BMJ Rapid Recommendation: Remdesivir for patients with severe COVID-19

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Bram Rochwerg

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MAGIC Evidence Ecosystem Foundation

Contact

Bram Rochwerg
711 Concession St, Hamilton, Ontario, Canada L8V 1C3 rochwerg@mcmaster.ca
bram.rochwerg@gmail.com

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Sections

Summary of recommendations

1 - Background

Recommendation Strength Not Set

Trustworthy and living evidence and guidance for COVID-19 treatments
The COVID-19 pandemic – also, given the explosion of research combined with misinformation and hoaxes, characterized as an infodemic – has demonstrated a need for trustworthy, accessible and living guidance. This has triggered the MAGIC Evidence Ecosystem Foundation (MAGIC, https://magicevidence.org) to focus their BMJ Rapid Recommendations on COVID-19, starting out with treatments that hold the potential to change clinical practice, informed by a living systematic review and network meta-analysis (NMA) *[4]*.

Here we report our first initiative; a guideline recommendation for the use of remdesevir in patients with severe COVID-19 infection, triggered by the recent publication of two RCTs comparing remdesivir to placebo *[1][3]*. We describe the standards, methods and processes applied for this guideline in the section below.

Please find the BMJ publication with user-friendly infographics and more extensive information about the remdesivir recommendations here: https://www.bmj.com/content/370/bmj.m2924

WHO guidance to come: Subsequent recommendations for COVID-19 drug treatments will primarily be developed as WHO guidance, through a recently established collaboration with MAGIC, building on innovations in the BMJ Rapid Recommendations. The first WHO guidance on corticosteroids for patients with COVID-19 infection will soon be published, including new trial data that was made available to the guideline panel through the WHO. Our collaboration reflects an urgent need for global collaboration to provide trustworthy and living evidence and guidance informing policy and practice worldwide. MAGIC supports WHO with the living systematic review, methodological support in development of recommendations and use of MAGICapp. This trustworthy and living guidance will be available through the WHO website as well as through BMJ Rapid Recommendations following soon thereafter together with updates of the living systematic review. Here, BMJ has innovated their publication process, moving from weeks to days in editorial processing, making the manuscript available for peer-review and public review immediately.

The trustworthy and living guidance will - once it becomes relevant - include comparative effectiveness of drug treatment options, informed by the living systematic review and NMA. Our common goal is also to allow countries and health care systems to re-use and adapt these recommendations, and to avoid unnecessary duplication of work and undue delays in transforming new evidence into guidance for policy and practice, faciliated by the use of digitally structured content in MAGICapp, soon to be applied by the WHO. Please contact Per Olav Vandvik (CEO of MAGIC, per@magicevidence.org) if you want to make use of MAGICapp for re-use and adaptation of BMJ Rapid Recommendations, made freely available for COVID-19 guideline efforts.

2 - Recommendation for remdesivir

Patients with severe COVID-19 infection (requiring hospital or intensive care admission, respiratory rate >30, respiratory distress, Sp02 <94% on room air)

Weak Recommendation

We suggest remdesivir rather than no remdesivir for the treatment of patients with severe COVID-19 infection.

This recommendation applies to all adult patients with severe confirmed COVID-19. As criteria for hospitalization vary amongst jurisdictions, we anchored our definition of severe infection to the initial WHO criteria, which includes either respiratory rate >30 per minute, respiratory distress or SpO2 <94% on room air [5]. This definition of severe disease matches closely with that used in the included trials. Following GRADE (Grading of Recommendations Assessment, Development and Evaluation) guidance, a weak recommendation implies that most patients with severe COVID-19 infection would choose to take remdesivir; a minority will, depending on individual shared decision-making, decline.

Practice Statement

Randomized controlled trials examining remdesivir in patients with COVID-19 should continue.

3 - Standards, methods and processes for BMJ Rapid Recommendations

1 - Background

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Practical Info

There are some practicalities that must be considered in the administration of remdesivir that may limit its use. To date, it can only be administered intravenously, and it is relatively costly with, at least for now, limited availability. Remdesivir is contraindicated in those with liver (ALT >5 times normal at baseline) or renal dysfunction (eGFR <30 mL/minute).

Rationale

The panel made its recommendation on the basis of the low certainty evidence of a modest reduction in time to clinical improvement and no effect on duration of hospitalization. We made this recommendation despite an uncertain impact on survival. The panel was reassured that the risk for adverse effects with remdesivir appears minimal (4 out of 1063 patients randomized in the ACTT trial, 2 in each group, had severe adverse events judged to be secondary to remdesivir or placebo), although a full safety analysis will require documentation of adverse effects in much larger numbers of patients *[6]*. Potential adverse events associated with remdesivir include hyperglycemia, liver dysfunction, and renal failure. Administration of remdesivir should always be in addition to, and not instead of, routine supportive therapy.

Values and Preferences:
We did not perform a systematic review of values and preferences for this guideline and therefore views expressed are those of the panel members that included patient partners. As with other Rapid Recommendations, the panel took an individual patient perspective to values and preferences. The panel also placed a high value on considering the impact of resource allocation in economically constrained health systems when generating this recommendation, a perspective in which widespread provision of novel therapies for COVID-19 may require higher quality evidence of important benefits. Resource constrained environments exist in low- and middle- income countries (LMICs), as well as, to varying degrees, in high-income countries. In such environments opportunity costs – that is, drawing resources away from alternative, perhaps more worthwhile, expenditures - become a particularly salient concern. This is especially relevant in COVID-19, as even centres in high resource settings may experience resource constraints with diversion of time, funds, attention and workforce during a pandemic surge.

The panel felt that uncertainty remains regarding the extent to which patients would find a three day reduction in time to clinical improvement, in the absence of reduction in hospital stay, important. Guidance for remdesivir also has implications for priority setting in health systems with limited resources, as the opportunity cost of remdesivir may be associated with exacerbation of health inequities. Under these circumstances, widespread use may indeed be unwise. Indeed, some on the panel were sufficiently worried about this contribution to health inequities, an issue magnified by the COVID pandemic, as to consider only recommending remdesivir in the context of clinical trials. Ultimately, however, the panel achieved consensus regarding a weak recommendation in favour.

Clinical Question/ PICO

Population:	Patients with COVID-19
Intervention:	Remdesivir
Comparator:	Standard of care/ placebo

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard of care/ placebo	Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Mortality [1]	Odds Ratio 0.66 (CI 95% 0.4 - 1.14) Based on data from 1,080 patients in 2 studies. [2] (Randomized controlled)	330 per 1000	245 per 1000 Difference: **85 fewer** per 1000 (CI 95% 165 fewer - 30 more)	**Low** Due to very serious imprecision [3]	Remdesivir may decrease mortality.
Mechanical ventilation [4] Risk	Odds Ratio 1.03 (CI 95% 0.5 - 2.13) Based on data from 236 patients in 1 studies. [5] (Randomized controlled) Follow up 28 days	116 per 1000	119 per 1000 Difference: **3 more** per 1000 (CI 95% 54 fewer - 102 more)	**Low** Due to very serious imprecision [6]	Remdesivir may have little to no effect on mechanical ventilation
Serious adverse events leading to discontinuation [7]	Odds Ratio 1.26 (CI 95% 0.52 - 3.94) Based on data from 1,077 patients in 2 studies. [8] (Randomized controlled)	80 per 1000	99 per 1000 Difference: **19 more** per 1000 (CI 95% 37 fewer - 175 more)	**Low** Due to very serious imprecision [9]	Remdesivir may increase serious adverse events leading to discontinuation
Hospitalization Duration	Lower better Based on data from: 236 patients in 1 studies. [10] (Randomized controlled) Follow up 28 days	24 days (Median)	25 days (Median) Difference: **0 lower** (CI 95% 4 lower - 4 higher)	**Low** Due to very serious imprecision [11]	Remdesivir may have little to no effect on hospitalization duration
Time to symptoms resolution [12]	Lower better Based on data from: 1,295 patients in 2 studies. [13] (Randomized controlled) Follow up 29 days	19 days (Mean)	16 days (Mean) Difference: **MD 3.04 lower** (CI 95% 5.19 lower - 0.89 lower)	**Low** Due to serious indirectness; Due to serious imprecision [14]	Remdesivir may reduce the time to symptoms resolution
Mechanical ventilation [15] Duration	Measured by: Days Lower better Based on data from: 236 patients in 1 studies. [16] (Randomized controlled) Follow up 28 days	15.5 days (Median)	7 days (Median) Difference: **4 lower** (CI 95% 14 lower - 2 higher)	**Low** Due to very serious imprecision [17]	Remdesivir may reduce the duration of mechanical ventilation
Intensive care unit length of stay	Based on data from 0 patients in 0 studies.	The systematic review did not identify any published trials reporting data for this outcome			

Practical issues	Standard of care/ placebo	Remdesivir	Both
 Medication routine		• Remdesivir involves administration via intravenous infusion • Optimal timing, duration and dosing of Remdesivir remain unclear	
 Adverse effects, interactions and antidote		Remdesivir • may increase adverse events leading to discontinuation of medication • is not a significant inducer or inhibitor of CYP enzymes, but should be monitored when co-administrated with strong inducers or inhibitors • is contraindicated in those with liver (ALT >5 times normal at baseline) or renal dysfunction (eGFR <30 mL/ minute).	
 Costs and access		Remdesivir may be relatively costly, and there may be limited availability.	

1. Based on Network estimate, using Bayesian random-effect models. Direct estimate using Bayesian random effect models 0.66 (0.39-1.11)
2. Systematic reviewwith included studies: [3], [1]. **Baseline/comparator:** Primary study[2].
3. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** When rating the certainty that there is any benefit, the 95% CI suggests the possibility of important harm. The imprecision is likely to be linked to some concerns of inconsistency. We rated down 2 levels for imprecision.. **Publication bias: No serious.**
4. Based on direct evidence only (Bayesian random effects, but there is 1 study only so random = fixed), as this is the estimate of effect for which there is the highest certainty. (NMA estimate: 1.04 (0.27 to 4.21))
5. Systematic reviewwith included studies: [1]. **Baseline/comparator:** Control arm of reference used for intervention[4].
6. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** The confidence interval crosses from small benefit to large harm. We rated down for 2 levels. . **Publication bias: No serious.**
7. Based on network estimate. Direct estimate 1.23 (0.48 to 3.65). Both using Bayesian random effects model
8. Systematic reviewwith included studies: [1], [3]. **Baseline/comparator:** Control arm of reference used for intervention[4].
9. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Rating the certainty that there is harm, the 95% CI suggests the possibility of important benefit as well as important harm.. **Publication bias: No serious.**
10. Systematic reviewwith included studies: [1]. **Baseline/comparator:** Control arm of reference used for intervention[4].
11. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Rating the certainty that there is little to no difference, the CI suggests the possibility of important benefit and important harm. **Publication bias: No serious.**
12. Based on frequentist fixed effects pairwise meta-analysis
13. Systematic reviewwith included studies: [1], [3]. **Baseline/comparator:** Control arm of reference used for intervention[4].
14. **Inconsistency: No serious. Indirectness: Serious. Imprecision: Serious.** Rating the certainty that there is an important

benefit, the CI suggests the possibility that the benefit is not important (< 1 day). **Publication bias: No serious.**

15. Based on comparison reported by trial ("Differences are expressed as rate differences or Hodges-Lehmann estimator and 95% CI."). The difference is not an MD

16. Systematic reviewwith included studies: [1]. **Baseline/comparator:** Control arm of reference used for intervention[4].

17. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Rating the certainty that there is any benefit, the CI suggests the possibility great benefit and important harm. **Publication bias: No serious.**

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Practice Statement

Randomized controlled trials examining remdesivir in patients with COVID-19 should continue.

Rationale

Although the panel made a weak recommendation for Remdesivir, uncertainty regarding any mortality benefit, possible reduction in hospitalization, and the magnitude of any benefit in time to clinical improvement mandate continuing enrolment in RCTs examining remdesivir in comparison to placebo or usual care for patients with severe COVID-19.

Clarification of the benefits and harms of remdesivir is even more important in economically constrained hospital systems in which resource constraints are a more important consideration.

3 - Standards, methods and processes for BMJ Rapid Recommendations

The BMJ Rapid Recommendations was initiated by the MAGIC Evidence Ecosystem Foundation (MAGIC, https://magicevidence.org/) together with BMJ in 2016 to circumvent organisational barriers and to provide clinicians with guidance based on the most current practice-changing evidence. Here, an international panel of patients, clinicians, and methodologists without important conflicts of interest produce recommendations using robust standards for guideline development and the GRADE approach. We consider an individual patient perspective and allow contextual factors (e.g. resources) to be taken into account for countries and health care systems. These guidelines are available for global re-use and adaptation through the BMJ and MAGIC authoring and publication platform (MAGICapp, http://www.magicapp.org/. 18 published BMJ Rapid Recommendations (https://www.bmj.com/rapid-recommendations) demonstrate feasibility of this innovative approach. Publications include user-friendly formats of guidelines, evidence summaries and decision aids. These are produced, published and ready for re-use and adaptation through MAGICapp.

This BMJ Rapid Recommendation addressing the use of remdesevir in patients with severe COVID-19 infection represents a first response to the COVID-19 pandemic and infodemic with trustworthy, accessible and living guidance based on the results of a network meta-analysis. In this section, we detail the standards, methods and processes applied to arrive at trustworthy and living guidance for COVID-19 treatments. The COVID-19 pandemic and infodemic warrants increased speed in providing timely guidance after the publication of practice-changing evidence, often through press-releases or pre-prints rather than peer-reviewed journal publications. Following this first remdesevir guideline we therefore aim for a very ambitious time frame from trigger trials to Rapid Recommendation publication (e.g. 2-3 weeks), without sacrificing standards and methods for trustworthy guidelines. This is made possible through increased efficiency at each step of the process established in the BMJ Rapid Recommendations, as outlined below.

MAGIC has, since the remdesevir guideline was created, entered a formal collaboration with WHO to support their trustworthy and living guidance for COVID-19 treatments, through the living systematic review, methodological support in guideline development and the use of MAGICapp. The release of WHO guidance - first to appear for steroids in patients with COVID-19 - will be followed by publication of the BMJ Rapid Recommendations providing front-line clinicians, patients and policy-makers with a more comprehensive presentation and understanding of the rapidly evolving evidence and guidance for COVID-19 treatments. These BMJ Rapid Recommendations will adhere to WHO standards, methods and processes, as detailed in future publications.

GOVERNANCE

A **joint steering committee** comprised of representatives from WHO and representatives from MAGIC has been set up to prepare for the planned full collaboration between WHO and MAGIC for future COVID-19 guidance. The steering committee is responsible for decision-making to meet the needs of both parties for the production of guidance for COVID-19. MAGIC representatives include their academic partners at McMaster University (e.g. leading systematic reviews) and the BMJ (to coordinate editorial processes for BMJ Rapid Recommendations). For remdesevir, the steering committee decided to create a BMJ Rapid Recommendation that could subsequently inform WHO guidance as the formal collaboration between MAGIC and WHO was not in place when the guideline development was initiated.

The steering committee will jointly determine which clinical questions to pursue, among the identified potentially practice changing evidence from the living systematic review, or other sources. In situations where BMJ Rapid Recommendations will not be performed to inform subsequent WHO guidance (e.g. topics of relevance beyond drugs, lack of capacity on MAGIC side or lack of interest from the BMJ) the steering committee will also make decisions to allocate tasks and share work between the partners (e.g. development of separate WHO guidance or MAGIC guidance with opportunities to share guideline panellists or evidence synthesis).

The **guideline development group** (GDG) was identified according to WHO criteria, to ensure regional representation, gender balance and appropriate technical expertise as well as patient representation, all without conflicts of interest. MAGIC contributed with methodological experts in a joint process where both parties agreed on the composition of the final panel, also to constitute the BMJ Rapid Recommendations panel. For the remdesevir recommendation WHO assisted in finding experts with no further input in the guideline development process, orchestrated by MAGIC and BMJ as in previous BMJ Rapid Recommendations.

7 STEPS FOR TRUSTWORTHY AND LIVING GUIDANCE (describing processes and methods)

Step 1: Evidence monitoring and mapping
The process for identifying potentially practice-changing evidence is based on continuous and comprehensive monitoring of all emerging randomized controlled trials. The monitoring is performed within the context of a living systematic review and network meta-analysis *[4]* (see step 3). MAGIC monitors, with the support of experienced information specialists, on a daily basis all relevant information sources for new randomized trials addressing interventions for COVID-19. Once identified, the joint steering committee is immediately convened to make decisions while newly eligible studies are incorporated into the evidence summaries addressing the intervention of interest.

Step 2: Selection process for **triggering evidence synthesis** and **production of rapid recommendations**
Once MAGIC has alerted WHO of potentially practice-changing evidence, the WHO will convene the **joint steering committee** to advise whether to trigger evidence synthesis and recommendation development based on the relevance to the global audience, widespread interest, and likelihood to change practice. The need for specific rapid recommendations will be based on the following:

- Sufficient RCT data on therapeutics to inform the high-quality living systematic review.
- Evaluation of such trial data necessary to inform clinical practice

Step 3: Evidence synthesis
MAGIC, as requested by the steering committee, coordinates and performs systematic reviews on benefits and harms of COVID-19 drugs, as well as for other topics to the extent they have capacity. Additional systematic reviews on prognosis and values and preferences will be performed as needed.
1. a high-quality living systematic review and network meta-analysis will examine the benefits and harms with a focus on outcomes that matter to patients. A large team of systematic review experts, clinical experts, clinical epidemiologists, graduate students and biostatisticians are creating this living review. The team includes the methodologists who developed GRADE methodology for rating quality/certainty of evidence, including advances in applying that methodology to network meta-analyses *[4]*. A separate protocol describes the living systematic review and network meta-analysis addressing drug intervention (Appendix A).
2. a systematic review of observational studies or risk prediction models to identify baseline risk estimates that most closely represent the target population for the clinical question, a key component required to estimate the absolute effects of the intervention required to trade off benefits and harms.
3. a systematic review addressing the preferences and values of patients on the topic, for situations where we anticipate available published studies to better inform panel judgments.

Step 4: Standing GDG panel
The GDG members is a standing guideline panel that includes clinicians, content- experts, methodologists and patient-partners ready to immediately convene and start the guidance creation once the need for new recommendations arises. All panelists will ensure availability and will meet WHO standards for freedom from conflict of interest. WHO will be responsible for nomination of clinical experts to ensure global representation in the context of their requirements for COVID-19 guidance, and MAGIC is responsible for nomination of patient-partners as well as the methodologists to support the guideline development process. WHO will nominate the clinical co-chair and MAGIC the methods co-chair for the GDG. The GDG will work on issuing the recommendations.

Step 5: Methods and processes for rapid recommendations
The GDG is committed to follow all standards for trustworthy guidelines and to utilize a transparent and systematic process to decide on the strength of recommendations - GRADE methodology *[7][8][9][10]*. These are detailed below (see "how is a trustworthy guideline made").

The GDG communicates via online teleconferences and e-mail exchange of written documents. Minutes from teleconferences are audio-recorded, transcribed, and stored for later documentation (available for peer-reviewers on request).

Teleconferences typically occur at three time points for BMJ Rapid Recommendations, with circulated documents by e-mail in advance:
- At the initiation of the process to provide feedback on the scope of the guideline. The panel will receive a document with the proposed clinical question to be answered by trustworthy recommendations, in the format of PICO questions (e.g. selection of patient-important outcomes) with particular emphasis on need for subgroup analysis (from the living effectiveness and harms systematic review), baseline risk estimates for risk stratification of patients (determining the need for prognosis review) and values and preferences (determining need for surveys, systematic reviews or other evidence sources).
- At the evidence summary stage, with discussion, feedback and agreement on draft GRADE evidence profiles prepared by the clinical co-chair and the methods co-chair, with support from methodologists, based on the living systematic review and baseline risk data.
- At the recommendation formulation phase, with discussion, feedback and agreement on draft recommendations and other content underlying the recommendation (e.g. GRADE SoF-table, key information, rationale, practical advice)

Following the last teleconference, the final version of the recommendations will be circulated by e-mail specifically requesting feedback from all panel members to document agreement before submission. Additional teleconferences are arranged as needed. Given the need for increased speed in providing timely COVID-19 guidance one teleconference may be sufficient, covering the two last steps after agreeing on the scope, question formulation and needs from the systematic review(s) through e-mail and written feedback on documents.

Step 6: Dissemination of evidence synthesis and rapid recommendations
The remdesevir guideline is published as a BMJ Rapid Recommendation, together with the living systematic review and network meta-analysis published in the BMJ. For the subsequent COVID-19 guidance on drug treatments performed in a collaboration between MAGIC and WHO we plan multiple publications from this process with guidance from WHO and from the BMJ Rapid Recommendations distributed globally to allow widespread uptake, re-use and adaptation. These publications include:
- A publication of one or more systematic reviews in BMJ journals, according to previous BMJ Rapid Recommendations, where these are directly linked to the guideline publications.
- The publication of the rapid recommendation in a coordinated manner between WHO and MAGIC.
  - WHO will be responsible solely for the publication via WHO's website.
  - MAGIC will be responsible for publication in the BMJ according to their established BMJ Rapid Recommendations processes. Here MAGIC will abide by WHO requirements; WHO will receive the draft publication for comments in the peer-review and proofing phase to approve formulations of relevance to WHO, including their role and contributions in the guideline development.

- MAGIC (and WHO, pending signed contract) will publish the guideline content through MAGICapp, an online authoring and publication platform which provides recommendations and all underlying content in digitally structured multilayered formats for clinicians and others users and stakeholders, including those who wish to create national or local adaptation of the recommendations.

Step 7: Living guidance
WHO Guidance for COVID-19 on drug treatments is intended to become living guidance, with a commitment to publish updated recommendations based on need of new and practice-changing evidence emerging after the first recommendations published. To achieve this the living NMA produced by MAGIC, will inform the Steering committee to trigger evidence synthesis and development of rapid recommendations on a systematic basis according to need arising in the global community *[4]*. These updates will be decided ultimately by the GDG.

BMJ Rapid Recommendations is also planned to represent living guidance, with MAGIC responsible for the process of triggering updates, in a coordinated process with WHO, through the steering committee (step 2).

How is a trustworthy guideline made?

The Institute of Medicine (IOM)'s issued guidance on how trustworthy guidelines should be developed and articulated key standards as outlined below *[7]*. The standards are similar to those developed by the Guideline International Network (G-I-N) as well as WHO *[8]*. These standards have been widely adopted by the international guideline community. Peer reviewers of the recommendation article are asked whether they found the guideline trustworthy (in accordance with IOM standards). Here we outline how we hope to meet the standards (in italics) for our WHO/ BMJ RapidRecs:

1. Establishing transparency
"The processes by which a CPG is developed and funded should be detailed explicitly and publicly accessible."
This method is available and published as a supplementary file as well as in MAGICapp where all recommendations and underlying content is available. We ask the peer-reviewers to judge whether the guidance is trustworthy and will respond to concerns raised.

2. Managing conflicts of interest
"Prior to selection of the guideline development group, individuals being considered for membership should declare all interests and activities potentially resulting in COI with development group activity."
Interests of each panel member are declared prior to involvement and published with the rapid recommendations. No one with any potential financial interests in the past three years, or forthcoming 12 months will participate - as judged by the panel clinical chair and methods co-hair, WHO, The BMJ RapidRec Executive Committee and the BMJ. No more than two panel members have declared an intellectual conflict of interest. Such conflicts include having taken a position on the issue for example by a written an editorial, commentary, or conflicts related to performing a primary research study. The co-chairs must content expertise (clinical and methodological) and strictly no financial or intellectual interests. Funders and pharmaceutical companies will have no role in these recommendations.

3. Guideline development group composition
"The guideline development group should be multidisciplinary and balanced, comprising a variety of methodological experts and clinicians, and populations expected to be affected by the CPG."
The GDG will include representation from every major geographic region in the world, with specific efforts made to achieve gender-balance. We will facilitate patient and public involvement by including patient experience, via patient-partners and systematic reviews addressing values and preferences to guide outcome choices and relative weights of each outcome, where available. Patient-partners will be given priority during panel meetings and will have an explicit role in vetting the panel's judgements of values and preferences.

4. Clinical practice guideline - systematic review intersection
"CPG developers should use systematic reviews that meet standards set by the IOM. The Guideline development group and systematic review team should interact regarding the scope, approach, and output of both processes."

Each rapid recommendation will be based on the living, high-quality systematic review and network meta-analysis and published in parallel with our BMJ Rapid Recommendations. The GDG and systematic review teams will interact, with up to three members participating in both teams to facilitate communication and continuity in the process.

5. Establishing evidence foundations for and rating strength of recommendations
"For each recommendation: explain underlying reasoning, including a clear description of potential benefits and harms, a summary of relevant available evidence and description of the quality., explain the part played by values, opinion, theory, and clinical experience in deriving the recommendation, "provide rating of strength of recommendations."

The GRADE approach will provide the framework for establishing evidence foundations and rating strength of recommendations. For each recommendation systematic and transparent assessments are made across the following key factors:
- Absolute benefit and harms for all patient-important outcomes through structured evidence summaries (e.g. GRADE Summary of Findings tables)*[10]*;
- Quality of the evidence*[13]*

- Values and preferences of patients
- Resources and other considerations (including considerations of Feasibility, Applicability, Equity)
- Each outcome will - if data are available through systematic reviews - include an effect estimate and confidence interval, with a measure of certainty in the evidence, as presented in Summary of Findings tables. If such data are not available narrative summaries will be provided.
- A summary of the underlying reasoning and all additional information (e.g. key factors, practical advice, references) will be available online in an interactive format in MAGICapp.*[15]* This summary will include descriptions of how theory (e.g. pathophysiology) and clinical experience played into the evidence assessment and recommendation development.
- Recommendations will be rated either weak or strong, as defined by GRADE.*[14]* If the panel members disagree regarding evidence assessment or strength of recommendations, we will follow a structured consensus process customized to the GRADE system and report any final differences in opinion, with their rationale, in the online supplement and online in MAGICapp.

6. Articulation of recommendations

"Recommendations should be articulated in a standardized form detailing precisely what the recommended action is, and under what circumstances it should be performed, and so that compliance with the recommendation(s) can be evaluated."

Each BMJ Rapid Recommendation will appear at the top of the guideline infographic, published in the BMJ, and will be available in standardised formats in MAGICapp, articulated to be actionable based on best current evidence on presentation formats of guidelines.*[15]* There will be a statement included in each summary article in The BMJ and in the MAGICapp that these are recommendations to provide clinicians with guidance. They do not form a mandate of action and should be contextualised to healthcare systems, the environment clinicians work in, and or with an individual patient.

WHO Guidance will articulate recommendations according to their requirements and standards, as detailed in upcoming guideline recommendations performed in the WHO-MAGIC collaboration on COVID-19 drug treatments.

7. External review

"External reviewers should comprise a full spectrum of relevant stakeholders...., authorship should be kept confidential....., all reviewer comments should be considered....a rationale for modifying or not should be recorded in writing.... a draft of the recommendation should be made available to general public for comment..."

The remdesevir guideline underwent comprehensive peer-review as for previous BMJ Rapid Recommendations. For BMJ Rapid Recommendations on COVID-19 to come the BMJ has now established a standing peer-review committee to further increase speed in the process following submission, administered by the BMJ. These peer-reviewers have approved of the protocol for the WHO/BMJ Rapid Recommendations project, as well as the living systematic reviews on effectiveness and prognosis. At least two external peer-reviewers and one patient reviewer will review the article for The BMJ within 1 week and provide open peer review. Each will have access to all the information in the package. They will be asked for general feedback as well as to make an overall judgement on whether they view the guidelines as trustworthy.

In addition, a BMJ series adviser with methodological and/or statistical expertise will review the BMJ Rapid Recommendations protocols in advance of the project, as well as the submitted scientific papers. The panel will be asked to read and respond to the peer review comments and make appropriate modifications.

The BMJ and COVID-19 Collaboration Steering Group may, on a case-by-case basis, choose to invite key organizations, agencies, or patient/public representatives to provide and submit public peer-review. A post-publication public review process will provide a forum for comments and feedback through MAGICapp and through the BMJ. The co-chairs will, on behalf of panel authors, respond to each publicly-available peer-review within 30 days, for a period of six months after publication.

WHO Guidance: The WHO will follow their process for review and clearance, as detailed in subsequent guideline recommendations.

8. Updating

"The date for publication, systematic review and proposed date for future review should be documented, the literature should be monitored regularly and recommendations updated when warranted by new evidence"

The BMJ RapidRecs and WHO Guidance for COVID-19 represent living guidance, with a commitment to publish updated recommendations based on new and practice-changing evidence emerging after the first recommendations published.

To achieve this the GDG panel will, through the living NMA and through monitoring of new research evidence for published BMJ Rapid Recommendations and WHO Guidance aim to provide updates of the recommendations within few weeks of trigger study publication. These updates will be initially performed in MAGICapp and submitted to The BMJ for consideration of publication of a new Rapid Recommendation. WHO will follow their internal processes for review and clearance before publication.

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