concussions, airborne allergen and pollutant exposure, as well as psychosocial stressors.

Future research goals are to examine how to best monitor, prevent and treat psychiatric, behavioral and cognitive consequences of COVID-19. For clinicians treating depression in patients with SARS-CoV-2 infection, a thorough history and clinical examination are paramount. There is evidence that immune-inflammatory dysregulation is limiting the efficacy of antidepressants, as high plasma levels of CRP and interleukins have been found to be predictors of poor treatment response[9]. Consequently, whether antidepressants are effective in treating COVID-19-related depression deserves specific confirmation.

In the meantime, we can assume that any major advances in vaccines and antiviral treatments targeting SARS-CoV-2, as well as immune targeted therapies (such as anti-cytokines and cytokine receptor blockers), will not only prevent severe illness but also benefit the brain and mental health.

Brenda W.J.H. Penninx
Department of Psychiatry, Amsterdam UMC, Vrije Universiteit, Amsterdam, The Netherlands

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Learning from the global response to COVID-19 to accelerate innovation in mental health trials

The past two decades have seen an increasing recognition of the contribution of mental disorders to global disease burden. There has also been an awareness that therapeutic innovation based on sound understanding of disease mechanisms has evaded single companies working within a conventional competitive market-based model. Governments, charities and philanthropists are increasingly willing to fund research programmes, and several collaborative initiatives and networks have emerged in recent years. For example, we soon expect the launch of the Health Brains Global Initiative (https://www.hbgi.org), which aims to "address market failures by galvanizing new science and new finance to enable new life trajectories".

Those of us involved in brain health research have a responsibility to take this opportunity, but we need to identify clear objectives and priorities to ensure that we deliver real advances. Inspiration and exemplars can be drawn from many areas of collaborative science. An example is the global response to the COVID-19 pandemic, where, alongside the dreadful death toll and enormous human suffering, we have observed the extraordinary acceleration in research success that is possible when researchers and funders collaborate with shared purpose, and prioritize and coordinate their efforts.

The extraordinary response to COVID-19 has not emerged out of the blue. The global research community had learned from previous inadequate responses to infectious disease outbreaks and created the partnerships and platforms to ensure a state of preparedness for emerging epidemics. The International Severe Acute Respiratory and emerging Infection Consortium (https://isaric.tghn.org) was funded in 2011 to ensure a rapid clinical research response to epidemics. The Coalition for Epidemic Preparedness Innovations (https://cepi.net) was launched in 2017 with a mission to "stimulate and accelerate the development of vaccines against emerging infectious diseases and enable access to these vaccines for people during outbreaks".

What are the key areas in trial design and conduct that have delivered the vaccines? A key area has been the standardization of early phase clinical trials. Vaccine development is not alone here – the critical contribution of phase II trials in providing crucial go-no-go evidence at earlier phases of development (rather than waiting to discover lack of efficacy in highly costly phase III trials) has been recognized for almost two decades[1]. This is most effective when illness mechanism is understood and biomarkers/interim outcomes can be reliably linked to clinical outcomes. Hence, phase II vaccine trials assess immune response rather than clinical outcomes[2].

Pathogenetic understanding of mental disorders is still limited, but the tactic of reverse translation, investigating the effects of treatments of known efficacy on biomarkers, has been productive. For example, antidepressant drugs have rapid effects on emotional bias, and this is a useful experimental measure of potential longer-term therapeutic effect[3]. Emotional bias is now used frequently in early phase studies as an indicator of longer-term clinical benefit of putative antidepressants.

An additional striking feature of the COVID-19 vaccine development has been the disruption of the standard linear sequential approach. Phase II/III trials have been planned and set up – using efficient combination designs – while preliminary studies were just getting underway. We have previously suggested that a non-linear, iterative approach might also be of benefit in drug development in psychiatry[4].

The COVID-19 pandemic also provides an excellent example of the power of embedding a highly simplified, randomized trial platform comparing available and licensed medicines in real world settings. The RECOVERY trial was rapidly designed and set up in March 2020[5]. It randomized over 35,000 patients by February 2021. By that time, it had demonstrated the benefits of dexamethasone

and tocilizumab and, equally importantly, the lack of benefits of hydroxychloroquine, lopinavir-ritonavir and azithromycin in patients hospitalized with COVID-19. The speed and power of the results obtained from a trial of extreme simplicity, with a single-minded dedication to maximizing recruitment across a health system, are impressive.

By radical simplification of procedures to minimize patient and clinician burden, RECOVERY has provided an example of a sustainable rolling trial platform which allows the sequential evaluation of multiple agents. The simplicity and speed of RECOVERY did not come at the cost of sacrificing quality or the short-cutting of ethical or regulatory oversight. Instead, the RECOVERY investigators worked closely with both the ethics committees and the UK regulator in parallel with setting up the trial, achieving a hitherto unimagined speed of trial set-up.

I believe that we urgently need to apply the lessons learned from RECOVERY in mental health trials. We have previously identified the potential for large, streamlined trials in mental health[6], although this approach remains unusual. One exception is the BALANCE trial comparing long-term treatments in bipolar disorder[7]. In this trial, we did radically simplify procedures and achieved a reasonably sized sample with a clear primary outcome. Building on the example of RECOVERY, we now need to scale up trials such as BALANCE by an order of magnitude to allow multiple arms and deliver strong evidence of modest (but worthwhile) treatment effects.

There is no shortage of important clinical questions that need answering via large-scale, streamlined, directly randomized studies. As with RECOVERY, we should initially focus on comparative efficacy of existing, licensed interventions, adding more innovative treatments once the platform is up-and-running. A prime illustrative example is the comparative efficacy of antidepressant drugs. A network meta-analysis reported that there are potentially clinically important differences between 21 available antidepressants, but that nearly all the comparative data are indirect and based on pre-regulatory approval trials[8]. This is a major gap in the evidence base and a substantial barrier to knowing which antidepressant might be most likely to be effective for any specific patient – the goal of precision psychiatry[9].

Large-scale, streamlined trials should be designed in partnership with a broad range of stakeholders, including patients, regulators and industry, and recruiting a broad range of patients from routine clinical settings. Large-scale recruitment can be facilitated by using electronic health records. Progressing this idea using the momentum and learning from RECOVERY seems to be an outstanding opportunity for mental health clinicians, researchers and patients, and needs to be supported by funders.

Finally, the COVID pandemic helps to clarify the relative strengths of randomized and observational studies. Early on, considerable publicity was given to small, uncontrolled reports of the potential benefits of hydroxychloroquine. A report of routinely collected observational data seemed to confirm this, only to be quickly retracted. RECOVERY found no benefit of hydroxycholoquine in severely ill patients, although there remains the possibility that it might be effective in very early or mild cases. This demonstrates the danger of retrospective analyses of data of uncertain provenance as well as the power of large simple randomized controlled trials.

On the other hand, observational data of infection rates following vaccinations were hugely reassuring, given the remaining uncertainties around vaccine efficacy in specific patient subgroups. Observational data can extend and confirm the results of randomized trials, which will always remain smaller and less representative. These data are increasingly available via electronic care records and, although susceptible to residual confounding even after multivariate propensity score matching, may be very valuable for post-marketing safety surveillance and confirmation of treatment effects in larger, more representative datasets.

In conclusion, despite the human tragedy and suffering, the COVID-19 pandemic has inspired some outstandingly creative responses from the international research community. We need to capture this and apply it to the major global challenge of mental illness, building on the developing international collaborative efforts. We should draw inspiration from just how much can be achieved so quickly with a clearly defined objective and common sense of purpose and urgency.

John R. Geddes
National Institute for Health Research (NIHR) Oxford Health Biomedical Research Centre, University of Oxford and Oxford Health NHS Foundation Trust, Oxford, UK

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Metacognition in psychosis: a renewed path to understanding of core disturbances and recovery-oriented treatment

Consistent with early definitions of schizophrenia as marked by a fragmentation of thought, emotion and desire[1], psychosis is currently understood as involving deep disturbances in the sense that persons have of themselves and their connection with the world[2]. Though endemic across psychosis[3], it has remained unclear how to operationalize and measure the processes which underlie and sustain these alterations in self-experience.

One challenge for empirical research is that the sense anyone has of him/herself, given its intimacy, immediacy and elusiveness, is not easily measured. Validated assessments, for example,