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Development of an international standard set of outcomes measures for clinical use in patients with COVID-19: a report of the International Consortium for Health Outcomes Measurement (ICHOM) COVID-19 working group

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ABSTRACT

OBJECTIVES: The COVID-19 pandemic has resulted in widespread morbidity and mortality with the consequences expected to be felt for many years. Significant variation exists in the care even of similar patients with COVID-19, including treatment practices within and between institutions. Outcome measures vary among clinical trials on the same therapies. Understanding which therapies are of most value is not possible unless consensus can be reached on which outcomes are most important to measure. Furthermore, consensus on the most important outcomes may enable patients to monitor and track their care, and may help providers to improve the care they offer through quality improvement. To develop a standardised minimum set of outcomes for clinical care, the International Consortium for Health Outcomes Measurement (ICHOM) assembled a Working Group (WG) of 30 volunteers, including health professionals, patients and patient representatives.

DESIGN: A list of outcomes important to patients and professionals was generated from a systematic review of the published literature using the MEDLINE database, from review of outcomes being measured in ongoing clinical trials, from a survey distributed to patients and patient networks, and from previously published ICHOM standard sets in other disease areas. Using an online-modified Delphi process, the WG selected outcomes of greatest importance.

RESULTS: The outcomes considered by the WG to be most important were selected and categorised into five domains: 1) functional status and quality of life, 2) mental functioning, 3) social functioning, 4) clinical outcomes and 5) symptoms. The WG identified demographic and clinical variables for use as case-mix risk adjusters. These included baseline demographics, clinical factors, and treatment-related factors.

CONCLUSION: Implementation of these consensus recommendations could help institutions to monitor, compare and improve the quality and delivery of care to COVID-19 patients. Their consistent definition and collection could also broaden the implementation of more patient-centric clinical outcomes research.

Strengths & limitations of this study

- These consensus recommendations were generated by a large international working group consisting of all relevant stakeholders with an interest in outcomes of care for patients with COVID-19 e.g. patients, patient representatives, epidemiologists and clinicians.
- The diversity of the working group means that the recommendations included in the Standard Set are applicable to all settings and not just to European or North American practices.
- The methodology employed in the generation of the Standard Set meant that the focus was on outcomes of relevance to patients throughout and there is a deliberate emphasis on the use of patient-reported outcome measures in the Set.
- The virus was first discovered just over one year ago and so while we cannot yet be certain about the long-term outcomes of the disease, our work provides a starting point and there is scope for additional measures to be included as our understanding of the disease improves.
- ICHOM Standard Sets typically undergo an open review process prior to publication, in which the draft Set is distributed to patients and their representative groups for feedback however this was not possible for this project given the timeframe.

INTRODUCTION

SARS-CoV-2, the virus responsible for the COVID-19 pandemic, has infected nearly 120 million people resulted in the deaths of 2.5 million.[1]. Although knowledge about the acute illness has rapidly expanded, there is increasing evidence that COVID-19 may have long-term sequelae, with adverse health outcomes and poor health-related quality of life lasting far longer than the acute disease.[2]

Significant variation exists in the care even of similar patients with COVID-19, including treatment practices within and between institutions and countries.[3] Furthermore, outcome measures vary among the largest clinical trials on the same therapies.[4] Understanding which therapies are of most value will remain a challenge unless consensus can be reached on which outcomes are most important to patients to measure. While survival or indirect measures of patient's health status e.g. hospitalisation, the need for mechanical or non-invasive ventilation, as well as measures of resource utilisation, are frequently recorded in trials, direct measures of patient-reported outcomes are rarely measured and/or recorded.[5] Furthermore, the follow-up period of many trials is insufficient to detect some outcomes affecting patients long after hospital discharge. There is, therefore, a need for a standardised approach to outcome measurement in COVID-19 to inform clinical practice and real-world therapeutic research and to allow healthcare providers to monitor outcomes and to identify areas for quality improvement. A standard set of outcomes i.e. standardised outcomes, measurement tools and time points and risk adjustment factors for COVID-19,[6] could help benchmark best practice across institutions, facilitating improvements in care during future outbreaks and providing value in healthcare. It could also standardise approaches to global research for patient benefit.

To support the development of a standardised outcome set in COVID-19 for integration into clinical practice (and to inform clinical research), the International Consortium for Health Outcomes Measurement (ICHOM) convened an international multidisciplinary Working Group (WG) of experts and patient representatives. As a not-for-profit organisation, ICHOM has developed 38 standard sets of value-based outcomes for use in routine clinical practice in a range of medical conditions, such as coronary artery disease, stroke, and cancer.[7] Over 600 organisations have implemented ICHOM sets including 15 national registries. Standard sets are reviewed and updated annually by ICHOM.

The aim of this paper is to present a standardised minimum set of outcomes for COVID-19, including patient-reported outcomes, and case-mix variables, for comparisons across treatment modalities and institutions.

METHODS

Composition of the WG (including patient and public involvement)

ICHOM established a geographically diverse WG covering a broad range of specialties relevant to COVID-19. The WG consisted of 30 members, including clinicians, epidemiologists, research scientists, and patients and patient advocates/representatives from 13 countries across North and South America, Europe, Africa, the Middle East, South Asia and Australia. A project team (W.H.S., L.F., N.S., C.N., and K.B.) guided the efforts of the WG.

Development of the COVID-19 standard set

The WG convened during six teleconferences between July 2020 and September 2020, following a structured process similar to that of previous ICHOM WGs. The development of the standard set involved four phases, as illustrated in **Figure 1**: defining the scope of the project; prioritising and defining outcome domains; evaluating and selecting outcome measures that would be used to measure the outcome domains, including clinical data and patient-reported outcome measures (PROMs); and selecting and defining case-mix variables.

Figure 1. Timeline and data collection process

Identification of potential outcomes and case-mix variables

A systematic literature review was performed, following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[8] to identify potential outcome domains, patient-reported outcome measures, and case-mix variables. The search strategy is included in a supplement to this article.

Outcomes measured in published trials were extracted as well as outcomes being measured in ongoing trials, as identified by the WHO International Clinical Trials Registry Platform

(ICTRP) database.[9] Studies involving specific populations e.g. gender, ethnicity, as well as interventions targeting specific clinical outcomes e.g. resolution of fever, and laboratory-based outcome measures e.g. inflammatory markers were excluded as these were deemed by the WG to represent process measures rather than outcomes that in and of themselves mattered directly to patients.

In addition, an electronic survey was distributed at the start of the project to patients and patient representatives, through WG members' healthcare institutions, in line with their ethical guidelines. It was also distributed through the ICHOM newsletter and social media platforms, as well as to the European Heart Network and European Lung Foundation patient fora, in order to identify any additional outcomes that were of particular importance to patients. Finally, outcomes were extracted from previously published ICHOM standard sets that were of potential relevance to patients with COVID-19, for example patient-reported measures such as health-related quality of life, and clinical outcomes such as survival.

Consensus process

Following each teleconference, the project team circulated an electronic survey via the Qualtrics platform to the WG to gather feedback on each key decision. An online modified Delphi process was performed over three rounds for the selection of outcomes, following the RAND/University of California (Los Angeles) methodology[10] and based on a literature review,[11] to achieve consensus on which outcomes should be included. Inclusion in the standard set required that at least 80% of the WG voted an item as 'essential' (score 7-9 on a 9-point Likert scale) in each voting round. Outcomes were excluded if at least 80% of the WG voted an item as 'not recommended' (Score 1-3). Inconclusive domains were discussed and revised and put to a second round of voting. Outcomes that still had not garnered the required consensus for inclusion were put to a final third round vote.

Selection of patient-reported outcome measures and case-mix variables

After patient-reported outcomes (PROs) were chosen for inclusion in the standard set, corresponding measures were identified from the literature review of outcome domains, from tools previously used in other ICHOM standard sets for similar outcome domains, and by outcome experts in the WG. The original and validation studies of the instruments were examined in order to evaluate the psychometric quality, domain coverage, and feasibility of measurement and implementation. A breakout group consisting of academics and clinicians

with particular expertise in PRO measures convened to decide on the most appropriate measures to use.

A similar process, requiring 70% consensus from the WG for each item, was used to agree on which measures and case-mix variables should be recommended, as well as the time points for measuring each outcome. The results of each vote were reviewed by the WG at the subsequent teleconference. The criteria by which outcome domains were assessed for inclusion in the set were in accordance with the concepts of value-based healthcare as described by Porter.[12] Variables to be used as case-mix factors were assessed on: (i) relevance, (ii) independence, and (iii) measurement feasibility.

RESULTS

Scope

The outcomes and measures included in the COVID-19 standard set were defined for a target population of all adults over the age of 18 years with confirmed or highly suspected SARS-CoV-2 infection, as defined by WHO,[13] in primary, secondary or tertiary care settings. Children under the age of 18 years, as well as asymptomatic individuals with positive diagnostic tests, were excluded from the set. Different geographical and resource contexts were considered so that the standard set can be applied globally.

Outcomes

Out of 51 possible outcomes identified through the methodology as described, the WG selected 13 outcomes. The Reference Guide containing the definitions of all outcome domains included, as agreed by the WG, is published on the ICHOM website at www.ichom.org. The outcomes were categorised into five major groups: functional status and quality of life, clinical outcomes, mental functioning, social functioning, and symptoms. The set of outcomes and measures that were selected are detailed in **Table 1**.

Table 1: Summary of ICHOM C19 Standard Set of Outcomes

Outcome domain	Outcome sub-domains	Definition	Outcome measure
	Health-related quality of life	The perceived quality of an individual's daily life, assessing their health and wellbeing or lack thereof. A multi-dimensional concept that includes domains	PROMIS Global Health 1.2

Functional Status and Quality of Life		related to physical, mental, emotional and social functioning.	
	General physical functioning	An individual's ability to perform and/or participate in usual daily activities required to meet essential needs, fulfil usual roles, meet usual responsibilities, and maintain health and well-being.	PROMIS Global Health 1.2
	Vitality/energy	Capacity for work and leisure activities, and efficiency of accomplishment related to a feeling of weariness or tiredness.	FLU-PRO
Mental Functioning	Mental health symptoms and emotional wellbeing	An individual's emotional, psychological, and social wellbeing, including negative feelings and fears, as well as moderate to high levels of anxiety or psychological distress.	PROMIS Global Health 1.2
	Cognitive status	An individual's mental process of knowing, including awareness, perception, reasoning, and judgement.	Clinician Measures
Social Functioning	Feelings of loneliness and isolation	An individual's negative feelings related to the perception of being alone, disconnected or isolated.	PROMIS Social Isolation 4a
	Productivity	An individual's ability to carry out tasks, actions or participate in life situations.	PROMIS Global Health 1.2
Clinical Outcomes	Survival	Any cause of death in a patient with COVID-19.	Clinician Measures
	Meeting criteria for critical care admission	Patients whose medical needs cannot be met through standard ward-based care in an acute hospital, who would meet criteria for a high dependency or critical care unit. Patients who meet criteria for critical care admission may not in fact be admitted to critical care facilities for other reasons e.g. resource constraints, however should be included under this definition.	FLU-PRO
	Disease course severity	Mild: No need for hospitalisation Moderate: Hospitalisation without need for non-invasive or mechanical ventilation Severe: Received non-invasive and/or mechanical ventilation, or died; admission to HDU/ICU.	FLU-PRO

	Persisting organ damage	End-organ damage, including the central or peripheral nervous system, as a result of the COVID-19 infection that results in impaired function in the individual.	Clinician Measures
	Duration of hospitalisation	Number of nights spent in hospital being treated for symptoms related to COVID-19 (irrespective of whether COVID-19 was the reason for admission or if the patient developed COVID-19 while in hospital for another reason). This includes nights spent in hospital on subsequent hospital admissions during the follow-up period if the individual being readmitted was being treated for symptoms related to COVID-19 on that admission.	Clinician Measures
Symptoms	Symptoms	A subjective perception suggesting bodily impairment or malfunction, affecting the individual in a negative manner.	FLU-PRO

Each domain has a number of sub-domains to capture what is important to patients. The domain on clinical outcomes is to be assessed by clinicians. For each of the remaining domains, the WG identified an appropriate outcome measure to use. Considering the overlap among measures, the WG identified the following measures: PROMIS Global 1.2,[14] PROMIS Social Isolation 4a,[15] and FLU-PRO.[16]

Baseline characteristics and case-mix variables

In addition to the outcomes and outcome measures, the WG selected important baseline health characteristics to enable comparison between providers (**Table 2**). These baseline health characteristics include: demographic factors e.g. age, sex, race, ethnicity, level of education, clinical factors e.g. comorbidities and body mass index, and treatment-related factors e.g. need for ventilation, type of ventilation, duration of ventilation, duration of critical care admission.

Table 2: Summary of COVID-19 Standard Set Case Mix Variables

Case Mix Category	Variable	Measure	Timing	Data Source
Demographic Factors	Age	Year of birth.	Baseline	Patient record
	Sex	The patient's sex at birth.		
	Race	The biological race of the patient.		Patient record
	Ethnicity	The cultural ethnicity of the patient that they most closely identify with.		
	Level of Education	Highest level of education completed based on local standard definitions of education levels.		Patient record
Clinical Factors	Comorbidities	Prior and current diagnosis of disease or no presence of diagnosis.	Baseline	Patient/Clinician
	Body Mass Index	Height and weight are used to calculate BMI.		Clinician/Healthcare provider
Treatment-Related Factors	Need for ventilation	Did the patient require any ventilation during their hospital admission?	Baseline/ Updated monthly	Clinician/Healthcare provider
	Type of ventilation	What type of ventilation was administered?		
	Duration of ventilation	How long did the patient require ventilation?		

	Duration of critical care admission	How long was the patient's initial stay in critical care?		

Timeline for follow-up

The WG decided to track patient outcomes over a three-month period following the diagnosis or following criteria being met for highly suspected SARS-CoV-2 infection (**Figure 2)**. The outcome collection period can be extended for a further three months if the patient has not yet fully recovered. The WG delegated to the treating physicians the decision whether or not to extend data collection.

Figure 2: Follow Up Timeline and Data Collection Guidance:

DISCUSSION

In this project, an international WG developed a consensus set of the most important outcomes and outcome measures in COVID-19. By measuring and reporting the same outcomes, and adjusting for the case-mix variables, providers may be able to improve the quality of care offered to patients by learning from other institutions using the same standard set. The standard set could also benefit patients directly by allowing them to track their progress over time and seek care when appropriate. The standard set could also be considered for use in future respiratory viral pandemics.

This is the first global effort to develop a standardised minimum set of patient-centred outcomes in COVID-19 for use in clinical practice. While we cannot yet be certain about the long-term outcomes of the disease, this work provides a starting point and there is scope for additional measures to be included as our understanding of the disease improves. Other groups, including the WHO Clinical Characterisation and Management Working Group, have sought to define sets of standardised outcomes in COVID-19. This group published a core outcome set primarily for research use. As such, the outcomes recommended by that group have a clinical and technical focus and include many indirect measures of patient outcomes.[17] Our project focused on clinical practice, however could also be used to inform real-world clinical research by incorporating direct patient outcomes, both in evaluating the course of

illness and the effects of therapeutics. This standard set is patient-centric, utilising patient-reported outcomes as a key component of the set, and focusing primarily on outcomes that matter to patients e.g. an individual's ability to perform and/or participate in usual daily activities rather than on clinical metrics.

The predominant use of indirect outcomes in clinical trials of COVID-19 and in monitoring patients' progress with the disease runs the risk of missing issues of equal or more significance to those suffering with the illness – the disease burden of symptoms and impaired function that may persist long after the acute illness. While measuring survival and clinician-reported outcomes like hospitalisations is essential, it is equally important to measure PROs which add valuable information in those who do survive or who are discharged/remain in hospital. PROs can be used for long-term follow-up to assess the effect of the disease on a patient's quality of life, and to alert treating physicians to the development of complications.[18] There is an increasing body of literature suggesting benefit to patients of various drugs and vaccines against COVID-19. Validated, standardised PROs that comprehensively assess the symptom experience and patient function in COVID-19 across multiple domains could also facilitate meta-analyses and more precise estimates of treatment effects.

When considering which PRO measures to use in the set to measure overall quality of life, the WG felt that a generic as well as respiratory-specific measure would be most appropriate given the multi-system nature of COVID-19. One such universal measurement system is the Patient-Reported Outcomes Measurement Information System (PROMIS). The PROMIS Global Health (v 1.2) instrument, which is freely available, consists of ten global health items that represent five core PROMIS domains (physical function, pain, fatigue, emotional distress, social health).[19] The majority of PRO measures included in this set that are not symptoms are covered within the PROMIS Global Health questionnaire. One outcome that the WG felt important to include which is not adequately covered in this instrument is loneliness/isolation, which is captured via the short PROMIS Social Isolation 4a tool.

In addition to the PROs included in the set, there are a number of clinical outcomes that the WG felt it essential to include. The WG felt it important to ensure that the direct end-points used took account of the varying practices and resources that exist across the world. As such, the standard set is suitable for any primary, secondary or tertiary care setting in any country.

Of note, while many COVID-19 studies report ICU admission as an outcome, the WG took the view that because ICU provision and therefore the thresholds for admission to ICU vary so significantly depending on the context in which one practices, a more appropriate outcome measure would be 'meeting criteria for ICU admission' rather than admission itself i.e. explaining the reason for ICU admission and not solely the event. A similar approach was taken when considering the issue of non-invasive ventilation, the use of which varied from being widespread to prohibited based on factors such as availability of oxygen and concerns around staff infection. The WG considered that 'need for non-invasive ventilation,' while important, could not be classed as an outcome since the criteria determining 'need' varied too much. Instead, this is included as a case-mix factor so that it can be controlled for in analyses.

The presence or absence of symptoms was included in the set on the basis that persistence of symptoms e.g. as part of 'long COVID' may be modifiable and may represent a significant disease burden. The WG elected to utilise a symptom scale that has been developed and validated for comprehensively measuring symptoms in viral respiratory tract diseases – the FLU-PRO scale.[20] The scale was developed with patient input and its psychometric properties have been evaluated in a study with over 500 patients including those with influenza virus, respiratory syncytial virus, enterovirus, rhinovirus, adenovirus, and endemic coronaviruses and is being used currently in studies of COVID-19.[21,22,23] The scale was adapted during COVID-19, but in general, can be used to measure symptoms in any viral respiratory illness.

Consideration was given during WG discussions as to the appropriate timeline of data collection for patient symptoms. Although the FLU-PRO asks patients about symptoms in the previous 24 hours, the WG felt it infeasible to ask patients to rate their symptoms daily for the entire course of the three-month follow-up period. The WG's recommendation for practical use was to ask patients to complete the FLU-PRO fortnightly for the first month and then monthly thereafter.

An important aspect of this project is the standardisation of outcome measurement in COVID-19 across differing regions and healthcare systems. To achieve this, we have published a comprehensive reference guide summarising the set, outcome reporting tools, adjustment variables, and collection time points which is freely available at www.ichom.org.

Our approach does have some limitations. The standard set methodology is reliant on the composition of the WG. Although the WG recruited as diverse members as was possible given the time constraints, it is possible that a different WG would have come to different conclusions. Further, ICHOM standard sets typically undergo an open review process prior to publication in which the draft set is distributed to patients and their representative groups for feedback. Unfortunately, this was not possible within the timeframe of this project. The standard set was developed not as a static document but firmly with implementation in mind. As such, feasibility of measuring outcomes was a key concern during the outcome selection stage and therefore not all outcomes could be included in the set, despite being recognised by some members of the WG as important. Furthermore, feasibility of measuring and global adoption of the set were important determinants of the symptom scales and PROs that were selected by the WG.

The next stage of this project is to promote implementation of the standard set. Issues to overcome when considering implementing the COVID-19 set include: 1) budget 2) availability of clinical leaders to champion the set and promote its adoption given pressing clinical commitments to direct patient care in the ongoing pandemic 3) ensuring efficient and intuitive means of collecting and storing clinical data and 4) ensuring consistent and accurate collection of patient-reported outcomes. Implementation of the set involves several phases as described previously.[24]

CONCLUSION

We have developed a consensus recommendation for a standardised minimum set of outcomes that our working group considered most important to patients with COVID-19 comprising functional status and quality of life, clinical outcomes, mental functioning, social functioning, and symptoms. The use of patient-reported outcomes is central to the set, and makes the recommendations particularly relevant. This standard set is targeted for integration into routine clinical practice and research. Use of the set may enable institutions to monitor, compare, and most importantly improve the quality of the care they deliver for patients with COVID-19 as the pandemic unfolds.

Patient and Public Involvement: Patients and members of the public were involved at the centre of the work described in this manuscript. Patients were at the heart of the Working Group that produced the standard set, and patients (and their representatives at patient organisations) were directly asked which outcomes they felt were most important for them at the start of the project. Most of these outcomes are included in the final list of outcomes selected by the Working Group. The patient members of the Working Group contributed to the review and final drafts of this manuscript.

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Contributorship Statement: The project was conceived by the ICHOM Project Team – LF, NS, CN and WHS. The WG was chaired by KB who provided oversight to the Project Team throughout. All other authors listed in the manuscript met the authorship requirement criteria through consistent engagement in WG teleconferences, voting in the Delphi consensus process, and reviewing drafts of the manuscript.

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Figure 1. Timeline and data collection process

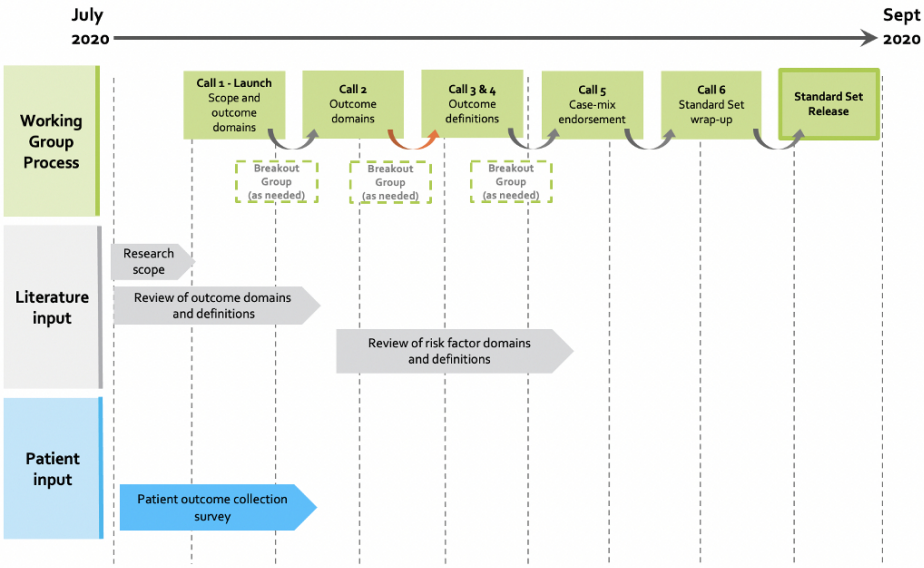

Figure 1

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Figure 2: Follow Up Timeline and Data Collection Guidance:

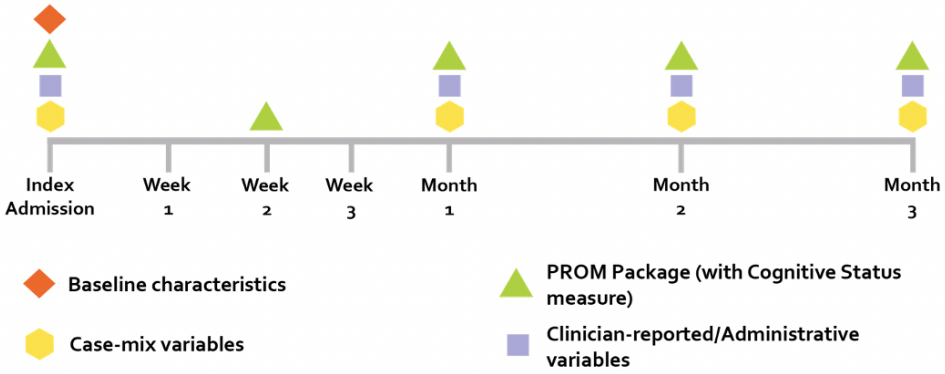

Figure 2

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Which outcomes are most important to measure in patients with COVID-19 and how and when should these be measured? Development of an international standard set of outcomes measures for clinical use in patients with COVID-19: a report of the International Consortium for Health Outcomes Measurement (ICHOM) COVID-19 working group

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Which outcomes are most important to measure in patients with COVID-19 and how and when should these be measured? Development of an international standard set of outcomes measures for clinical use in patients with COVID-19: a report of the International Consortium for Health Outcomes Measurement (ICHOM) COVID-19 working group

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ABSTRACT

OBJECTIVES: The COVID-19 pandemic has resulted in widespread morbidity and mortality with the consequences expected to be felt for many years. Significant variation exists in the care even of similar patients with COVID-19, including treatment practices within and between institutions. Outcome measures vary among clinical trials on the same therapies. Understanding which therapies are of most value is not possible unless consensus can be reached on which outcomes are most important to measure. Furthermore, consensus on the most important outcomes may enable patients to monitor and track their care, and may help providers to improve the care they offer through quality improvement. To develop a standardised minimum set of outcomes for clinical care, the International Consortium for Health Outcomes Measurement (ICHOM) assembled a Working Group (WG) of 28 volunteers, including health professionals, patients and patient representatives.

DESIGN: A list of outcomes important to patients and professionals was generated from a systematic review of the published literature using the MEDLINE database, from review of outcomes being measured in ongoing clinical trials, from a survey distributed to patients and patient networks, and from previously published ICHOM standard sets in other disease areas. Using an online-modified Delphi process, the WG selected outcomes of greatest importance.

RESULTS: The outcomes considered by the WG to be most important were selected and categorised into five domains: 1) functional status and quality of life, 2) mental functioning, 3) social functioning, 4) clinical outcomes and 5) symptoms. The WG identified demographic and clinical variables for use as case-mix risk adjusters. These included baseline demographics, clinical factors, and treatment-related factors.

CONCLUSION: Implementation of these consensus recommendations could help institutions to monitor, compare and improve the quality and delivery of care to COVID-19 patients. Their consistent definition and collection could also broaden the implementation of more patient-centric clinical outcomes research.

Strengths & limitations of this study

- These consensus recommendations were generated by a large international working group consisting of all relevant stakeholders with an interest in outcomes of care for patients with COVID-19.
- The diversity of the working group means that the recommendations included in the Standard Set are applicable to all settings.
- The methodology employed in the generation of the Standard Set meant that the focus was on outcomes of relevance to patients throughout and there is a deliberate emphasis on the use of patient-reported outcome measures in the Set.
- SARS-CoV-2 was discovered just over one year ago and so we cannot yet be certain about the long-term outcomes of the disease.
- ICHOM Standard Sets typically undergo an open review process prior to publication, in which the draft Set is distributed to patients and their representative groups for feedback however this was not possible for this project given the timeframe.

INTRODUCTION

SARS-CoV-2, the virus responsible for the COVID-19 pandemic, has infected over 200 million people and resulted in the deaths of over 4 million.[1]. Although knowledge about the acute illness has rapidly expanded, there is increasing evidence that COVID-19 may have long-term sequelae, with adverse health outcomes and poor health-related quality of life lasting far longer than the acute disease.[2]

Significant variation exists in the care even of similar patients with COVID-19, including treatment practices within and between institutions and countries.[3] Furthermore, outcome measures vary among the largest clinical trials on the same therapies.[4] Understanding which therapies are of most value will remain a challenge unless consensus can be reached on which outcomes are most important to patients to measure. While survival or indirect measures of patient's health status e.g. hospitalisation, the need for mechanical or non-invasive ventilation, as well as measures of resource utilisation, are frequently recorded in trials, direct measures of patient-reported outcomes are rarely measured and/or recorded.[5] Furthermore, the follow-up period of many trials is insufficient to detect some outcomes affecting patients long after hospital discharge. There is, therefore, a need for a standardised approach to outcome measurement in COVID-19 to inform clinical practice and real-world therapeutic research and to allow healthcare providers to monitor outcomes and to identify areas for quality improvement. A standard set of outcomes i.e. standardised outcomes, measurement tools and time points and risk adjustment factors for COVID-19,[6] could help benchmark best practice across institutions, facilitating improvements in care during future outbreaks and providing value in healthcare. It could also standardise approaches to global research for patient benefit.

To support the development of a standardised outcome set in COVID-19 for integration into clinical practice (and to inform clinical research), the International Consortium for Health Outcomes Measurement (ICHOM) convened an international multidisciplinary Working Group (WG) of experts and patient representatives. As a not-for-profit organisation, ICHOM has developed 38 standard sets of value-based outcomes for use in routine clinical practice in a range of medical conditions, such as coronary artery disease, stroke, and cancer.[7] Over 600 organisations have implemented ICHOM sets including 15 national registries. Standard sets are reviewed and updated annually by ICHOM.

The aim of this paper is to present a standardised minimum set of outcomes for COVID-19, focusing on the inclusion of patient-reported outcomes, and case-mix variables, for comparisons across treatment modalities and institutions.

METHODS

Composition of the WG (including patient and public involvement)

WG members were identified through several avenues. A rapid review was conducted by the project team in the project initiation phase to identify relevant patient organisations, measurement initiatives, professional bodies, and publications actively addressing questions relating to outcome measurement for COVID-19 with a particular focus on patient-centred outcomes. Relevant organisations were contacted and information about the role of WG members shared both directly as well as through social media channels. Open recruitment calls were then held inviting interested individuals to participate in the WG. A matrix of candidates was composed to facilitate the representation of diverse geographies, disciplines, types of expertise, and a balance of specialist interests e.g. infectious diseases, respiratory disease, mental health, primary care, intensive care. A shortlist was created that would represent different matrix cells, and ICHOM subsequently invited shortlisted individuals to participate. In addition, individuals or organisations were given the opportunity to recommend additional candidates for consideration by the ICHOM project team.

Development of the COVID-19 standard set

The WG convened during six teleconferences between July 2020 and September 2020, following a structured process similar to that of previous ICHOM WGs. The development of the standard set involved four phases, as illustrated in **Figure 1**: defining the scope of the project; prioritising outcome domains; defining outcome domains and evaluating and selecting outcome measures that would be used to measure these domains, including clinical data and patient-reported outcome measures (PROMs); and selecting and defining case-mix variables.

Figure 1. Timeline and data collection process

Identification of potential outcomes, outcome measures and case-mix variables

A systematic literature review of the MEDLINE database was performed, following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[8] to identify potential outcome domains, outcome measures, patient-reported outcome measures, and case-mix variables. The search strategy used for the MEDLINE search was:

(("COVID-19"[Title]) OR ("novel coronavirus"[Title])) AND ("Outcome"[Title])

Outcomes measured in published trials were extracted as well as outcomes being measured in ongoing trials, as identified by the WHO International Clinical Trials Registry Platform (ICTRP) database.[9] Studies involving specific populations, such as gender, ethnicity, as well as interventions targeting specific clinical outcomes e.g. resolution of fever, and laboratory-based outcome measures such as inflammatory markers were excluded as these were deemed by the WG to represent process measures rather than outcomes that in and of themselves mattered directly to patients. In addition to extracting the outcomes, the outcome measures used to measure these outcomes in the trials included in the literature review were also extracted. These outcome measures were discussed after the outcomes themselves had been selected.

In addition, an electronic survey was distributed at the start of the project to patients and patient representatives, through WG members' healthcare institutions, in line with their ethical guidelines (see **Supplementary File 1)**. It was also distributed through the ICHOM newsletter and social media platforms, as well as to the European Heart Network and European Lung Foundation patient fora, in order to identify any additional outcomes that were of particular importance to patients. Finally, outcomes were extracted from previously published ICHOM standard sets that were of potential relevance to patients with COVID-19, for example patient-reported measures such as health-related quality of life, and clinical outcomes such as survival.

Consensus process

WG teleconferences were held every two weeks. Following each teleconference, the project team circulated an electronic survey via the Qualtrics platform to the WG to gather feedback on each key decision. An online modified Delphi process was performed over three rounds for the selection of outcomes, following the RAND/University of California (Los Angeles) methodology[10] and based on a literature review,[11] to achieve consensus on which outcomes should be included. Inclusion in the standard set required that at least 80% of the WG voted an item as 'essential' (score 7-9 on a 9-point Likert scale) in each voting round. WG members were given one week to complete each survey. Outcomes were excluded if at least 80% of the WG voted an item as 'not recommended' (Score 1-3). Inconclusive domains were discussed and revised and put to a second round of voting. Outcomes that still had not garnered the required consensus for inclusion were put to a final third round vote. These three rounds were completed prior to considering the selection of outcome measures to capture the outcomes, which did not use the same Delphi methodology.

Selection of patient-reported outcome measures and case-mix variables

After patient-reported outcomes (PROs) were chosen for inclusion in the standard set, corresponding measures were identified from the literature review of outcome domains, from tools previously used in other ICHOM standard sets for similar outcome domains, and by outcome experts in the WG. The original and validation studies of the instruments were examined in order to evaluate the psychometric quality, domain coverage, and feasibility of measurement and implementation. A breakout group consisting of academics and clinicians with particular expertise in PRO measures convened to decide on the most appropriate measures to use.

A different consensus-gathering process, this time requiring 70% consensus from the WG for each item, was used to agree on which measures and case-mix variables should be recommended in line with the methodology used in all ICHOM standard sets for this part of the study, as well as the time points for measuring each outcome. The 70% consensus level is thought to be sufficient for the selection of outcome measures and case-mix variables whereas a more stringent threshold of 80% or more of the WG voting an outcome as 'essential to include' on the Likert scale is required in ICHOM methodology for the selection of the outcomes themselves. The results of each vote were reviewed by the WG at the subsequent teleconference. The criteria by which outcome domains were assessed for

inclusion in the set were in accordance with the concepts of value-based healthcare as described by Porter.[12] Variables to be used as case-mix factors were assessed on: (i) relevance, (ii) independence, and (iii) measurement feasibility.

RESULTS

Working Group

ICHOM established a geographically diverse WG covering a broad range of specialties relevant to COVID-19. The WG consisted of 28 members, including clinicians, epidemiologists, research scientists, and patients and patient advocates/representatives from 13 countries across North and South America, Europe, Africa, the Middle East, South Asia and Australia (**Table 1)**. A project team (W.H.S., L.F., N.S., C.N., and K.B.) guided the efforts of the WG.

Scope

The outcomes and measures included in the COVID-19 standard set were defined for a target population of all adults over the age of 18 years with confirmed or highly suspected SARS-CoV-2 infection, as defined by WHO,[13] in primary, secondary or tertiary care settings. Children under the age of 18 years, as well as asymptomatic individuals with positive diagnostic tests, were excluded from the set. Different geographical and resource contexts were considered so that the standard set can be applied globally.

Outcomes

86%, 89% and 82% of WG members participated in the first, second, and third rounds of the modified Delphi process respectively. Out of 64 possible outcomes (see **Supplementary File 2** for a list of the sources of preliminary outcomes) identified through the methodology as described, the WG selected 13 outcomes. There was significant overlap between the outcomes identified from the different sources, and during the WG teleconferences, decisions were taken to merge or rename outcomes. The Reference Guide containing the definitions of all outcome domains included, as agreed by the WG, is published on the ICHOM website at www.ichom.org. The outcomes were categorised into five major groups: functional status and quality of life, clinical outcomes, mental functioning, social functioning, and symptoms. The set of outcomes and measures that were selected are detailed in **Table 1**.

Table 1: Summary of ICHOM C19 Standard Set of Outcomes

Outcome domain	Outcome sub-domains	Definition	Outcome measure
Functional Status and Quality of Life	Health-related quality of life	The perceived quality of an individual's daily life, assessing their health and wellbeing or lack thereof. A multi-dimensional concept that includes domains related to physical, mental, emotional and social functioning.	PROMIS Global Health 1.2
	General physical functioning	An individual's ability to perform and/or participate in usual daily activities required to meet essential needs, fulfil usual roles, meet usual responsibilities, and maintain health and well-being.	PROMIS Global Health 1.2
	Vitality/energy	Capacity for work and leisure activities, and efficiency of accomplishment related to a feeling of weariness or tiredness.	FLU-PRO
Mental Functioning	Mental health symptoms and emotional wellbeing	An individual's emotional, psychological, and social wellbeing, including negative feelings and fears, as well as moderate to high levels of anxiety or psychological distress.	PROMIS Global Health 1.2
	Cognitive status	An individual's mental process of knowing, including awareness, perception, reasoning, and judgement.	Clinician Measures
Social Functioning	Feelings of loneliness and isolation	An individual's negative feelings related to the perception of being alone, disconnected or isolated.	PROMIS Social Isolation 4a
	Productivity	An individual's ability to carry out tasks, actions or participate in life situations.	PROMIS Global Health 1.2
	Survival	Any cause of death in a patient with COVID-19.	Clinician Measures
	Meeting criteria for critical care admission	Patients whose medical needs cannot be met through standard ward-based care in an acute hospital, who would meet criteria for a high dependency or critical care unit. Patients who meet criteria for critical care admission may not in fact be admitted to critical care facilities for other reasons e.g.	Clinician Measures

Clinical Outcomes		resource constraints, however should be included under this definition.	
	Disease course severity	Mild: No need for hospitalisation Moderate: Hospitalisation without need for non-invasive or mechanical ventilation Severe: Received non-invasive and/or mechanical ventilation, or died; admission to HDU/ICU.	Clinician Measures FLU-PRO
	Persisting organ damage	End-organ damage, including the central or peripheral nervous system, as a result of the COVID-19 infection that results in impaired function in the individual.	Clinician Measures
	Duration of hospitalisation	Number of nights spent in hospital being treated for symptoms related to COVID-19 (irrespective of whether COVID-19 was the reason for admission or if the patient developed COVID-19 while in hospital for another reason). This includes nights spent in hospital on subsequent hospital admissions during the follow-up period if the individual being readmitted was being treated for symptoms related to COVID-19 on that admission.	Clinician Measures
Symptoms	Symptoms	A subjective perception suggesting bodily impairment or malfunction, affecting the individual in a negative manner.	FLU-PRO

Each domain has a number of sub-domains to capture what is important to patients. The domain on clinical outcomes is to be assessed by clinicians. For each of the remaining domains, the WG identified an appropriate outcome measure to use. Considering the overlap among measures, the WG identified the following measures: PROMIS Global 1.2,[14] PROMIS Social Isolation 4a,[15] and FLU-PRO.[16]

Baseline characteristics and case-mix variables

In addition to the outcomes and outcome measures, the WG selected important baseline health characteristics to enable comparison between providers (**Table 2**). These baseline health characteristics include: demographic factors e.g. age, sex, race, ethnicity, level of education, clinical factors e.g. comorbidities and body mass index, and treatment-related factors e.g. need for ventilation, type of ventilation, duration of ventilation, duration of critical care admission.

Table 2: Summary of COVID-19 Standard Set Case Mix Variables

Case Mix Category	Variable	Measure	Timing	Data Source
Demographic Factors	Age	Year of birth.	Baseline	Patient record
	Sex	The patient's sex at birth.		
	Race	The biological race of the patient.		Patient record
	Ethnicity	The cultural ethnicity of the patient that they most closely identify with.		
	Level of Education	Highest level of education completed based on local standard definitions of education levels.		Patient record
Clinical Factors	Comorbidities	Prior and current diagnosis of disease or no presence of diagnosis.	Baseline	Patient/Clinician
	Body Mass Index	Height and weight are used to calculate BMI.		Clinician/Healthcare provider
Treatment-Related Factors	Need for ventilation	Did the patient require any ventilation during their hospital admission?	Baseline/ Updated monthly	Clinician/Healthcare provider
	Type of ventilation	What type of ventilation was administered?		
	Duration of ventilation	How long did the patient require		

		ventilation?		
	Duration of critical care admission	How long was the patient's initial stay in critical care?		

Timeline for follow-up

The WG decided to track patient outcomes over a three-month period following the diagnosis or following criteria being met for highly suspected SARS-CoV-2 infection (**Figure 2)**. The outcome collection period can be extended for a further three months if the patient has not yet fully recovered. The WG delegated to the treating physicians the decision whether or not to extend data collection.

Figure 2: Follow Up Timeline and Data Collection Guidance

DISCUSSION

In this project, an international WG developed a consensus set of the most important outcomes and outcome measures in COVID-19. By measuring and reporting the same outcomes, and adjusting for the case-mix variables, providers may be able to improve the quality of care offered to patients by learning from other institutions using the same standard set. The standard set could also benefit patients directly by allowing them to track their progress over time and seek care when appropriate through heightened awareness of symptoms that they may not necessarily realise are problems e.g. mental health symptoms, or waning productivity. The standard set could also be considered for use in future respiratory viral pandemics.

This is the first global effort to develop a standardised minimum set of patient-centred outcomes in COVID-19 for use in clinical practice. While we cannot yet be certain about the long-term outcomes of the disease, this work provides a starting point and there is scope for additional measures to be included as our understanding of the disease improves. Other groups, including the WHO Clinical Characterisation and Management Working Group, have sought to define sets of standardised outcomes in COVID-19. This group published a core outcome set primarily for research use. As such, the outcomes recommended by that group

have a clinical and technical focus and include many indirect measures of patient outcomes.[17] Our project focused on clinical practice, however could also be used to inform real-world clinical research by incorporating direct patient outcomes, both in evaluating the course of illness and the effects of therapeutics. This standard set is patient-centric, utilising patient-reported outcomes as a key component of the set, and focusing primarily on outcomes that matter to patients e.g. an individual's ability to perform and/or participate in usual daily activities rather than on clinical metrics.

The predominant use of indirect outcomes in clinical trials of COVID-19 and in monitoring patients' progress with the disease runs the risk of missing issues of equal or more significance to those suffering with the illness – the disease burden of symptoms and impaired function that may persist long after the acute illness. While measuring survival and clinician-reported outcomes like hospitalisations is essential, it is equally important to measure PROs which add valuable information in those who do survive or who are discharged/remain in hospital. PROs can be used for long-term follow-up to assess the effect of the disease on a patient's quality of life, and to alert treating physicians to the development of complications.[18] There is an increasing body of literature suggesting benefit to patients of various drugs and vaccines against COVID-19. Validated, standardised PROs that comprehensively assess the symptom experience and patient function in COVID-19 across multiple domains could also facilitate meta-analyses and more precise estimates of treatment effects.

When considering which PRO measures to use in the set to measure overall quality of life, the WG felt that a generic as well as respiratory-specific measure would be most appropriate given the multi-system nature of COVID-19. One such universal measurement system is the Patient-Reported Outcomes Measurement Information System (PROMIS). The PROMIS Global Health (v 1.2) instrument, which is freely available, consists of ten global health items that represent five core PROMIS domains (physical function, pain, fatigue, emotional distress, social health).[19] The majority of PRO measures included in this set that are not symptoms are covered within the PROMIS Global Health questionnaire. One outcome that the WG felt important to include which is not adequately covered in this instrument is loneliness/isolation, which is captured via the short PROMIS Social Isolation 4a tool.

In addition to the PROs included in the set, there are a number of clinical outcomes that the WG felt it essential to include. The WG felt it important to ensure that the direct end-points used took account of the varying practices and resources that exist across the world. As such, the standard set is suitable for any primary, secondary or tertiary care setting in any country. Of note, while many COVID-19 studies report ICU admission as an outcome, the WG took the view that because ICU provision and therefore the thresholds for admission to ICU vary so significantly depending on the context in which one practices, a more appropriate outcome measure would be 'meeting criteria for ICU admission' rather than admission itself i.e. explaining the reason for ICU admission and not solely the event. A similar approach was taken when considering the issue of non-invasive ventilation, the use of which varied from being widespread to prohibited based on factors such as availability of oxygen and concerns around staff infection. The WG considered that 'need for non-invasive ventilation,' while important, could not be classed as an outcome since the criteria determining 'need' varied too much. Instead, this is included as a case-mix factor so that it can be controlled for in analyses.

The presence or absence of symptoms was included in the set on the basis that persistence of symptoms e.g. as part of 'long COVID' may be modifiable and may represent a significant disease burden. The WG elected to utilise a symptom scale that has been developed and validated for comprehensively measuring symptoms in viral respiratory tract diseases – the FLU-PRO scale.[20] The scale was developed with patient input and its psychometric properties have been evaluated in a study with over 500 patients including those with influenza virus, respiratory syncytial virus, enterovirus, rhinovirus, adenovirus, and endemic coronaviruses and is being used currently in studies of COVID-19.[21,22,23] The scale was adapted during COVID-19, but in general, can be used to measure symptoms in any viral respiratory illness.

Consideration was given during WG discussions as to the appropriate timeline of data collection for patient symptoms. Although the FLU-PRO asks patients about symptoms in the previous 24 hours, the WG felt it infeasible to ask patients to rate their symptoms daily for the entire course of the three-month follow-up period. The WG's recommendation for practical use was to ask patients to complete the FLU-PRO fortnightly for the first month and then monthly thereafter, in line with the timeline for collection of other PRO measures as part of the 'PROM package' depicted in the timeline in **Figure 2.**

An important aspect of this project is the standardisation of outcome measurement in COVID-19 across differing regions and healthcare systems. To achieve this, we have published a comprehensive reference guide summarising the set, outcome reporting tools, adjustment variables, and collection time points which is freely available at www.ichom.org.

Our approach does have some limitations. The standard set methodology is reliant on the composition of the WG. Although the WG recruited as diverse members as was possible given the time constraints, it is possible that a different WG would have come to different conclusions. Our methodology is reliant on the continued involvement of WG members over several months, and although we did not experience significant attrition during the various stages of the consensus-gathering process, nevertheless there remains the potential for attrition bias to have affected the results of the rounds of voting. Further, ICHOM standard sets typically undergo an open review process prior to publication in which the draft set is distributed to patients and their representative groups for feedback. Unfortunately, this was not possible within the timeframe of this project. The standard set was developed not as a static document but firmly with implementation in mind. As such, feasibility of measuring outcomes was a key concern during the outcome selection stage and therefore not all outcomes could be included in the set, despite being recognised by some members of the WG as important. Furthermore, feasibility of measuring and global adoption of the set were important determinants of the symptom scales and PROs that were selected by the WG.

The next stage of this project is to promote implementation of the standard set. Issues to overcome when considering implementing the COVID-19 set include: 1) budget 2) availability of clinical leaders to champion the set and promote its adoption given pressing clinical commitments to direct patient care in the ongoing pandemic 3) ensuring efficient and intuitive means of collecting and storing clinical data and 4) ensuring consistent and accurate collection of patient-reported outcomes. Implementation of the set involves several phases as described previously.[24]

CONCLUSION

We have developed a consensus recommendation for a standardised minimum set of outcomes that our working group considered most important to patients with COVID-19 comprising functional status and quality of life, clinical outcomes, mental functioning, social

functioning, and symptoms. The use of patient-reported outcomes is central to the set, and makes the recommendations particularly relevant. This standard set is targeted for integration into routine clinical practice and research. Use of the set may enable institutions to monitor, compare, and most importantly improve the quality of the care they deliver for patients with COVID-19 as the pandemic unfolds.

Patient and Public Involvement: Patients and members of the public were involved at the centre of the work described in this manuscript. Patients were at the heart of the Working Group that produced the standard set, and patients (and their representatives at patient organisations) were directly asked which outcomes they felt were most important for them at the start of the project. Most of these outcomes are included in the final list of outcomes selected by the Working Group. The patient members of the Working Group contributed to the review and final drafts of this manuscript.

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Data Availability: Data are available upon reasonable request. These include complete survey results as well as results of the consensus-gathering processes described within the manuscript.

Transparency Declaration: WHS affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Contributorship Statement: The project was conceived by the ICHOM Project Team – LF, NS, CN and WHS. The WG was chaired by KB who provided oversight to the Project Team throughout. All other authors (FMB, PC, IKMD, MPF, MAF, LEKG, JJG, AK, AL, IILL, CL, AMD, NM, GANB, CWO, JHP, A-MR, MKS, TYPW, EKW, DCW, EZ) listed in the manuscript met the authorship requirement criteria through consistent engagement in WG teleconferences, voting in the Delphi consensus process, and reviewing drafts of the manuscript. The specific authorship requirements for ICHOM standard sets include participation in at least 50% of WG meetings, completion of at least 50% of the post-meeting surveys, and reviewing and providing feedback on drafts of the manuscript.

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Figure 1. Timeline and data collection process

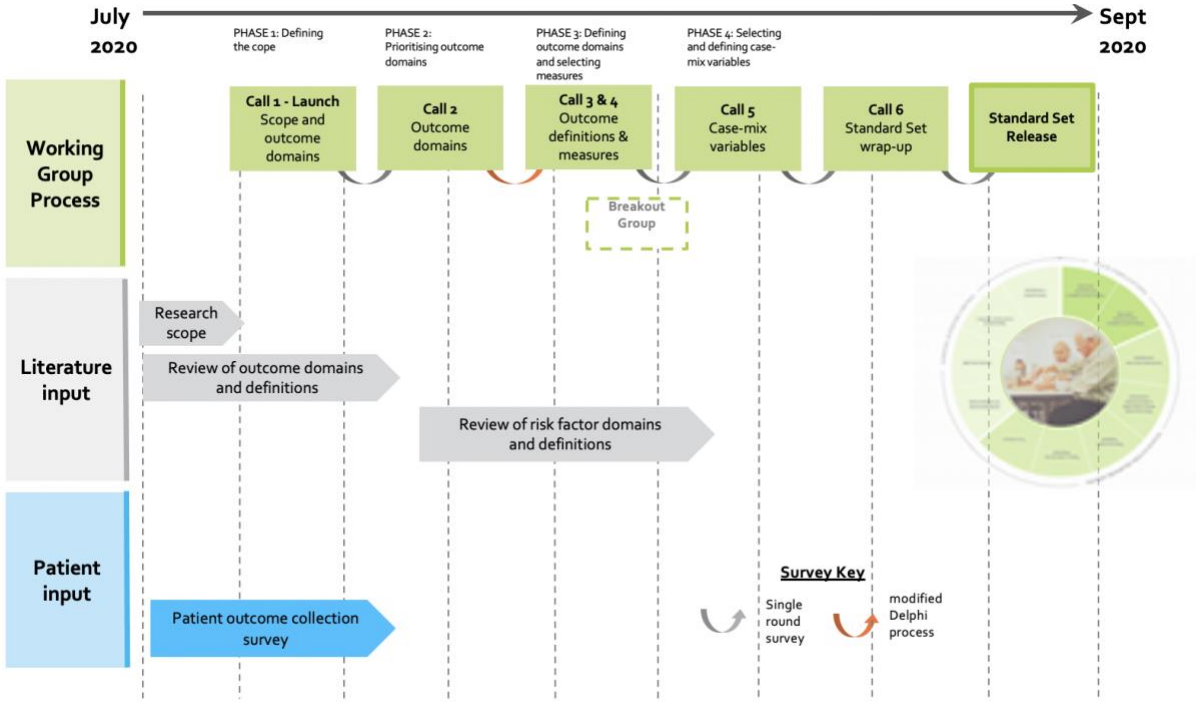
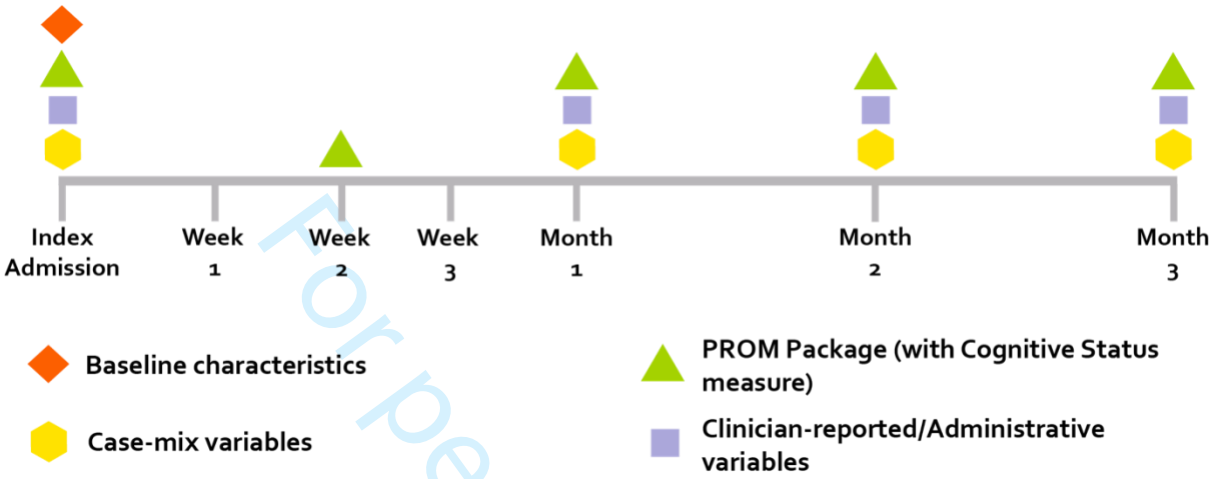


Figure 2: Follow Up Timeline and Data Collection Guidance:



Default Question Block

Dear Participant,

The International Consortium for Health Outcomes Measurement (ICHOM, www.ichom.org) is an independent not-for-profit organisation. We are launching a project which aims to create a measurement set to be used by clinicians to assess the health of patients who have had COVID-19 by focusing on the outcomes that patients feel are important.

To help us better understand, we are asking people who have had COVID-19 to complete the short survey below, asking what matters most to them.

It should take no longer than 5 minutes to complete and yet it can change the way healthcare professionals manage the care of patients recovering from COVID-19. Your feedback will be invaluable.

Please note that answering this survey is on a voluntary basis, your responses will remain anonymous and no IP or personal data are recorded.

As of today, are you aged 18 years of age or older?

- ○ Yes
- ○ No

Thank you for your interest in this project. Unfortunately, you must be 18 years of age or older in order to participate in this survey.

1. From this list below, please give feedback on how important the following health outcomes are to patients recovering from COVID-19. These outcomes are grouped into domains (highlighted in bold) which we would also like you to rate.

	1-3= Not important			4-6= Nice to have			7-9= Essential to have	
	1	2	3	4	5	6	7	8

	1-3= Not important 1	2	3	4-6= Nice to have 4	5	6	7-9= Essential to have 7	8
Physical Functioning	○	○	○	○	○	○	○	○
Pain as a chronic condition that affects day-to-day life	○	○	○	○	○	○	○	○
Presence of a chronic cough	○	○	○	○	○	○	○	○
Shortness of breath	○	○	○	○	○	○	○	○
Fatigue and vitality	○	○	○	○	○	○	○	○
Ability to exercise	○	○	○	○	○	○	○	○
Speech and communication	○	○	○	○	○	○	○	○
Health-related quality of life (ie an individual's perceived physical health over time)	○	○	○	○	○	○	○	○
Mental Functioning	○	○	○	○	○	○	○	○
Emotional wellbeing	○	○	○	○	○	○	○	○
Depression	○	○	○	○	○	○	○	○
Anxiety	○	○	○	○	○	○	○	○
Social Functioning	○	○	○	○	○	○	○	○
Feelings of loneliness and isolation	○	○	○	○	○	○	○	○
Feeling able to return to work	○	○	○	○	○	○	○	○
Productivity and how health issues impact daily activities in and out of work	○	○	○	○	○	○	○	○
Clinical Outcomes	○	○	○	○	○	○	○	○
Survival	○	○	○	○	○	○	○	○
Whether any admission to a hospital was required, the length of stay and any subsequent readmission	○	○	○	○	○	○	○	○
Required use of a ventilator	○	○	○	○	○	○	○	○
Required any surgical intervention	○	○	○	○	○	○	○	○

Do you feel that this list broadly captures all the important outcomes that matter most to patients recovering from COVID-19?

- ○ Yes
- ○ No

Which additional outcomes would you include? Please list these in the box below with a brief explanation of each.

Thank you for completing this survey. If you have any questions or would like further information on this work, please do not hesitate to contact us using the email address below. Please click the grey arrow on the right-hand side below to finish the survey and submit your answers.

Nick Sillett
n.sillett@ichom.org

Sources of the Preliminary Outcome List

1. **Outcomes identified from previously published ICHOM Standard Sets (18 outcomes):**
    1. Pain as a chronic condition that affects day-to-day life (Outcome used on multiple Standard Sets)
    2. Cough (used on Lung Cancer Standard Set)
    3. Fatigue and vitality (used on Lung Cancer Standard Set)
    4. Shortness of breath (used on Lung Cancer Standard Set)
    5. Ability to work (used on Atrial Fibrillation Standard Set)
    6. Exercise tolerance (used on Atrial Fibrillation Standard Set)
    7. Loneliness and Isolation (used on Older Person Standard Set)
    8. Speech and Communication (used on Cleft Lip and Palate Standard Set)
    9. Readmission (used on multiple Standard Sets)
    10. Social Functioning (used on multiple Standard Sets)
    11. Mental Functioning (used on multiple Standard Sets)
    12. Health-related quality of life (used on multiple Standard Sets)
    13. Survival (used on multiple Standard Sets)
    14. Productivity (used on multiple Standard Sets, but relates to ability to work)
    15. Emotional Wellbeing (used on multiple Standard Sets)
    16. Depression (used on multiple Standard Sets)
    17. Anxiety (used on multiple Standard Sets)
    18. Symptoms (*domain*) (used on multiple Standard Sets)

2. **Outcomes identified from the literature – published and ongoing trials (34 outcomes)**

REMAP-CAP Outcomes:

1. All cause mortality at 90 days
2. ICU mortality at 90 days
3. ICU length of stay
4. Ventilator free days at 28 days
5. Organ failure free days at 28 days
6. Proportion of intubated patients who receive a tracheostomy at 28 days
7. Hospital length of stay at 90 days
8. Destination at time of hospital discharge
9. Readmission to the index ICU within 90 days following index admission
10. Survival at 6 months
11. HRQoL at 6 months, using EQ5D-5L
12. Disability status at 6 months using WHODAS2.0

RECOVERY Outcomes:

1. In-hospital death
2. Duration of hospital stay
3. Need for mechanical or non-invasive ventilation, and if so, duration
4. Need for renal replacement therapy

UCL COVID-19 Social Study

1. Current isolation status and motivations for isolation
2. Length of isolation, length of time not leaving the home, length of time not contacting others
3. Trust in government
4. Trust in the health service, adherence to health advice,
5. Experience of adverse events due to Covid-19
6. Mental health
    - including wellbeing, depression, anxiety, which factors were causing stress, sleep quality, loneliness, social isolation

7. Changes in health behaviours such as smoking, drinking and exercise
8. How people are spending their time whilst in isolation, including working, functional household activities, care and schooling of any children in the household, hobbies, and relaxation
9. Resilience
10. Coping style
11. Fear of COVID-19
12. Volunteering behaviours
13. Gambling behaviours
14. Use of financial support
15. Arts and creative engagement
16. Life events
17. Optimism
18. Locus of control

3. Outcomes prioritised by the results of the patient survey (12 outcomes):

1. General physical functioning
2. Shortness of breath
3. Fatigue and vitality
4. Health-related quality of life
5. General mental functioning
6. Emotional wellbeing
7. General social functioning
8. Productivity and how health issues impact daily activities in and out of work
9. General clinical outcomes
10. Survival
11. Hospital admission
12. Required use of a ventilator

BMJ Open

Which outcomes are most important to measure in patients with COVID-19 and how and when should these be measured? Development of an international standard set of outcomes measures for clinical use in patients with COVID-19: a report of the International Consortium for Health Outcomes Measurement (ICHOM) COVID-19 working group

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Primary Subject	Public health

Heading:	
Secondary Subject Heading:	Infectious diseases
Keywords:	COVID-19, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, International health services < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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Which outcomes are most important to measure in patients with COVID-19 and how and when should these be measured? Development of an international standard set of outcomes measures for clinical use in patients with COVID-19: a report of the International Consortium for Health Outcomes Measurement (ICHOM) COVID-19 working group

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ABSTRACT

OBJECTIVES: The COVID-19 pandemic has resulted in widespread morbidity and mortality with the consequences expected to be felt for many years. Significant variation exists in the care even of similar patients with COVID-19, including treatment practices within and between institutions. Outcome measures vary among clinical trials on the same therapies. Understanding which therapies are of most value is not possible unless consensus can be reached on which outcomes are most important to measure. Furthermore, consensus on the most important outcomes may enable patients to monitor and track their care, and may help providers to improve the care they offer through quality improvement. To develop a standardised minimum set of outcomes for clinical care, the International Consortium for Health Outcomes Measurement (ICHOM) assembled a Working Group (WG) of 28 volunteers, including health professionals, patients and patient representatives.

DESIGN: A list of outcomes important to patients and professionals was generated from a systematic review of the published literature using the MEDLINE database, from review of outcomes being measured in ongoing clinical trials, from a survey distributed to patients and patient networks, and from previously published ICHOM standard sets in other disease areas. Using an online-modified Delphi process, the WG selected outcomes of greatest importance.

RESULTS: The outcomes considered by the WG to be most important were selected and categorised into five domains: 1) functional status and quality of life, 2) mental functioning, 3) social functioning, 4) clinical outcomes and 5) symptoms. The WG identified demographic and clinical variables for use as case-mix risk adjusters. These included baseline demographics, clinical factors, and treatment-related factors.

CONCLUSION: Implementation of these consensus recommendations could help institutions to monitor, compare and improve the quality and delivery of care to COVID-19 patients. Their consistent definition and collection could also broaden the implementation of more patient-centric clinical outcomes research.

Strengths & limitations of this study

- These consensus recommendations were generated by a large international working group consisting of all relevant stakeholders with an interest in outcomes of care for patients with COVID-19.
- The diversity of the working group means that the recommendations included in the Standard Set are applicable to all settings.
- The methodology employed in the generation of the Standard Set meant that the focus was on outcomes of relevance to patients throughout and there is a deliberate emphasis on the use of patient-reported outcome measures in the Set.
- SARS-CoV-2 was discovered just over one year ago and so we cannot yet be certain about the long-term outcomes of the disease.
- ICHOM Standard Sets typically undergo an open review process prior to publication, in which the draft Set is distributed to patients and their representative groups for feedback however this was not possible for this project given the timeframe.

INTRODUCTION

SARS-CoV-2, the virus responsible for the COVID-19 pandemic, has infected over 200 million people and resulted in the deaths of over 4 million.[1]. Although knowledge about the acute illness has rapidly expanded, there is increasing evidence that COVID-19 may have long-term sequelae, with adverse health outcomes and poor health-related quality of life lasting far longer than the acute disease.[2]

Significant variation exists in the care even of similar patients with COVID-19, including treatment practices within and between institutions and countries.[3] Furthermore, outcome measures vary among the largest clinical trials on the same therapies.[4] Understanding which therapies are of most value will remain a challenge unless consensus can be reached on which outcomes are most important to patients to measure. While survival or indirect measures of patient's health status e.g. hospitalisation, the need for mechanical or non-invasive ventilation, as well as measures of resource utilisation, are frequently recorded in trials, direct measures of patient-reported outcomes are rarely measured and/or recorded.[5] Furthermore, the follow-up period of many trials is insufficient to detect some outcomes affecting patients long after hospital discharge. There is, therefore, a need for a standardised approach to outcome measurement in COVID-19 to inform clinical practice and real-world therapeutic research and to allow healthcare providers to monitor outcomes and to identify areas for quality improvement. A standard set of outcomes i.e. standardised outcomes, measurement tools and time points and risk adjustment factors for COVID-19,[6] could help benchmark best practice across institutions, facilitating improvements in care during future outbreaks and providing value in healthcare. It could also standardise approaches to global research for patient benefit.

To support the development of a standardised outcome set in COVID-19 for integration into clinical practice (and to inform clinical research), the International Consortium for Health Outcomes Measurement (ICHOM) convened an international multidisciplinary Working Group (WG) of experts and patient representatives. As a not-for-profit organisation, ICHOM has developed 38 standard sets of value-based outcomes for use in routine clinical practice in a range of medical conditions, such as coronary artery disease, stroke, and cancer.[7] Over 600 organisations have implemented ICHOM sets including 15 national registries. Standard sets are reviewed and updated annually by ICHOM.

The aim of this paper is to present a standardised minimum set of outcomes for COVID-19, focusing on the inclusion of patient-reported outcomes, and case-mix variables, for comparisons across treatment modalities and institutions.

METHODS

Composition of the WG (including patient and public involvement)

WG members were identified through several avenues. A rapid review was conducted by the project team in the project initiation phase to identify relevant patient organisations, measurement initiatives, professional bodies, and publications actively addressing questions relating to outcome measurement for COVID-19 with a particular focus on patient-centred outcomes. Relevant organisations were contacted and information about the role of WG members shared both directly as well as through social media channels. Open recruitment calls were then held inviting interested individuals to participate in the WG. A matrix of candidates was composed to facilitate the representation of diverse geographies, disciplines, types of expertise, and a balance of specialist interests e.g. infectious diseases, respiratory disease, mental health, primary care, intensive care. A shortlist was created that would represent different matrix cells, and ICHOM subsequently invited shortlisted individuals to participate. In addition, individuals or organisations were given the opportunity to recommend additional candidates for consideration by the ICHOM project team.

Development of the COVID-19 standard set

The WG convened during six teleconferences between July 2020 and September 2020, following a structured process similar to that of previous ICHOM WGs. The development of the standard set involved four phases, as illustrated in **Figure 1**: defining the scope of the project; prioritising outcome domains; defining outcome domains and evaluating and selecting outcome measures that would be used to measure these domains, including clinical data and patient-reported outcome measures (PROMs); and selecting and defining case-mix variables.

Figure 1. Timeline and data collection process

Identification of potential outcomes, outcome measures and case-mix variables

The MEDLINE database was used to search for relevant publications from which potential outcome domains, outcome measures, patient-reported outcome measures, and case-mix variables were extracted in order to generate a long-list for the WG to consider. The search strategy used for the MEDLINE search was:

(("COVID-19"[Title]) OR ("novel coronavirus"[Title])) AND ("Outcome"[Title])

Two members of the project team (WHS and NS) carried out the MEDLINE search using the above strategy on 1st July 2020, and included papers published in English language between 1st December 2019 and 1st July 2020.

Outcomes measured in published trials (apart from reviews which were excluded in order to generate a list of primary outcomes from trials) were extracted as well as outcomes being measured in ongoing trials, as identified by the WHO International Clinical Trials Registry Platform (ICTRP) database.[8] Studies involving specific populations, such as gender, ethnicity, as well as interventions targeting specific clinical outcomes e.g. resolution of fever, and laboratory-based outcome measures such as inflammatory markers were excluded as these were deemed by the WG to represent process measures rather than outcomes that in and of themselves mattered directly to patients. In addition to extracting the outcomes, the outcome measures used to measure these outcomes in the trials included were also extracted. These outcome measures were discussed after the outcomes themselves had been selected.

In addition, an electronic survey was distributed at the start of the project to patients and patient representatives, through WG members' healthcare institutions, in line with their ethical guidelines (see **Supplementary File 1)**. It was also distributed through the ICHOM newsletter and social media platforms, as well as to the European Heart Network and European Lung Foundation patient fora, in order to identify any additional outcomes that were of particular importance to patients. Finally, outcomes were extracted from previously published ICHOM standard sets that were of potential relevance to patients with COVID-19, for example patient-reported measures such as health-related quality of life, and clinical outcomes such as survival.

Consensus process

WG teleconferences were held every two weeks. Following each teleconference, the project team circulated an electronic survey via the Qualtrics platform to the WG to gather feedback on each key decision. An online modified Delphi process was performed over three rounds for the selection of outcomes, following the RAND/University of California (Los Angeles) methodology[9] and based on a literature review,[10] to achieve consensus on which outcomes should be included. Inclusion in the standard set required that at least 80% of the WG voted an item as 'essential' (score 7-9 on a 9-point Likert scale) in each voting round. WG members were given one week to complete each survey. Outcomes were excluded if at least 80% of the WG voted an item as 'not recommended' (Score 1-3). Inconclusive domains were discussed and revised and put to a second round of voting. Outcomes that still had not garnered the required consensus for inclusion were put to a final third round vote. These three rounds were completed prior to considering the selection of outcome measures to capture the outcomes, which did not use the same Delphi methodology.

Selection of patient-reported outcome measures and case-mix variables

After patient-reported outcomes (PROs) were chosen for inclusion in the standard set, corresponding measures were identified from the literature, from tools previously used in other ICHOM standard sets for similar outcome domains, and by outcome experts in the WG. The original and validation studies of the instruments were examined in order to evaluate the psychometric quality, domain coverage, and feasibility of measurement and implementation. A breakout group consisting of academics and clinicians with particular expertise in PRO measures convened to decide on the most appropriate measures to use.

A different consensus-gathering process, this time requiring 70% consensus from the WG for each item, was used to agree on which measures and case-mix variables should be recommended in line with the methodology used in all ICHOM standard sets for this part of the study, as well as the time points for measuring each outcome. The 70% consensus level is thought to be sufficient for the selection of outcome measures and case-mix variables whereas a more stringent threshold of 80% or more of the WG voting an outcome as 'essential to include' on the Likert scale is required in ICHOM methodology for the selection

of the outcomes themselves. The results of each vote were reviewed by the WG at the subsequent teleconference. The criteria by which outcome domains were assessed for inclusion in the set were in accordance with the concepts of value-based healthcare as described by Porter.[11] Variables to be used as case-mix factors were assessed on: (i) relevance, (ii) independence, and (iii) measurement feasibility.

RESULTS

Working Group

ICHOM established a geographically diverse WG covering a broad range of specialties relevant to COVID-19. The WG consisted of 28 members, including clinicians, epidemiologists, research scientists, and patients and patient advocates/representatives from 13 countries across North and South America, Europe, Africa, the Middle East, South Asia and Australia (**Table 1)**. A project team (W.H.S., L.F., N.S., C.N., and K.B.) guided the efforts of the WG.

Scope

The outcomes and measures included in the COVID-19 standard set were defined for a target population of all adults over the age of 18 years with confirmed or highly suspected SARS-CoV-2 infection, as defined by WHO,[12] in primary, secondary or tertiary care settings. Children under the age of 18 years, as well as asymptomatic individuals with positive diagnostic tests, were excluded from the set. Different geographical and resource contexts were considered so that the standard set can be applied globally.

Outcomes

86%, 89% and 82% of WG members participated in the first, second, and third rounds of the modified Delphi process respectively. Out of 64 possible outcomes (see **Supplementary File 2** for a list of the sources of preliminary outcomes) identified through the methodology as described, the WG selected 13 outcomes. There was significant overlap between the outcomes identified from the different sources, and during the WG teleconferences, decisions were taken to merge or rename outcomes. The Reference Guide containing the definitions of all outcome domains included, as agreed by the WG, is published on the ICHOM website at www.ichom.org. The outcomes were categorised into five major groups: functional status and quality of life, clinical outcomes, mental functioning, social functioning, and symptoms. The set of outcomes and measures that were selected are detailed in **Table 1**.

Table 1: Summary of ICHOM C19 Standard Set of Outcomes

Outcome domain	Outcome sub-domains	Definition	Outcome measure
Functional Status and Quality of Life	Health-related quality of life	The perceived quality of an individual's daily life, assessing their health and wellbeing or lack thereof. A multi-dimensional concept that includes domains related to physical, mental, emotional and social functioning.	PROMIS Global Health 1.2
	General physical functioning	An individual's ability to perform and/or participate in usual daily activities required to meet essential needs, fulfil usual roles, meet usual responsibilities, and maintain health and well-being.	PROMIS Global Health 1.2
	Vitality/energy	Capacity for work and leisure activities, and efficiency of accomplishment related to a feeling of weariness or tiredness.	FLU-PRO
Mental Functioning	Mental health symptoms and emotional wellbeing	An individual's emotional, psychological, and social wellbeing, including negative feelings and fears, as well as moderate to high levels of anxiety or psychological distress.	PROMIS Global Health 1.2
	Cognitive status	An individual's mental process of knowing, including awareness, perception, reasoning, and judgement.	Clinician Measures
Social Functioning	Feelings of loneliness and isolation	An individual's negative feelings related to the perception of being alone, disconnected or isolated.	PROMIS Social Isolation 4a
	Productivity	An individual's ability to carry out tasks, actions or participate in life situations.	PROMIS Global Health 1.2
	Survival	Any cause of death in a patient with COVID-19.	Clinician Measures
	Meeting criteria for critical care admission	Patients whose medical needs cannot be met through standard ward-based care in an acute hospital, who would meet criteria for a high dependency or critical care unit.	Clinician Measures

Clinical Outcomes		Patients who meet criteria for critical care admission may not in fact be admitted to critical care facilities for other reasons e.g. resource constraints, however should be included under this definition.	
	Disease course severity	Mild: No need for hospitalisation Moderate: Hospitalisation without need for non-invasive or mechanical ventilation Severe: Received non-invasive and/or mechanical ventilation, or died; admission to HDU/ICU.	Clinician Measures FLU-PRO
	Persisting organ damage	End-organ damage, including the central or peripheral nervous system, as a result of the COVID-19 infection that results in impaired function in the individual.	Clinician Measures
	Duration of hospitalisation	Number of nights spent in hospital being treated for symptoms related to COVID-19 (irrespective of whether COVID-19 was the reason for admission or if the patient developed COVID-19 while in hospital for another reason). This includes nights spent in hospital on subsequent hospital admissions during the follow-up period if the individual being readmitted was being treated for symptoms related to COVID-19 on that admission.	Clinician Measures
Symptoms	Symptoms	A subjective perception suggesting bodily impairment or malfunction, affecting the individual in a negative manner.	FLU-PRO

Each domain has a number of sub-domains to capture what is important to patients. The domain on clinical outcomes is to be assessed by clinicians. For each of the remaining domains, the WG identified an appropriate outcome measure to use. Considering the overlap among measures, the WG identified the following measures: PROMIS Global 1.2,[13] PROMIS Social Isolation 4a,[14] and FLU-PRO.[15]

Baseline characteristics and case-mix variables

In addition to the outcomes and outcome measures, the WG selected important baseline health characteristics to enable comparison between providers (**Table 2**). These baseline health characteristics include: demographic factors e.g. age, sex, race, ethnicity, level of education, clinical factors e.g. comorbidities and body mass index, and treatment-related

factors e.g. need for ventilation, type of ventilation, duration of ventilation, duration of critical care admission.

Table 2: Summary of COVID-19 Standard Set Case Mix Variables

Case Mix Category	Variable	Measure	Timing	Data Source
Demographic Factors	Age	Year of birth.	Baseline	Patient record
	Sex	The patient's sex at birth.		
	Race	The biological race of the patient.		Patient record
	Ethnicity	The cultural ethnicity of the patient that they most closely identify with.		
	Level of Education	Highest level of education completed based on local standard definitions of education levels.		Patient record
Clinical Factors	Comorbidities	Prior and current diagnosis of disease or no presence of diagnosis.	Baseline	Patient/Clinician
	Body Mass Index	Height and weight are used to calculate BMI.		Clinician/Healthcare provider
Treatment-Related Factors	Need for ventilation	Did the patient require any ventilation during their hospital admission?	Baseline/ Updated monthly	Clinician/Healthcare provider
	Type of ventilation	What type of ventilation was administered?		

	Duration of ventilation	How long did the patient require ventilation?		
	Duration of critical care admission	How long was the patient's initial stay in critical care?		

Timeline for follow-up

The WG decided to track patient outcomes over a three-month period following the diagnosis or following criteria being met for highly suspected SARS-CoV-2 infection (**Figure 2)**. The outcome collection period can be extended for a further three months if the patient has not yet fully recovered. The WG delegated to the treating physicians the decision whether or not to extend data collection.

Figure 2: Follow Up Timeline and Data Collection Guidance

DISCUSSION

In this project, an international WG developed a consensus set of the most important outcomes and outcome measures in COVID-19. By measuring and reporting the same outcomes, and adjusting for the case-mix variables, providers may be able to improve the quality of care offered to patients by learning from other institutions using the same standard set. The standard set could also benefit patients directly by allowing them to track their progress over time and seek care when appropriate through heightened awareness of symptoms that they may not necessarily realise are problems e.g. mental health symptoms, or waning productivity. The standard set could also be considered for use in future respiratory viral pandemics.

This is the first global effort to develop a standardised minimum set of patient-centred outcomes in COVID-19 for use in clinical practice. While we cannot yet be certain about the long-term outcomes of the disease, this work provides a starting point and there is scope for additional measures to be included as our understanding of the disease improves. Other groups, including the WHO Clinical Characterisation and Management Working Group, have sought to define sets of standardised outcomes in COVID-19. This group published a core

outcome set primarily for research use. As such, the outcomes recommended by that group have a clinical and technical focus and include many indirect measures of patient outcomes.[16] Our project focused on clinical practice, however could also be used to inform real-world clinical research by incorporating direct patient outcomes, both in evaluating the course of illness and the effects of therapeutics. This standard set is patient-centric, utilising patient-reported outcomes as a key component of the set, and focusing primarily on outcomes that matter to patients e.g. an individual's ability to perform and/or participate in usual daily activities rather than on clinical metrics.

The predominant use of indirect outcomes in clinical trials of COVID-19 and in monitoring patients' progress with the disease runs the risk of missing issues of equal or more significance to those suffering with the illness – the disease burden of symptoms and impaired function that may persist long after the acute illness. While measuring survival and clinician-reported outcomes like hospitalisations is essential, it is equally important to measure PROs which add valuable information in those who do survive or who are discharged/remain in hospital. PROs can be used for long-term follow-up to assess the effect of the disease on a patient's quality of life, and to alert treating physicians to the development of complications.[17] There is an increasing body of literature suggesting benefit to patients of various drugs and vaccines against COVID-19. Validated, standardised PROs that comprehensively assess the symptom experience and patient function in COVID-19 across multiple domains could also facilitate meta-analyses and more precise estimates of treatment effects.

When considering which PRO measures to use in the set to measure overall quality of life, the WG felt that a generic as well as respiratory-specific measure would be most appropriate given the multi-system nature of COVID-19. One such universal measurement system is the Patient-Reported Outcomes Measurement Information System (PROMIS). The PROMIS Global Health (v 1.2) instrument, which is freely available, consists of ten global health items that represent five core PROMIS domains (physical function, pain, fatigue, emotional distress, social health).[18] The majority of PRO measures included in this set that are not symptoms are covered within the PROMIS Global Health questionnaire. One outcome that the WG felt important to include which is not adequately covered in this instrument is loneliness/isolation, which is captured via the short PROMIS Social Isolation 4a tool.

In addition to the PROs included in the set, there are a number of clinical outcomes that the WG felt it essential to include. The WG felt it important to ensure that the direct end-points used took account of the varying practices and resources that exist across the world. As such, the standard set is suitable for any primary, secondary or tertiary care setting in any country. Of note, while many COVID-19 studies report ICU admission as an outcome, the WG took the view that because ICU provision and therefore the thresholds for admission to ICU vary so significantly depending on the context in which one practices, a more appropriate outcome measure would be 'meeting criteria for ICU admission' rather than admission itself i.e. explaining the reason for ICU admission and not solely the event. A similar approach was taken when considering the issue of non-invasive ventilation, the use of which varied from being widespread to prohibited based on factors such as availability of oxygen and concerns around staff infection. The WG considered that 'need for non-invasive ventilation,' while important, could not be classed as an outcome since the criteria determining 'need' varied too much. Instead, this is included as a case-mix factor so that it can be controlled for in analyses.

The presence or absence of symptoms was included in the set on the basis that persistence of symptoms e.g. as part of 'long COVID' may be modifiable and may represent a significant disease burden. The WG elected to utilise a symptom scale that has been developed and validated for comprehensively measuring symptoms in viral respiratory tract diseases – the FLU-PRO scale.[19] The scale was developed with patient input and its psychometric properties have been evaluated in a study with over 500 patients including those with influenza virus, respiratory syncytial virus, enterovirus, rhinovirus, adenovirus, and endemic coronaviruses and is being used currently in studies of COVID-19.[20,21,22] The scale was adapted during COVID-19, but in general, can be used to measure symptoms in any viral respiratory illness.

Consideration was given during WG discussions as to the appropriate timeline of data collection for patient symptoms. Although the FLU-PRO asks patients about symptoms in the previous 24 hours, the WG felt it infeasible to ask patients to rate their symptoms daily for the entire course of the three-month follow-up period. The WG's recommendation for practical use was to ask patients to complete the FLU-PRO fortnightly for the first month and then monthly thereafter, in line with the timeline for collection of other PRO measures as part of the 'PROM package' depicted in the timeline in **Figure 2.**

An important aspect of this project is the standardisation of outcome measurement in COVID-19 across differing regions and healthcare systems. To achieve this, we have published a comprehensive reference guide summarising the set, outcome reporting tools, adjustment variables, and collection time points which is freely available at www.ichom.org.

Our approach does have some limitations. The standard set methodology is reliant on the composition of the WG. Although the WG recruited as diverse members as was possible given the time constraints, it is possible that a different WG would have come to different conclusions. Our methodology is reliant on the continued involvement of WG members over several months, and although we did not experience significant attrition during the various stages of the consensus-gathering process, nevertheless there remains the potential for attrition bias to have affected the results of the rounds of voting. Further, ICHOM standard sets typically undergo an open review process prior to publication in which the draft set is distributed to patients and their representative groups for feedback. Unfortunately, this was not possible within the timeframe of this project. The standard set was developed not as a static document but firmly with implementation in mind. As such, feasibility of measuring outcomes was a key concern during the outcome selection stage and therefore not all outcomes could be included in the set, despite being recognised by some members of the WG as important. Furthermore, feasibility of measuring and global adoption of the set were important determinants of the symptom scales and PROs that were selected by the WG.

The next stage of this project is to promote implementation of the standard set. Issues to overcome when considering implementing the COVID-19 set include: 1) budget 2) availability of clinical leaders to champion the set and promote its adoption given pressing clinical commitments to direct patient care in the ongoing pandemic 3) ensuring efficient and intuitive means of collecting and storing clinical data and 4) ensuring consistent and accurate collection of patient-reported outcomes. Implementation of the set involves several phases as described previously.[23]

CONCLUSION

We have developed a consensus recommendation for a standardised minimum set of outcomes that our working group considered most important to patients with COVID-19 comprising functional status and quality of life, clinical outcomes, mental functioning, social

functioning, and symptoms. The use of patient-reported outcomes is central to the set, and makes the recommendations particularly relevant. This standard set is targeted for integration into routine clinical practice and research. Use of the set may enable institutions to monitor, compare, and most importantly improve the quality of the care they deliver for patients with COVID-19 as the pandemic unfolds.

Patient and Public Involvement: Patients and members of the public were involved at the centre of the work described in this manuscript. Patients were at the heart of the Working Group that produced the standard set, and patients (and their representatives at patient organisations) were directly asked which outcomes they felt were most important for them at the start of the project. Most of these outcomes are included in the final list of outcomes selected by the Working Group. The patient members of the Working Group contributed to the review and final drafts of this manuscript.

Funding Statement: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Ethical Approval: not required as the study was a consensus-gathering process about COVID-19 outcomes.

Data Availability: Data are available upon reasonable request. These include complete survey results as well as results of the consensus-gathering processes described within the manuscript.

Transparency Declaration: WHS affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Competing Interests Statement: All authors completed and submitted ICMJE uniform disclosure forms and declared no support from any organisations that might have an interest in the submitted work, and no other relationships or activities that could appear to have influenced the submitted work. The exception to this is the Project Team – NS, LF & CN who are paid employees of ICHOM, and WHS who received a stipend from ICHOM as Research Fellow to the project

Contributorship Statement: The project was conceived by the ICHOM Project Team – LF, NS, CN and WHS. The WG was chaired by KB who provided oversight to the Project Team throughout. All other authors (FMB, PC, IKMD, MPF, MAF, LEKG, JJG, AK, AL, IILL, CL, AMD, NM, GANB, CWO, JHP, A-MR, MKS, TYPW, EKW, DCW, EZ) listed in the manuscript met the authorship requirement criteria through consistent engagement in WG teleconferences, voting in the Delphi consensus process, and reviewing drafts of the manuscript. The specific authorship requirements for ICHOM standard sets include participation in at least 50% of WG meetings, completion of at least 50% of the post-meeting surveys, and reviewing and providing feedback on drafts of the manuscript.

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Figure 1. Timeline and data collection process

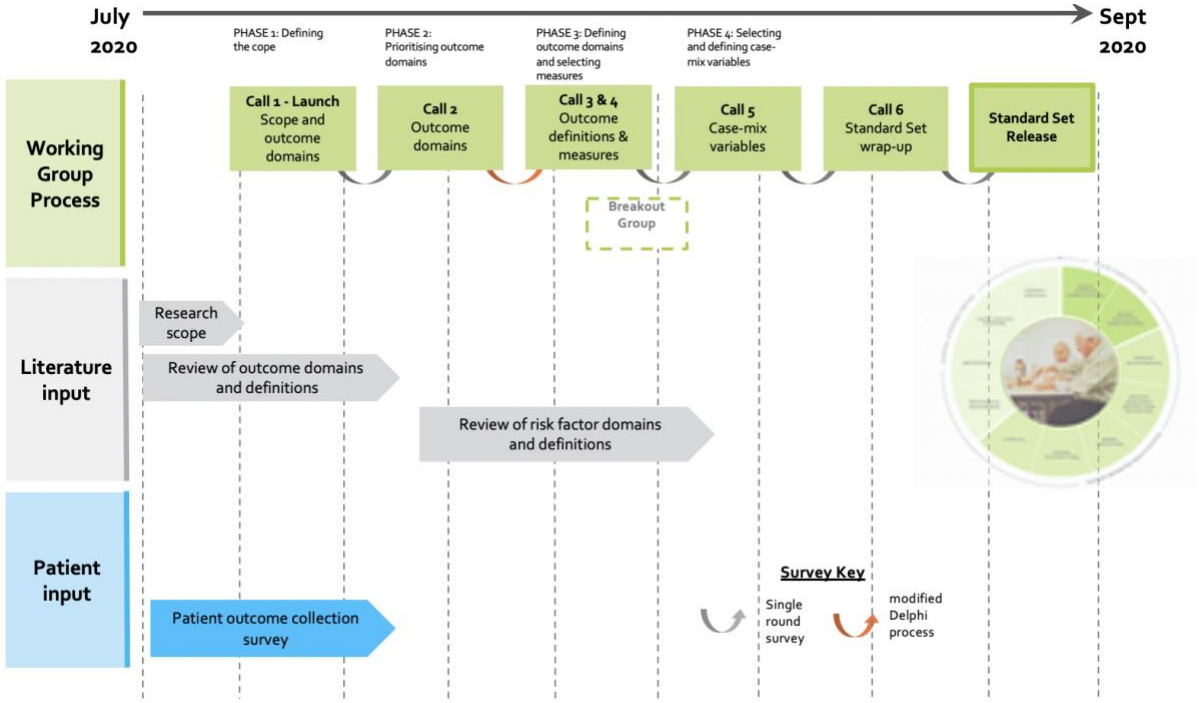
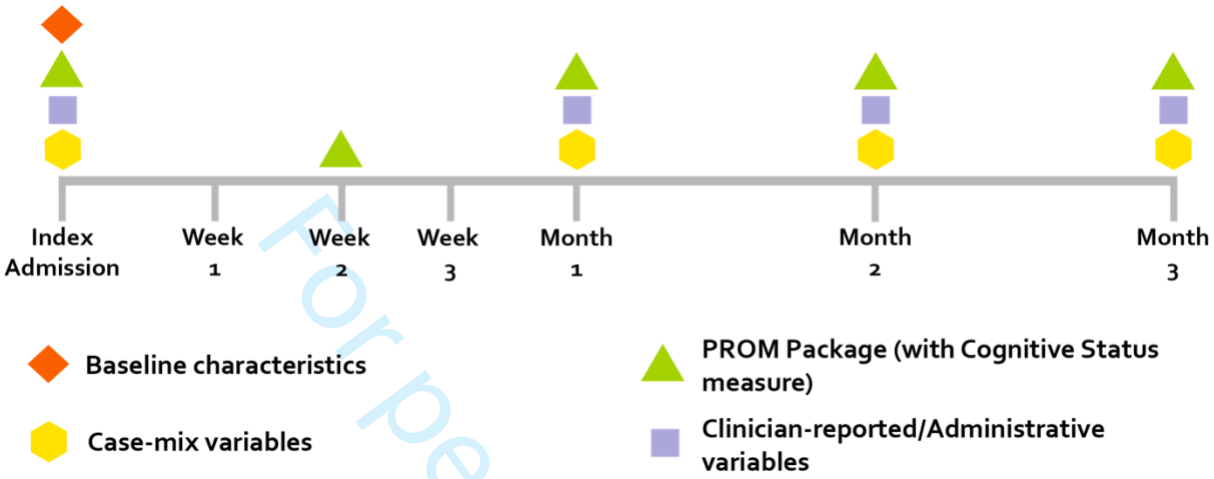


Figure 2: Follow Up Timeline and Data Collection Guidance:



Default Question Block

Dear Participant,

The International Consortium for Health Outcomes Measurement (ICHOM, www.ichom.org) is an independent not-for-profit organisation. We are launching a project which aims to create a measurement set to be used by clinicians to assess the health of patients who have had COVID-19 by focusing on the outcomes that patients feel are important.

To help us better understand, we are asking people who have had COVID-19 to complete the short survey below, asking what matters most to them.

It should take no longer than 5 minutes to complete and yet it can change the way healthcare professionals manage the care of patients recovering from COVID-19. Your feedback will be invaluable.

Please note that answering this survey is on a voluntary basis, your responses will remain anonymous and no IP or personal data are recorded.

As of today, are you aged 18 years of age or older?

- ○ Yes
- ○ No

Thank you for your interest in this project. Unfortunately, you must be 18 years of age or older in order to participate in this survey.

1. From this list below, please give feedback on how important the following health outcomes are to patients recovering from COVID-19. These outcomes are grouped into domains (highlighted in bold) which we would also like you to rate.

	1-3= Not important			4-6= Nice to have			7-9= Essential to have	
	1	2	3	4	5	6	7	8

	1-3= Not important 1	2	3	4-6= Nice to have 4	5	6	7-9= Essential to have 7	8
Physical Functioning	○	○	○	○	○	○	○	○
Pain as a chronic condition that affects day-to-day life	○	○	○	○	○	○	○	○
Presence of a chronic cough	○	○	○	○	○	○	○	○
Shortness of breath	○	○	○	○	○	○	○	○
Fatigue and vitality	○	○	○	○	○	○	○	○
Ability to exercise	○	○	○	○	○	○	○	○
Speech and communication	○	○	○	○	○	○	○	○
Health-related quality of life (ie an individual's perceived physical health over time)	○	○	○	○	○	○	○	○
Mental Functioning	○	○	○	○	○	○	○	○
Emotional wellbeing	○	○	○	○	○	○	○	○
Depression	○	○	○	○	○	○	○	○
Anxiety	○	○	○	○	○	○	○	○
Social Functioning	○	○	○	○	○	○	○	○
Feelings of loneliness and isolation	○	○	○	○	○	○	○	○
Feeling able to return to work	○	○	○	○	○	○	○	○
Productivity and how health issues impact daily activities in and out of work	○	○	○	○	○	○	○	○
Clinical Outcomes	○	○	○	○	○	○	○	○
Survival	○	○	○	○	○	○	○	○
Whether any admission to a hospital was required, the length of stay and any subsequent readmission	○	○	○	○	○	○	○	○
Required use of a ventilator	○	○	○	○	○	○	○	○
Required any surgical intervention	○	○	○	○	○	○	○	○

Do you feel that this list broadly captures all the important outcomes that matter most to patients recovering from COVID-19?

- ○ Yes
- ○ No

Which additional outcomes would you include? Please list these in the box below with a brief explanation of each.

Thank you for completing this survey. If you have any questions or would like further information on this work, please do not hesitate to contact us using the email address below. Please click the grey arrow on the right-hand side below to finish the survey and submit your answers.

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Sources of the Preliminary Outcome List

1. **Outcomes identified from previously published ICHOM Standard Sets (18 outcomes):**
    1. Pain as a chronic condition that affects day-to-day life (Outcome used on multiple Standard Sets)
    2. Cough (used on Lung Cancer Standard Set)
    3. Fatigue and vitality (used on Lung Cancer Standard Set)
    4. Shortness of breath (used on Lung Cancer Standard Set)
    5. Ability to work (used on Atrial Fibrillation Standard Set)
    6. Exercise tolerance (used on Atrial Fibrillation Standard Set)
    7. Loneliness and Isolation (used on Older Person Standard Set)
    8. Speech and Communication (used on Cleft Lip and Palate Standard Set)
    9. Readmission (used on multiple Standard Sets)
    10. Social Functioning (used on multiple Standard Sets)
    11. Mental Functioning (used on multiple Standard Sets)
    12. Health-related quality of life (used on multiple Standard Sets)
    13. Survival (used on multiple Standard Sets)
    14. Productivity (used on multiple Standard Sets, but relates to ability to work)
    15. Emotional Wellbeing (used on multiple Standard Sets)
    16. Depression (used on multiple Standard Sets)
    17. Anxiety (used on multiple Standard Sets)
    18. Symptoms (*domain*) (used on multiple Standard Sets)

2. **Outcomes identified from the literature – published and ongoing trials (34 outcomes)**

REMAP-CAP Outcomes:

1. All cause mortality at 90 days
2. ICU mortality at 90 days
3. ICU length of stay
4. Ventilator free days at 28 days
5. Organ failure free days at 28 days
6. Proportion of intubated patients who receive a tracheostomy at 28 days
7. Hospital length of stay at 90 days
8. Destination at time of hospital discharge
9. Readmission to the index ICU within 90 days following index admission
10. Survival at 6 months
11. HRQoL at 6 months, using EQ5D-5L
12. Disability status at 6 months using WHODAS2.0

RECOVERY Outcomes:

1. In-hospital death
2. Duration of hospital stay
3. Need for mechanical or non-invasive ventilation, and if so, duration
4. Need for renal replacement therapy

UCL COVID-19 Social Study

1. Current isolation status and motivations for isolation
2. Length of isolation, length of time not leaving the home, length of time not contacting others
3. Trust in government
4. Trust in the health service, adherence to health advice,
5. Experience of adverse events due to Covid-19
6. Mental health
    - including wellbeing, depression, anxiety, which factors were causing stress, sleep quality, loneliness, social isolation

7. Changes in health behaviours such as smoking, drinking and exercise
8. How people are spending their time whilst in isolation, including working, functional household activities, care and schooling of any children in the household, hobbies, and relaxation
9. Resilience
10. Coping style
11. Fear of COVID-19
12. Volunteering behaviours
13. Gambling behaviours
14. Use of financial support
15. Arts and creative engagement
16. Life events
17. Optimism
18. Locus of control

3. Outcomes prioritised by the results of the patient survey (12 outcomes):

1. General physical functioning
2. Shortness of breath
3. Fatigue and vitality
4. Health-related quality of life
5. General mental functioning
6. Emotional wellbeing
7. General social functioning
8. Productivity and how health issues impact daily activities in and out of work
9. General clinical outcomes
10. Survival
11. Hospital admission
12. Required use of a ventilator