalence of mechanical ventilation	
		✓	✓	

Pulmonary imaging *- text describes additional information in each COS*		Lesions progression within 24–48 h in pulmonary imaging	Inflammation absorption or time to recovery	
Length of hospital stay *- text describes additional information in each COS*		✓		
		Length of hospital stay		
Clinical symptom: fever *- text describes additional information in each COS*		✓	✓	
		Score of clinical symptoms: a total score of six common and important clinical symptoms, including fever, cough, fatigue, shortness of breath, diarrhea, and body pain, each of which can be scored as 0 (no), 1 (mild), 2 (moderate), or 3 (significant).	Prevalence of fever and clearance time of fever	
Clinical symptom: cough *- text describes additional*		✓		
		Score of clinical symptoms: a total score of six common and important clinical		

information in each COS		symptoms, including fever, cough, fatigue, shortness of breath, diarrhea, and body pain, each of which can be scored as 0 (no), 1 (mild), 2 (moderate), or 3 (significant).		

Clinical symptom: fatigue *- text describes additional information in each COS*		✓		
		Score of clinical symptoms: a total score of six common and important clinical symptoms, including fever, cough, fatigue, shortness of breath, diarrhea, and body pain, each of which can be scored as 0 (no), 1 (mild), 2 (moderate), or 3 (significant).		
		✓	✓	✓

Clinical symptom: shortness of breath *- text describes additional information in each COS*		Score of clinical symptoms: a total score of six common and important clinical symptoms, including fever, cough, fatigue, shortness of breath, diarrhea, and body pain, each of which can be scored as 0 (no), 1 (mild), 2 (moderate), or 3 (significant).	Dyspnea prevalence Prevalence of dyspnea clearance	Shortness of breath
Clinical symptom: diarrhea *- text describes additional information in each COS*		✓		
		Score of clinical symptoms: a total score of six common and important clinical symptoms, including fever, cough, fatigue, shortness of breath, diarrhea, and body pain, each of which can be scored as 0 (no), 1 (mild), 2 (moderate), or 3 (significant).		
Clinical symptom score *- text describes additional information in each COS*		✓	✓	
		Score of clinical symptoms: a total score of six common and important clinical symptoms, including fever, cough, fatigue, shortness of breath, diarrhea, and body pain, each of which can be	Clinical symptom score	

		scored as 0 (no), 1 (mild), 2 (moderate), or 3 (significant).		
Shock *- text describes additional information in each COS*		✓		
		Shock occurrence		
Organ failure (in addition to pulmonary) *- text describes additional information in each COS*		✓		✓
		Complicated with other organ failure		Multiorgan failure
Need for ICU treatment *- text describes additional information in each COS*		✓		
		ICU treatment required		
Recovery *- text describes additional information in each COS*			✓	✓
			Recovery time or recovery prevalence	
			✓	

Improvement *- text describes additional information in each COS*			Improvement from severe type to ordinary type	
Progression *- text describes additional information in each COS*	✓		✓	
	WHO Clinical Progression Scale, measured daily over course of study – relevant components for hospitalised patients: - oxygen by mask or nasal prongs; - oxygen by NIV or high flow; - intubation & mechanical ventilation, $pO_2/F10_2 \geq 150$ or $SpO_2/ F10_2 \geq 200$; - mechanical ventilation $pO_2/F10_2 < 150$ ($SpO_2/F10_2 < 200$) or vasopressors; - mechanical ventilation $pO_2/F10_2 < 150$ and vasopressors, dialysis, or ECMO		Prevalence and time of progressing to severe or critical types	
Inflammation *- text describes additional information in each COS*			✓	
			CRP level and time for CRP recovery	
Lymphocyte *- text describes additional*			✓	
			Lymphocyte count	

information in each COS				
Virus antibody *- text describes additional information in each COS*			✓	
			Virus antibody level	
Arterial blood-gas analysis *- text describes additional information in each COS*			✓	
			Arterial blood-gas analysis	
Pneumonia *- text describes additional information in each COS*			✓	
			Pneumonia severity index	

COS for COVID-19 studies

[3] http://www.comet-initiative.org/Studies/Details/1528
Lead: John Marshall, University of Toronto, Canada on behalf of the WHO Working Group on the Clinical Characteristics of COVID-19 infection
Summary: WHO has published a master protocol for COVID-19 studies, which recommends the outcomes to be measured in each of these. The WHO Working Group undertook a consensus exercise to agree a COS and the report is now
published: https://doi.org/10.1016/S1473-3099(20)30483-7

[4] http://www.comet-initiative.org/Studies/Details/1523
Lead: Junhua Zhang, Evidence-Based Medicine Center, Tianjin University of Traditional Chinese Medicine, Tianjin, China
Summary: This COS is published
- https://www.sciencedirect.com/science/article/pii/S2095809920300424?via%3Dihub
A Case Report Form for this COS has been drafted. Please contact Janneke van't Hooft, janneke@stanford.edu, to obtain a copy.

[5] http://www.comet-initiative.org/Studies/Details/1507
Lead: Ruijin Qiu, Dongzhimen Hospital, Beijing University of Chinese Medicine, China
Summary: The COS is
published: https://www.frontiersin.org/articles/10.3389/fphar.2020.00781/full.

[6] http://www.comet-initiative.org/Studies/Details/1548
Lead: Allison Tong, University of Sydney, Australia
Summary: This COS is now
published: https://journals.lww.com/ccmjournal/Fulltext/2020/11000/Core_Outcomes_Set_for_Trials_in_People_With.10.aspx.
The study has a particular focus on patients, family and community members. You can visit the website for more information about this study: https://www.covid-19-cos.org.

[7] http://www.comet-initiative.org/Studies/Details/617
Lead: Calum Semple, University of Liverpool, UK on behalf of ISARIC
Summary: This work was done in 2014 with the aim to change how research is carried out during and between epidemics. Results of the work completed are available via the link. It informed the development of the WHO-ISARIC COVID-19 Clinical Platform (CCP) study case report form, which is available from Calum Semple, M.G.Semple@liverpool.ac.uk, prior to its publication on the WHO website.

Intervention-specific COS that may also be relevant for research in hospitalised patients with confirmed or suspected COVID-19

[8] http://www.comet-initiative.org/Studies/Details/292
Lead: Bronagh Blackwood, Queen's University Belfast, UK
Summary: This is a COS for trials of interventions intended to modify the duration of ventilation for patients being treated in an Intensive Care Unit.

[9] http://www.comet-initiative.org/Studies/Details/288
Lead: Bronwen Connolly, Queen's University Belfast, UK
Summary: This is an ongoing COS for trials of physical rehabilitation in critically ill patients, within intensive care units (ICU) and following their discharge from ICU and hospital. Please contact Bronwen Connolly for more information and preliminary results, bronwen.connolly@nhs.net.

Systematic review of outcomes measured in COVID-19 studies

[10] http://www.comet-initiative.org/Studies/Details/1745
Lead: Jørgen Vestbo, University of Manchester; Manchester University NHS Foundation Trust, UK
Summary: This systematic review describes the outcomes evaluated in RCTs on the management of COVID-19, that were registered with ClinicalTrials.gov, by 5 May 2020, and the instruments used to measure these outcomes. This systematic review is now published: https://www.mdpi.com/2075-1729/10/12/350

(3) COS for studies of any intervention in all settings (excluding prevention and post-recovery)

[6] http://www.comet-initiative.org/Studies/Details/1548
Lead: Allison Tong, University of Sydney, Australia
Summary: This COS is now published: https://journals.lww.com/ccmjournal/Fulltext/2020/11000/Core_Outcomes_Set_for_Trials_in_People_With.10.aspx.
The study has a particular focus on patients, family and community members. You can visit the website for more information about this study: https://www.covid-19-cos.org.

(4) COS for studies of any intervention post-discharge

[11] http://www.comet-initiative.org/Studies/Details/1019
Lead: Dale Needham, Johns Hopkins University, US
Summary: This is a published COS for all clinical research studies evaluating acute respiratory failure survivors after hospital discharge. This COS is appropriate for both observational and intervention studies that want to evaluate post-discharge outcomes.

Intervention-specific COS that may also be relevant for post-discharge studies

[9] http://www.comet-initiative.org/Studies/Details/288
Lead: Bronwen Connolly, Queen's University Belfast, UK

Summary: This is an ongoing COS for trials of physical rehabilitation in critically ill patients, within intensive care units (ICU) and following their discharge from ICU and hospital.

[12] http://www.comet-initiative.org/Studies/Details/786
Lead: M Major, European School of Physiotherapy, Amsterdam University of Applied Sciences, Amsterdam, The Netherlands
Summary: This is a COS for trials of physical therapy in the post-hospital rehabilitation of people who have survived critical illness.