

## Producing and using timely comparative evidence on drugs: key lessons from more than a thousand clinical trials on COVID-19 therapeutics

Huseyin Naci,<sup>1</sup> Aaron S. Kesselheim,<sup>2</sup> John-Arne Røttingen,<sup>3,4</sup> Georgia Salanti,<sup>5</sup> Per O. Vandvik,<sup>6</sup> Andrea Cipriani<sup>7,8</sup>

1. Department of Health Policy, London School of Economics and Political Science, London, UK
2. Program On Regulation, Therapeutics, And Law (PORTAL), Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA
3. Research Council of Norway, Oslo, Norway
4. Blavatnik School of Government, University of Oxford, Oxford, UK.
5. Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland
6. Department of Health Management and Health Economics, University of Oslo, Oslo, Norway
7. Department of Psychiatry, University of Oxford, Oxford, UK
8. Oxford Health NHS Foundation Trust, Warneford Hospital, Oxford, UK

**Standfirst:** *Research on COVID-19 therapeutics has exposed the persistent flaws and failures of the evidence ecosystem. Producing robust comparative evidence on drugs and translating it to trustworthy and timely guidance requires greater coordination and collaboration among trialists, meta-analysts, guidance-developers and other key stakeholders.*

Since the early days of the novel coronavirus outbreak, a record number of studies have been launched to test several repurposed and new medicines as potential therapeutic options for COVID-19.<sup>1</sup> According to an analysis by the news organisation STAT, over a thousand clinical trials were registered on ClinicalTrials.gov between January and June 2020.<sup>2</sup>

This is a testament to the research and clinical community's commitment to identify effective treatments for COVID-19. However, the large volume of studies may paradoxically limit the generation of robust evidence and complicate the formulation of trustworthy guidance and decisions related to drug use if the current research is duplicative and redundant or produces conflicting data.<sup>3-5</sup> Indeed, the multiplicity of research on candidate therapeutics for COVID-19 has exposed important flaws and failures in the current evidence ecosystem.<sup>6,7</sup> Crucially, these limitations are not specific to research on COVID-19 therapeutics and closely resemble problems that persist across the full spectrum of research on new health technologies.<sup>8,9</sup>

Users of evidence across the health care system (patients, clinicians, health technology assessment bodies, guideline developers, payers) need timely data on how different treatments compare to each other in terms of their benefits and harms – their comparative effectiveness. Producing comparative evidence and ensuring its rapid translation into trustworthy guidance requires extensive coordination and collaboration between the researchers conducting clinical trials, those conducting comparative effectiveness assessments and those producing guidance.<sup>8,9</sup> In this *Analysis* article, we document the limitations of COVID-19 clinical trials, explore the extent of collaboration to date, and outline several key areas for improvement.

### Limitations of research on COVID-19 therapeutics

Three main limitations have characterised the system for evaluating repurposed or investigational therapeutics for COVID-19. First, global clinical research activity is fragmented. Drug trials rarely have similar design features. For example, study endpoints have been shown to

be highly heterogeneous.<sup>10</sup> Only a small minority of late-stage RCTs measure all-cause mortality.<sup>11</sup> Even when RCTs evaluate seemingly similar endpoints such as time to clinical recovery, outcome definitions and follow-up durations vary.

Second, the research agenda appears to be partly driven by hype and anecdote rather than informativeness and social value,<sup>12</sup> skewing the amount of available data. For example, a disproportionately large number of studies have been launched to evaluate the anti-malarial agents hydroxychloroquine and chloroquine phosphate after the publication of a controversial uncontrolled study, which received significant attention.<sup>13</sup> About one in every six studies registered on ClinicalTrials.gov has focused on one of these anti-malarial agents.<sup>2</sup>

Third, studies have not routinely adopted robust designs. By our own estimate, fewer than one third of studies evaluating COVID-19 therapeutics on ClinicalTrials.gov are RCTs, which are the gold standard for evaluating treatments.<sup>14</sup> By contrast, many studies test investigational agents without a control group.<sup>15</sup> These single-arm studies can be misleading as they provide no data on what would have happened in the absence of the treatment.

The combination of these factors has fuelled confusion and sensationalism. Psychological distress and anxiety have increased in the general population.<sup>16</sup> Findings of individual studies are watched closely and with suspense. Doing “science by press release” – publicising study findings before they are shared as preprints or published in peer-reviewed journals – has become common. Health care professionals have not been immune to hype. During the early days of the pandemic, there were reported shortages of hydroxychloroquine driven by clinicians’ prescriptions after these products were hailed as potential breakthroughs.

Even regulators have been under pressure to act without sufficient evidence.<sup>17,18</sup> In the US, Food and Drug Administration (FDA) granted Emergency Use Authorization (EUA) for hydroxychloroquine on the basis of no solid data suggesting an effect in patients with COVID-19. FDA later revoked its EUA for hydroxychloroquine after evidence from RCTs failed to demonstrate any benefits. The European Medicines Agency (EMA) granted a conditional marketing authorisation for remdesivir on the basis of “non-comprehensive” data, and without access to clinical study reports.<sup>19</sup>

### **Progress on research coordination and collaboration**

There are existing mechanisms for global research coordination during public health emergencies. Initiatives such as the Global Research Collaboration for Infectious Disease Preparedness (GloPID-R),<sup>20</sup> established in 2013 after agreement by the Heads of International (biomedical) Research Funding Organisations, and WHO’s R&D Blueprint,<sup>21</sup> which originated after the Ebola outbreak in 2014-2016, are platforms for collaboration. New models are also emerging. The G20 countries together with WHO have established the Access to COVID-19 Tools (ACT) Accelerator, a global collaboration to accelerate the development, production and equitable access to new diagnostics, therapeutics and vaccines.<sup>22</sup>

These efforts have already paid off. Several large RCTs have been launched in record speed. Many of these compare multiple treatment alternatives simultaneously. Three of the largest ‘mega’ trials – the SOLIDARITY trial led by WHO, DISCOVERY initiated by Inserm in France and RECOVERY trial in the UK – have comparable protocols (including their simple, pragmatic, and adaptive designs) and collect data on similar endpoints (including death and need for ventilation). UK’s RECOVERY trial has recruited over 12,000 patients, accounting for 15% of those hospitalised with COVID-19 across the National Health Service.<sup>23</sup> Some of the most important insights about candidate therapeutics have emerged from RECOVERY, including the meaningful survival benefit associated with using dexamethasone among severely ill patients.<sup>24</sup> The SOLIDARITY trial, of which DISCOVERY is an add-on daughter trial, has included more than 7,000 patients across more than 20 countries from different regions of the world and is the largest trial that can now follow the pandemic where it is globally most active.

However, efforts to date have not managed to avoid research waste and ensure that all relevant studies contribute to the formulation of guidance and decisions in practice and policy.<sup>25</sup> Most studies on COVID-19 treatments suffer from methodological limitations (e.g. small studies, diverse designs and outcomes).<sup>26</sup> Therefore, a sizeable portion of studies collectively including thousands of patients may have little prospect to add to the growing evidence base on efficacy.

## Key areas for improvement

Determining the comparative effectiveness of drugs requires streamlining the design, analysis, reporting and data sharing practices of clinical studies. These objectives are not new but progress towards achieving them has been slow.<sup>25,27,28</sup> Despite the availability of several large multi-arm trials, most research on COVID-19 therapeutics is not fit for generating comparative evidence. We outline five priority areas for greater collaboration and coordination among trialists, meta-analysts, guideline developers and other stakeholders to facilitate producing and using trustworthy comparative evidence and guidance. These are also relevant to studies evaluating other types of interventions including supportive care and non-drug interventions.

### 1. *Selecting treatments to include in large trials*

Key trials differ in which treatments they included (**Table**), reflecting a lack of consensus on the most promising therapeutic candidates. Therefore, treatment selection even in large trials has not been fully complementary. For example, hydroxychloroquine was included in both RECOVERY and SOLIDARITY. By contrast, dexamethasone, the first agent that demonstrated a convincing survival benefit among hospitalised patients in the RECOVERY trial, was not included in some other ‘mega’ trials.

Evidence-based approaches to select treatments are emerging. For example, UK has launched ACCORD (Accelerating Covid-19 Research and Development), which is an adaptive platform study comprising almost 50 small RCTs of candidate agents for further testing in RECOVERY. In addition to conducting such *de novo* trials, evidence synthesis methods would provide an opportunity to learn from a fast-evolving body of research. Using network meta-analyses could reach conclusions on which treatments to test in larger trials more efficiently than other approaches.<sup>29</sup> Network meta-analyses could also be used to compare the safety of many repurposed products based on their historical data in other conditions. For example, safety of remdesivir was evaluated during the Ebola outbreak.<sup>30</sup> Using aggregate, trial-level data in network meta-analyses would provide sufficiently valid results when prioritising which treatment candidates to pursue in larger studies.<sup>31</sup> As a first step, WHO’s therapeutic landscape analysis could serve as a centralised global repository of the most promising molecules, and could be complemented with network meta-analyses of available data to guide rational prioritisation of candidate treatments.<sup>32</sup>

### 2. *Streamlining trial designs*

Harmonising RCTs in terms of their outcome measures is a prerequisite for their inclusion in comparative effectiveness assessments. Users of evidence have a key role in defining and prioritising outcome measures. There is some consensus that all-cause mortality and respiratory support use are the preferred core outcomes in the severe stages of COVID-19.<sup>33</sup> However, the availability of several core outcome sets has complicated efforts to streamline trial designs.<sup>34</sup>

Ensuring that future trials collect data on one set of core outcomes will depend on collaboration from diverse stakeholders. WHO has played an important role by convening experts for the development of model protocols, clinical reporting forms, and endorsing a set of core outcomes that are relevant to different stages of the disease (pre-exposure prophylaxis, post-exposure prophylaxis, early treatment, hospitalisation, intensive care, post-hospitalisation)<sup>35</sup>

and may span across different areas of medicine (for instance, long term effects of COVID-19 include medical, psychological and rehabilitation needs).<sup>36</sup>

Research funders, ethics review boards and clinical trial approval authorities should require the adoption of core outcomes in protocols. Streamlining regulatory and health technology assessment guidance across different settings would also help. In its conditional marketing authorisation of remdesivir in June 2020, EMA acknowledged the lack of “regulatory guidance or precedent specifying a particular preferred primary endpoint” for COVID-19 therapeutics.<sup>19</sup> FDA, EMA, and health technology assessment bodies should produce joint guidance and provide parallel advice on the trial protocols of candidate therapeutics.

### 3. *Sharing data*

Benefits of timely access to data from clinical trials are widely accepted. Such data could be re-analysed and combined with data from other studies to determine comparative effectiveness. Individual participant data could also identify subgroups of patients with differential responses to treatments, exploring characteristics that modify effectiveness and thus explain contradictory findings. While data sharing after trial completion is becoming more common, and several funders of health research are committed to this goal,<sup>37</sup> data sharing practices are still not the norm. According to ClinicalTrials.gov, Gilead has no plans to release data from its phase 3 trials of remdesivir (NCT04292730 and NCT04292899).

Sponsors’ transparency and data sharing practices should be periodically monitored and publicly reported.<sup>38</sup> Academic institutions should make data sharing an explicit criterion for promotion and tenure.<sup>39</sup> All trial sponsors, including industry, should pledge to share data rapidly through one of the existing platforms (e.g., Infectious Diseases Data Observatory). *Post hoc* requests for data are associated with poor retrieval rates in meta-analyses.<sup>40</sup> Therefore, data sharing plans and agreements should be finalised in advance. Ideally data sharing should accompany trial publication. When this is not feasible, data sharing should be prioritised for groups or institutions with plans to conduct comparative effectiveness assessments. New models of data sharing could also improve trial efficiency. For example, real-time data sharing across ongoing trials could provide early identification of efficacy and safety signals. However, such practices may be challenging since they may override the integrity of individual trials, and should therefore be agreed in advance and reflected in protocols.

### 4. *Assessing comparative effectiveness*

No single RCT can compare the efficacy of all potential candidate therapeutics for COVID-19. Inevitably, indirect comparisons across trials will generate evidence on the comparative benefits and harms of different products. Several groups are working in parallel to identify trials and pool results in network meta-analyses as they emerge.<sup>41,42</sup> Such ‘living’ syntheses could provide useful evidence, but even small differences in study eligibility criteria and analytic strategies may yield conflicting results,<sup>43</sup> which may delay the development of trustworthy guidance. It is therefore essential to coordinate ongoing activities, pool resources across groups, and minimise duplication.

A consortium should coordinate the design, implementation, and replication of comparative effectiveness assessments ideally using individual participant data network meta-analyses. A network of leading independent research organisations,<sup>44</sup> regulatory agencies, health technology assessment bodies, and payers could lead this effort in collaboration with WHO. A recent health technology assessment of biologic agents for rheumatoid arthritis in Germany has demonstrated the feasibility of this approach. The Institute for Quality and Efficiency in Health Care (IQWiG) requested re-analysis of individual participant data from several industry-sponsored RCTs to harmonise patient populations and primary endpoints before findings could be combined in network meta-analyses.<sup>45</sup>

Timing of when comparative data become available is critical. As there is an ethical imperative for any treatment with promising results to immediately become the new standard of care (as occurred with dexamethasone, and to a lesser extent remdesivir, in severely-ill patients with COVID-19), comparative assessments should ideally accompany the publication of individual trial results. This would allow for interpreting individual study results within their broader context and dramatically increase speed in updating guidance for policy and practice.

Prospectively designing comparative effectiveness assessments would balance speed with rigour. Pre-planning network meta-analyses would require establishing a close collaboration between trialists and meta-analysts.<sup>46</sup> At a minimum, data from the trials with the most robust designs should be shared with third party researchers to conduct prospectively designed network meta-analyses. Such close collaboration would ensure that data completeness, standardisation, and quality issues are resolved in a timely manner, and results can be re-analysed and combined shortly after database lock.

#### 5. *Translating data into living and trustworthy guidance to inform policy and practice*

COVID-19 reveals an unprecedented need for developing living and trustworthy guidance based on comparative evidence, which is an ethical obligation.<sup>47</sup> Recent experience with Australia's National COVID-19 Clinical Evidence Taskforce illustrates how a comprehensive set of recommendations can be dynamically updated based on new practice-changing evidence, facilitated by innovative processes and digitally structured data in interoperable platforms (e.g., MAGICapp).<sup>48</sup> Such platforms allow for immediate global dissemination of recommendations, interactive evidence summaries and decision aids that are available for re-use, adaptation and implementation. WHO and prominent guideline development organisations are now moving towards producing such living guidance for COVID-19. Some are dedicated to share evidence and recommendations in a globally-concerted effort, aiming for three weeks from evidence to publication. *The BMJ's* 'Rapid Recommendations' on remdesivir illustrates how such global collaboration and iterative guidance development can work, informed by living network meta-analysis.<sup>42,49</sup> WHO guidance on corticosteroids for COVID-19 was developed in a similar way, adding a prospective meta-analysis of ongoing trials to the network meta-analysis (in press). The guideline panel convened two days after and created recommendations, demonstrating the value of close collaboration between trialists, meta-analysts and guideline developers. Global dissemination of WHO guidance was however delayed for 3 weeks, having to wait for publication of results in a scientific journal, underscoring remaining challenges.

### **Conclusions**

The evidence-based medicine movement has for decades challenged the primacy of individual studies. No single study can provide adequate evidence to inform therapeutic decisions in clinical practice. Information on the comparative benefits and harms of alternative treatments is imperative and can only be obtained from a synthesis of several studies. Producing and using timely, trustworthy, and actionable evidence requires designing, analysing, and reporting each study in a way that optimises its contribution to subsequent comparative effectiveness assessments. Progress to date has been too slow. However, COVID-19 highlights the pressing need and the opportunity to harness new collaborations among relevant stakeholders, including trialists, meta-analysts, regulatory agencies, health technology assessment bodies, and payers.

**Contributors and sources**

HN and AC devised the idea for this article. HN developed the first draft and all authors contributed to the writing of subsequent versions. HN is the guarantor.

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## Key messages box

- The record number of studies evaluating the effectiveness of repurposed and investigational drugs for COVID-19 has exposed important shortcomings in the evidence ecosystem.
- Despite the availability of several large multi-arm trials, evidence on the comparative effectiveness of potential therapeutic alternatives may not emerge in a timely manner.
- Producing comparative evidence on COVID-19 therapeutics and ensuring its rapid translation into trustworthy guidance will require greater coordination and collaboration among trialists, meta-analysts, and other stakeholders.

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**Table 1.** Five key areas in need of greater collaboration and coordination to generate and use comparative evidence on COVID-19 therapeutics.

<b>Domain</b>	<b>Recommendation</b>	<b>Concrete next steps</b>	<b>Target stakeholders</b>
1. Selecting treatments to include in large trials	Use network meta-analyses to learn from the fast-evolving body of evidence and reach conclusions on which treatments to test in larger trials	<ul style="list-style-type: none"> <li>• Complement WHO’s therapeutic landscape analysis with network meta-analyses of available data</li> </ul>	<ul style="list-style-type: none"> <li>• WHO</li> <li>• Research funders (including industry)</li> <li>• Research community (trialists and meta-analysts)</li> </ul>
2. Streamlining trial designs	Ensure that future trials collect data on core outcome measures	<ul style="list-style-type: none"> <li>• Streamline core outcome sets</li> <li>• Encourage (or mandate, where possible) use of core outcome sets in trials</li> <li>• Develop and communicate regulatory and health technology assessment guidance on preferred trial designs</li> </ul>	<ul style="list-style-type: none"> <li>• WHO</li> <li>• Research funders (including industry)</li> <li>• Ethics committees</li> <li>• Regulatory agencies (e.g., FDA, EMA)</li> <li>• Health technology assessment bodies (e.g., NICE)</li> <li>• Research community (trialists and meta-analysts)</li> </ul>
3. Sharing data	Share individual participant data in a timely manner	<ul style="list-style-type: none"> <li>• Monitor and publicly report data sharing practices of all trial sponsors</li> <li>• Incentivise (or mandate, where possible) data sharing</li> <li>• Prioritise sharing trial data with researchers planning to conduct comparative effectiveness assessments</li> </ul>	<ul style="list-style-type: none"> <li>• WHO</li> <li>• Research funders (including industry sponsors)</li> <li>• Ethics committees</li> <li>• Regulatory agencies</li> <li>• Academic institutions</li> <li>• Research community (trialists and meta-analysts)</li> </ul>
4. Assessing comparative effectiveness	Pre-plan and conduct individual participant data network meta-analyses shortly after trial completion	<ul style="list-style-type: none"> <li>• Minimise (or eliminate, if possible) duplication across multiple groups planning comparative effectiveness assessments</li> <li>• Develop a consortium of researchers, regulatory agencies, health technology assessment bodies, and payers, convened by WHO</li> </ul>	<ul style="list-style-type: none"> <li>• WHO</li> <li>• Research funders (including industry sponsors)</li> <li>• Ethics committees</li> <li>• Regulatory agencies</li> <li>• Academic institutions</li> <li>• Non-profit organisations (e.g., Cochrane)</li> </ul>

		<ul style="list-style-type: none"> <li>• Prospectively design network meta-analyses in collaboration with trialists to ensure timely availability of results shortly after trial completion</li> </ul>	<ul style="list-style-type: none"> <li>• Research community (trialists and meta-analysts)</li> </ul>
5. Transforming data into guidance to inform policy and practice	Use comparative evidence to generate rapid, living and trustworthy guidance	<ul style="list-style-type: none"> <li>• Use interoperable platforms to digitally structure comparative data for rapid dissemination of recommendations and development of interactive evidence summaries</li> </ul>	<ul style="list-style-type: none"> <li>• WHO</li> <li>• Interoperable evidence platforms (e.g., MAGICapp)</li> <li>• Guideline developers</li> <li>• Health technology assessment bodies</li> <li>• Non-profit organisations (e.g., Cochrane)</li> <li>• Scientific journals and publishers (e.g., <i>The BMJ</i>)</li> </ul>

**Table 2.** Therapeutics included in selected large trials.

<b>Trial name</b>	<b>Primary sponsors</b>	<b>Comparators (as of 20 July 2020)</b>	<b>Target sample size</b>
GS-US-540-5774	Gilead	<ul style="list-style-type: none"> <li>• remdesivir</li> <li>• standard of care</li> </ul>	1,600
GS-US-540-5773	Gilead	<ul style="list-style-type: none"> <li>• remdesivir</li> <li>• standard of care</li> </ul>	6,000
SOLIDARITY	WHO	<ul style="list-style-type: none"> <li>• remdesivir</li> <li>• lopinavir/ritonavir (discontinued)</li> <li>• lopinavir/ritonavir + interferon beta-1a (discontinued)</li> <li>• hydroxychloroquine (discontinued)</li> <li>• standard of care</li> </ul>	No specific sample size (target enrolment of several thousand participants)
DISCOVERY	Institut National de la Santé Et de la Recherche Médicale, France	<ul style="list-style-type: none"> <li>• remdesivir</li> <li>• lopinavir/ritonavir (discontinued)</li> <li>• lopinavir/ritonavir + interferon beta-1a (discontinued)</li> <li>• hydroxychloroquine (discontinued)</li> <li>• standard of care</li> </ul>	3,100
RECOVERY	UK Research and Innovation, UK National Institute for Health Research	<ul style="list-style-type: none"> <li>• lopinavir-ritonavir (discontinued)</li> <li>• dexamethasone (only children)</li> <li>• hydroxychloroquine (discontinued)</li> <li>• azithromycin</li> <li>• tocilizumab</li> <li>• convalescent plasma</li> <li>• standard of care</li> </ul>	12,500
PRINCIPLE	UK Office of the Chief Medical Officer	<ul style="list-style-type: none"> <li>• azithromycin</li> <li>• standard of care</li> </ul>	3,000
REMAP-CAP	Canadian Institutes for Health Research, European Commission, UK National Institute for Health Research, Health Research Council of New Zealand, Australian National Health and Medical Research Council	<ul style="list-style-type: none"> <li>• antibiotics</li> <li>• antivirals</li> <li>• host immunomodulation with extended macrolide therapy</li> <li>• corticosteroid regimens</li> <li>• hydroxychloroquine</li> <li>• hydroxychloroquine + lopinavir/ritonavir</li> <li>• interferon-<math>\beta</math>1a</li> <li>• anakinra</li> <li>• tocilizumab</li> <li>• sarilumab</li> </ul>	7,100

**Notes:** The DISCOVERY trial is nested in SOLIDARITY as a “daughter” trial, allowing for more detailed data collection than its more simple and larger “mother” trial.