Strengthening research on COVID-19 during the pandemic

A Communiqué of the InterAcademy Partnership (IAP)

The unprecedented scope and scale of research during the COVID-19 pandemic has been of very great importance in understanding the genetic structure, pathophysiology and epidemiology of the virus, improving public health preparedness and responsiveness. Such knowledge has provided evidence to develop novel interventions. However, whilst there have been major advances in knowledge, it is apparent that not all COVID-19 research has been of a high enough quality to meaningfully inform understanding and action. There have been significant failures associated with the clarity of the research question, poor quality study design and conduct, and in the review, reporting and use of outputs. Poor quality research wastes resources, increases risks to patients, and can distort decision-making and public perceptions.

In this Communique, IAP urges the scientific community to learn from research inadequacies and failures, particularly those pertaining to unproven interventions with consequences for medical practice and the research record. In seeking to raise awareness of the challenges, IAP reaffirms its guidance for ensuring responsible and reproducible research and the need now to build on the examples of good COVID-19 research practice worldwide. Strengthening COVID-19 collaborative research can also capitalise on opportunities to involve the public, particularly from vulnerable groups, as participants and in co-designing research, and to share patient data for research worldwide and increase the proportion of studies on treatments for early-stage disease and their delivery in the community setting. There is also urgent need to strengthen research in ways that are responsive to rapidly emerging concerns.

1. Introduction

The COVID-19 pandemic presents extraordinary global challenges but has also stimulated a rapid and massive mobilisation of the research community. Research has already made considerable progress in identifying what is different about this coronavirus and its unfolding epidemiology and in providing the knowledge to deliver clinical care, including novel interventions – diagnostics, therapeutics and vaccines – at an unprecedented rate and scale. Demonstrably, large-scale, high-quality clinical trials have been performed expeditiously and ethically to yield reliable and useful results (Aronson et al. 2020, Anon 2020a).

In previous Communiques (IAP 2020a,b), IAP has welcomed the tremendous commitment to COVID-19 research, driven by global collaboration and sharing, delivering hugely positive impacts but also cautioned that problems can arise when conducting research in an emergency. In order to realise the public health benefits of innovation, it is essential not to cut corners in addressing efficacy and safety.

Inevitably, in the COVID-19 emergency there are uncertainties in the information available and definitive evidence – that is ascertainable, replicable, transferable and predictable (Rutter et al., 2020) – for decision-making, may be lacking. Acknowledging uncertainties is important, both for public trust and robust policy making (Davey Smith et al., 2020). While it is essential to act swiftly in the pandemic using evidence from research, how much research is enough? Emergencies accelerate the challenges for evidence-based policy and practice such that evidence collection, translation, decision-making and implementation of interventions must proceed simultaneously (Lancaster et al., 2020).

2. What are the concerns for research quality?

Unfortunately, a significant amount of COVID-19 research has been of inadequate quality for guiding clinical and public health decisions and tended to amplify deficiencies that were already present in the research environment. These failures provide important lessons for the future (Anon, 2020b).

Even before the pandemic, it had been estimated that a significant proportion of clinical research was wasted because of poorly defined research questions, poor study design, inefficiency of trial conduct and poor

reporting of results (Glasziou and Hoffmann, 2020). Some COVID-19 investigators had never conducted research before in patients with respiratory infections and were not embedded in research networks with the requisite expertise to deliver high-quality trials (Dobler, 2020). There has been a considerable imbalance in the choice of trial topics. For example, only a small proportion have focused on non-drug interventions (Glasziou and Hoffmann, 2020) or in the community setting. Many trials were too small. Many of the underpowered trials of COVID-19 treatments and a large number of the retrospective studies attempted to answer similar questions (Anon, 2020b). Underpowered trials may have been encouraged by fragmented clinical research and health care systems in some countries.

Some large-scale pilot studies had no published protocol, no clear comparator and no clear endpoint. A majority of COVID-19 controlled pharmacological intervention trials have not been adequately blinded (for patient and investigator) (Aronson et al. 2020). Furthermore, trials of non-pharmacological interventions have been even weaker, relying largely on retrospective studies and unvalidated mathematical models. Major programmes have been introduced in some countries without independent evaluation. Poor quality trials waste participants' and investigators' time, and biased results can distort decision-making, public perceptions, and the standing of medical research more broadly (Aronson et al., 2020). Inadequate research design has incurred large public health and economic costs (for example, Gill and Gray, 2020).

In order not to risk undermining the response to the pandemic and preparedness for future pandemics, it is vital to learn the lessons from COVID-19 research failures. Research failure can be compounded by failure in the appropriate evaluation of vital statistics to inform policy and practice. Although uncertainty is inevitable during a pandemic, it can be reduced by deploying standards for collective scrutiny and transparency of data (Rutter et al, 2020; Davey Smith et al., 2020). For example, in some countries, data uncertainties may have been downplayed because researchers had dual roles in generating data on disease progression from modelling and in advising decision-makers on the use of such data (Peare, 2020). A solution depends on greater clarity about methods by which expert consensus is achieved.

2.1 Unproven interventions

Many of the concerns are exemplified by problems arising in identifying and validating novel interventions. There has been widespread use of interventions based on inadequate evidence, often used at large scale and attributable in some cases to vested commercial or political interests. In addition to generating concerns for patient safety, pursuing unvalidated approaches delays or prevents adequate evaluation in well-controlled studies and may also prevent patients from getting treatments that have more proven value. The list below includes examples of approaches where there is no convincing evidence for effectiveness from adequately powered trials and of those where the evidence is currently inadequate.

Chloroquine and hydroxychloroquine. Cell studies in vitro indicated efficacy against SARS-CoV-2 which, together with early clinical claims, engendered significant public and political enthusiasm for these treatments, despite the known potential for cardiotoxicity. However, systematic review of the clinical literature on COVID-19 (Alexander et al., 2020) found that the research methodology was very poor – including problems of inadequate powering, inadequate attention to patient-important outcomes and poor reporting. The FDA revoked its emergency use authorization in June 2020 and the European Medicines Agency[l] concluded from large randomised trials (Solidarity and Recovery) that there were no beneficial effects.

Remdesivir. Initial promising results (Grein et al., 2020) came from an international study lacking a control group. Remdesivir was the first anti-viral drug fully licensed for the treatment of COVID-19. However, pooling data from the Solidarity trial[l] with other randomised controlled trials showed that, at best, there was only a small effect on deaths in hospitalised patients (Dal-Re et al., 2020). One lesson to be learnt is the importance of patient selection: anti-viral drugs might work best in primary care and community settings but are less likely to do so in late-stage disease in hospital settings.

Ivermectin. Inhibition of SARS-CoV-2 in vitro was seen at high concentrations and some pilot clinical studies produced encouraging results. However, the latest US government assessment (2021) has determined that there

l www.ema.europa.eu, accessed 26 January 2021. The Solidarity trial was organised by WHO and partners, see "Global research on coronavirus disease COVID-19, www.who.int, accessed 26 January 2021.

are insufficient data to recommend Ivermectin. Clinical data from several trials were judged to be contradictory or inconclusive and most of the study reports lacked information or exhibited significant methodological limitations. The weaknesses included small sample sizes, variable dosage, open label randomisation, variability in concomitant medications, insufficient description of COVID-19 severity, and lack of definition in study outcomes. Adequately powered high quality trials of ivermectin in early disease are urgently required.

Convalescent plasma. This has a long history of use in other infectious diseases. Following suggestions of benefit from observational studies, convalescent plasma was given to large numbers of COVID-19 patients in the USA under the FDA's expanded access treatment protocol. However, the PLACID trial, a rigorous, randomised controlled study in India, concluded there was no clinical benefit (Pathak, 2020) and raised some important issues for design of such trials in terms of safety monitoring (particularly for thrombotic events) and for the need to ensure that the plasma used had detectable titres of neutralising antibodies. Whether or not convalescent plasma is useful for COVID-19 is still under investigation, for example in the large-scale UK NHS-based Recovery and REMAP-CAP trials (www.recoverytrial.net, www.remapcap.org). However, the Recovery trial has now closed recruitment to the convalescent plasma arm (15 January 2021) and the independent Data Monitoring Committee saw no convincing evidence that would provide conclusive proof of worthwhile mortality benefit.

Stem cells. Similar considerations apply as for other therapeutic approaches: any use must be based on rigorous evidence of safety and efficacy, following stringent research protocols, that consider the ethical issues and characterise the stem cells used, focusing on a defined stage of the disease and in the hands of a team with capacity and validity to undertake the intervention. Unfortunately, as the FDA has observed (Marks and Hahn, 2020), some of the same clinics that have been offering unproven stem cell therapies for diverse conditions are now offering unproven treatments for the complications of COVID-19. There is additional concern if such approaches are used outside of the regular hospital setting, in that unproven claims for efficacy may encourage purchasers to refrain from taking other steps (such as social distancing) to protect themselves and others from COVID-19. While the early claims are premature and risk undermining confidence in regenerative medicine approaches, it remains the case that well-designed initial experimental medicine studies (e.g. Lanzoni et al. 2021) can form a starting point for larger, collaborative trials designed to evaluate efficacy.

2.2 Publication of results

A systematic review of initial COVID-19 clinical studies (Jung et al., 2021, albeit itself not yet peer-reviewed) indicated that such studies were accepted more quickly and were found to be of lower methodological quality than other studies published in the same journal. Poorly-designed studies are being published, even in major journals, because they address an important question, though methodologically flawed and with concomitant issues for lack of ethical approval (Bundgaard et al., 2020, discussed by an international group of experts[II]). One measure of the problems created by publishing inadequate research is the extent of retracted articles. Concern has been expressed (Arbritis et al., 2020) that the rate of COVID-19 article retractions is exceptionally high but more monitoring is needed to compare rates of retraction (and reasons for retraction)[III].There have been entirely understandable pressures to publish fast, often as pre-prints prior to peer review. Subsequent examination of COVID-19 papers by other researchers or by the authors themselves has revealed inconsistencies in data or interpretation, sometimes of sufficient scale to require retraction of the article (Soltani and Patin, 2020). Some pre-prints have been particularly problematic in leading to irresponsible media dissemination of claims (Glaziou and Hoffmann, 2020) and in stimulating a large amount of misdirected research. The advent of preprints in the biomedical sciences and the increasing activities of predatory journals[IV] create additional problems for clinicians and other decision-makers in deciding how to respond to new information, much of unknown quality. However, new initiatives to coordinate evidence synthesis, technology assessments and guidelines are of great value[V].

II https://www.sciencemediacentre.org/expert-reaction-to-paper-using-an-rct-to-assess-mask-use-as-a-public-health-measure-to=help-control-sars-cov-2-spread-danmask-19/.
III See https://retractionwatch.com/retracted-coronavirus-covid-19-papers for database on COVID-19 retractions.
IV IAP is currently conducting a project to evaluate the problems presented by predatory academic journals and conferences, see https://www.interacademies.org/project/predatorypublishing.
V For example, the McMaster-University networked repository that can rapidly share the best available research evidence about clinical and public health interventions, health system arrangements and economic and social responses, to support decision making, https://www.mcmasterforum.org/networks/covid-end.

3. Solutions for strengthening COVID-19 research

IAP has previously published general guidance aimed at ensuring responsible science and reproducibility of biomedical research (Box 1).

Box 1: Previous IAP work on the conduct of research

Responsible science (IAP, 2012)

Responsible conduct, together with clarity of the research questions is a prerequisite for scientific excellence. The IAP guidance includes recommendations for: researchers, to uphold standards of responsible conduct in planning and carrying out research, reporting and communicating outputs; research institutions, to establish policy and mechanisms; funding agencies, to emphasise quality in reward systems; and journals, to protect the integrity of the research record.

Reproducibility of biomedical research (IAP, 2016)

There is an acknowledged need to improve reproducibility of research studies. Common reasons for irreproducibility include incomplete reporting of methodological details; poor experimental design and inappropriate statistical analysis.

The previous IAP recommendations for improving the overall framework for the conduct of research are highly relevant to COVID-19 studies. In addition to reaffirming these general precepts, learning from research failures must address the requirements for requisite skills, testable hypothesis, robust study design, rigorous ethical review and research governance and avoidance of premature publication. Reforming publication practices has wider implications for researcher accountability, measurement of research success, and reward systems. Furthermore, training of all individuals carrying out research needs to be strengthened.

Strengthening research also requires that research systems have the resilience to adjust to new priorities while limiting disturbance to ongoing research. Commitment to collaboration is vitally important for research success (Anon, 2020a,b) as is the function in some countries of health systems themselves to serve as a research resource, acting as a testbed to recruit patients for interventions in real world settings. During the pandemic there have been some important examples of good practice whereby existing multicentre research networks could rapidly identify and study priorities for intervention, prioritise randomised, controlled trials in emergency settings, avoid competition for trial sites and patients, and generate interpretable results. Experienced research collaborations can also contribute more broadly in agenda setting and help research funders to identify their priorities at a sufficient level of detail. There is potential for an increased role for academies worldwide in developing research networks, agenda setting, protocol reviewing and monitoring progress: clarification of these roles will help in preparedness for the next epidemic/pandemic or other global emergency.

There is a broad agenda for clarifying methodological approaches to building the COVID-19 knowledge base. (Knottnerus and Tugwell, 2020).

The following points are also relevant to strengthening the research enterprise.

- **Public interest in, and engagement with, science.** The pandemic has stimulated strong interest in science and the merits of collaborative research (Anon 2020a,b). However, only a minority of COVID-19 patients have had the opportunity to participate in well-designed trials. The success of the vaccine trials shows that people are prepared to volunteer if they are given the opportunity. More must be done to involve the public in research, particularly those communities disproportionately affected by COVID-19 (Academy of Medical Sciences, 2020). Vulnerable groups include those from racial and ethnic minorities or those otherwise socially disadvantaged or deprived, and their involvement can help to ensure that research produces outcomes that are relevant and reduce health inequalities. This has not necessarily been the case for research to date. Considerations for inclusivity and social justice also have implications for ethical approval procedures to ensure that the science and protocol are adequate.

- **UN research roadmap for COVID-19 recovery.** The UN has recently published guidance (UN, 2020) on issues for research quality needed to inform the recovery after COVID-19. Such research, covering multiple disciplines, should conform to the same principles of responsible conduct as the research conducted during active management of the pandemic phase. The UN road map discusses strategies for strengthening research ecosystems in order to build a research culture that is more efficient, open, inclusive and impactful. These considerations are highly important and have to be addressed alongside the efforts to promote consistency in research design, conduct and reporting to deliver excellent and relevant outputs.
- **International sharing of personal data for health research.** The value of international initiatives to share COVID-19 patient data to accelerate collaborative research has been widely recognised (e.g. Moorthy et al., 2020; COVID-19 Research Coalition, 2020). Yet there are regional obstacles to such sharing, for example applicable to sharing data outside the European Economic Area. Although the European regulatory authorities loosened their data sharing restrictions during the pandemic (European Data Protection Board Guidelines 03/20, 2020), reflecting the criterion of "important public interest", this only applied to initial, not repetitive transfers of COVID-19 data. It is urgent for the European Commission to look again at the relevant provisions within its General Data Protection Regulation, in order to support sharing of data safely, quickly and efficiently between public sector research institutions (EASAC-FEAM-ALLEA, 2021).

In conclusion, the evidence generated by researchers must be gained according to the established principles and practices of responsible science (IAP, 2012). To reiterate, scientific excellence requires the involvement of researchers with the relevant skills, a testable hypothesis, rigorous ethical review and research governance, adoption of appropriate clinical trial design procedures and attention to issues for research reproducibility. In addition, scientific journals must maintain stringent editorial standards.

It is vitally important to learn the lessons from COVID-19 research failures because there is still a research agenda of wide scope and importance to pursue. It is the purpose of this Communique to raise awareness of the underlying concerns rather than to define in detail the scope and scale of research priorities but we emphasise that in addition to the need for quality research that can offer reliable and actionable data, there is need for a pro-active collaborative research agenda that identifies critical gaps in knowledge that are vital in terms of improving public health and medical care. This requires governments to work closely with WHO, academia and industry to ensure appropriate design and implementation of research endeavours: academies of science and medicine are ready to help play a critical role in supporting research standards.

Signed by the members of the Steering Committee of the InterAcademy Partnership (IAP) in May 2021

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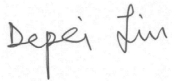

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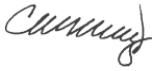

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About the InterAcademy Partnership (IAP)

Under the umbrella of the InterAcademy Partnership (IAP), more than 140 national, regional and global member academies work together to support the vital role of science in seeking evidence-based solutions to the world's most challenging problems. In particular, IAP harnesses the expertise of the world's scientific, medical and engineering leaders to advance sound policies, improve public health, promote excellence in science education, and achieve other critical development goals.

IAP's four regional networks - AASSA, EASAC, IANAS, and NASAC - are responsible for managing and implementing many IAP-funded projects and help make IAP's work relevant around the world. For more information about IAP see www.interacademies.org and follow @IAPartnership on Twitter, on LinkedIn and YouTube.

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This Communiqué can be downloaded at www.interacademies.org/publication/strengthening-research-covid-19-during-pandemic.

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