Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Commentary

Repurposed drugs for COVID-19: threshold and proof requirements for trials

In the current issue of the journal Ader et al. report results for hydroxychloroquine and lopinavir/ritonavir with or without interferon-β-1a against coronavirus disease 2019 (COVID-19) from the DisCoVeRy randomized controlled trial [1]. The DisCoVeRy trial is a French-led add-on trial to the WHO Solidarity trial. Hospitalized patients could be included at any time after symptom onset, provided that they had not been previously treated with any of the study medications, and that a PCR test was positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) within 72 hours of enrolment. The trial targeted the recruitment of 620 patients in each treatment arm, but after the inclusion of about 145 patients per arm it was stopped for futility before reaching the formal futility stopping criteria defined in the trial's protocol. Patients were included at a median of 9 days after symptom onset; about 60% required low-flow supplemental oxygen and more than 40% were in the ICU when recruited. There was no advantage to any of the treatment arms—hydroxychloroquine for 10 days, lopinavir/ritonavir for 14 days, or lopinavir/ritonavir with three doses of subcutaneous interferon-β-1a—compared with the standard of care. A trend for worse outcomes, that reached statistical significance in few outcomes, was seen among patients randomized to lopinavir/ritonavir and interferon-β-1a. Serious adverse events were significantly more frequent in both lopinavir/ritonavir arms. Confidence intervals of the treatment effects were broad, and the trial was not powered to prove equivalence between standard of care and the different treatments. However, results are similar to the ones observed in the Solidarity trial (which recruited 954, 1411 and 651 patients to three arms: hydroxychloroquine, lopinavir/ritonavir and lopinavir/ritonavir with interferon-β-1a, respectively) [2], the results of the RECOVERY study (which included 1616 patients randomized to lopinavir/ritonavir) [3], and the results of 12 randomized controlled trials (RCTs) involving 8569 participants randomized to hydroxychloroquine [4,5].

The efforts invested in examining treatments with no effects raises the question of the threshold required to launch an RCT of a repurposed drug. Was there a justifiable scientific rationale for launching large RCTs to assess all the repurposed drugs that were assessed for COVID-19? Was there a need to randomize more than 4000 patients to lopinavir/ritonavir and more than 8000 to hydroxychloroquine? Wasted efforts were invested in many more trials with the same drugs that were planned, designed, even launched, but discontinued [6]. Conversely, the situation where individual physicians, most of whom were not specialized in infectious diseases, started using medications based on opinions, limited experience, social media, non-peer-reviewed publications and poorly conducted observational studies is unacceptable, because it provides false hopes and may harm patients [7]. Off-label use of repurposed drugs, provided probably to many millions globally, further inflated biased data on these medications, leading to poorly designed observational studies conducted by investigators with strong personal or commercial biases, many with the good and sincere intention of finding cure for this severe new disease. Clearly, RCTs are the only appropriate design to examine the effects of repurposed drugs, and these should be launched as soon as possible during a pandemic such as COVID-19. Thus, there is a fine line between futility and need for RCTs assessing repurposed drugs for COVID-19 or other pandemics.

We believe that there is a need for a structured preclinical pathway for repurposed drugs that will serve as a threshold for testing the most promising drugs in RCTs. Subsequently, the entry of the drug into clinical use for a new indication must be evaluated and approved by a regulatory body. Possible stages in the preclinical pathway of repurposing drugs for infections, prior to testing in RCTs and clinical use, are presented in Box 1.

Pre-existing research networks of platform trials have shown that they can be launched in real time in this pandemic. SOLIDARITY, DisCoVeRy and RECOVERY trials all started recruitment together (22nd March, 22nd March and 19th March 2020, respectively) and discontinued the lopinavir-based arm on 4th July, 29th June and 29th June 2020, respectively). Such networks should coordinate the interventions tested globally as part of the pathway for repurposed drugs to improve global research efficiency. The adaptive design of the trials allowed rapid introduction and removal of treatments into the trial's basic platform, responding to accumulating clinical data as in the case of the early discontinuation of the hydroxychloroquine and lopinavir/ritonavir arms of the DisCoVeRy trial. The trial registries informed researchers worldwide that these interventions are being tested in large network platform trials, obviating the need for small, single-centre trials. Replication is important for proof of effects [8]. Negative trials are important to prevent and stop the use of inefficient or even harmful drugs. Yet, there is a need for better preclinical assessment of the drugs to be tested in parallel—those with the highest likelihood of showing benefit—in these high-resource trials during pandemics of a lethal disease in order to prevent unnecessary replication.

Repurposed drugs are selected for clinical testing based on *in vitro* activity against the virus. Thus, virological outcomes are

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Box 1
Possible stages in the preclinical pathway of repurposing drugs for infections, prior to testing in randomized controlled trials (RCTs) and clinical use.

Provide a mechanism of action
In vitro assays, including reproducibility, dose–response, orthogonal, cellular and resistance selection testing. Requirements similar to the preclinical development of new molecules, except for the toxicity and pharmacokinetic assays
In vivo preclinical/animal studies demonstrating biological plausibility and relevant outcomes
Systematic review of clinical studies evaluating the repurposed drug for other, preferably similar, infections, if there are such studies
Define the stage of the disease where the drug might have an optimal effect regarding efficacy and safety

of minor interest in such trials, while the question of interest is the clinical effect. All the large trials examined primarily clinical outcomes (mortality in RECOVERY and the seven-point ordinal scale of the WHO), reporting secondarily on the virological outcome. The COVID-19 experience has taught us that despite having been approved for another indication, pharmacokinetics and safety should be monitored for the repurposing indication because unexpected harm may occur for the same drug that has been safe before, but is not any more for a different disease, specifically, an infection [6,7]. In the DisCoVeRy trial, higher than expected drug levels of lopinavir were observed, possibly underlying the higher rate of adverse event events (specifically kidney injury) in the lopinavir-containing arms compared to the control arm [1]. Gastrointestinal adverse events were more common with lopinavir–ritonavir compared to standard of care in another small RCT [9]. Drug levels were not measured in the SOLIDARITY and RECOVERY trials, and monitoring of adverse events in these trials was sparse.

Finally, a word on medical journal editors' responsibility during the COVID-19 pandemic and future such events. Being the first to publish on a disease and on its treatment is attractive to journals, but this should be left to standard journalism. Medical journals should be attracted to evidence-based medicine. Even in pandemics, and especially in pandemics, the rigour of evaluating the quality of studies published needs to be maintained. Publication of poorly conducted studies claiming effects in peer-reviewed journals has many negative consequences: it misdirects patients' treatment, leads to wasted research efforts, affects trust in science, and delays the public health implementation of needed scientific measures to end the pandemic. During this pandemic we hope to have learned more on the positive and negative impacts of medical journals, as well as on the importance of effective clinical research and evidence-based medicine for the optimal management of this ongoing and future emerging events.

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