Are the Current Processes and Regulations Fit for Purpose to Deliver Novel Therapies During Pandemics? A Perspective on COVID-19 from the UK

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Abstract
The COVID-19 pandemic was the first ‘stress test’ to assess whether the current regulations in the United Kingdom (UK) are fit for purpose to develop novel therapies during pandemics. It saw innovations and collaborations across the spectrum of the drug development and regulatory pathways, including extraordinary collaborations between the various stakeholders involved in the process, the repositioning of medicines, the deployment of multi-arm, multi-interventional adaptive trials, the institution of operational simplicity and flexibility across various trial activities, and regulatory innovations. The question arises whether the innovative flexibilities and the urgency that were instituted could have resulted in compromises to the integrity of the process. An assessment of the conduct of the RECOVERY trial and the speedy approval of dexamethasone by the UK Medicines and Healthcare products Regulatory Agency demonstrates that no compromises were made to the ethical and scientific integrity of the process. Lessons learnt could be applied for future pandemics and to enhance R&D productivity and contribute to global health by improving access to medicines, especially in low- and middle-income countries and for neglected or rare diseases. What is needed is not a major transformation in the process but the flexible adaptation of existing regulations to reduce bureaucracy and handover times. Arriving at an optimal balance between scientific standards, regulations and commercial conflicts of interest will pose considerable challenges but what the COVID-19 pandemic has shown is that where there is will, there is always a way.

Key Points
Successful and rapid development of medicines for COVID-19 were delivered through innovative adaptations and flexible interpretation of existing development and regulatory pathways in the United Kingdom and other developed nations.

The lessons learnt could be incorporated more widely into global drug development and regulatory systems.

Such an approach would contribute to improvements in public health and enhance global access to medicines.

1 Introduction
The COVID-19 pandemic has been the first ‘stress test’ to assess whether the current regulations are fit for purpose to develop novel therapies during pandemics. Previous epidemics such as Avian flu, Ebola, SARS and MERS did not have the magnitude and global impact of the current pandemic [1] to meaningfully test the integrity of the global regulatory system. The COVID-19 pandemic spread rapidly around the globe with considerable morbidity and mortality [2] due to the absence of effective therapeutics and vaccines. Repositioning some existing medications was attempted with limited evidence generated primarily from in vitro studies or inadequately powered clinical studies [3]. There was therefore an urgent need to innovate within the existing regulatory systems to speedily deliver novel therapies. The primary question was whether the existing system and processes, which have evolved over many decades, were adequate or whether fundamental changes were needed.
2 The Response to COVID-19

Although we describe a perspective from the vantage point of the United Kingdom (UK), our experience was also seen across many other developed nations. Drug development, regulations and supply chains have become inherently interlinked across the world and no nation can hold monopoly for these activities within its national boundaries. As the pandemic evolved, the response of the global community was dramatic with innovations and collaborations across the full spectrum of the drug development process and regulatory pathways. These included stakeholder collaborations, repositioning of medicines, deployment of adaptive clinical trials, operational excellence and regulatory innovations.

2.1 Stakeholder Collaborations

The COVID-19 pandemic necessitated the ‘coming together’ of the various stakeholders spread across academia, industry, regulators, governments and non-governmental organizations in a manner never seen in the past. Such collaborations facilitated the acceleration of the clinical development pathways and regulatory processes by eliminating or reducing many of the administrative interfaces and processing times. The innovative collaboration between the University of Oxford and AstraZeneca not only speeded up the development and market access of a viral vector vaccine but also, through the out-licensing relationship with the Serum Institute in India, enhanced global access to the vaccine. The impact of the UK National Institute for Health and Care Research (NIHR) established in 2006 [4] exemplified the role national and international agencies could play to proactively build research capabilities. “Building bridges and not walls” should be the future mantra to enhance access of medicinal products and improve global health.

2.2 Repositioning of Medicines

The screening and repositioning of approved medicines for activity against the SARS-CoV-2 virus [5] was an integral part of the response to COVID-19. The early part of the pandemic saw a clinical trial environment that resembled a cacophony rather than a symphony with a disjointed deployment of a plethora of poorly designed and inadequately powered clinical trials across the globe. Many of these trials were limited to single centers, were duplicative and poorly designed [6] and led to confusing and conflicting outcomes on the value of the interventions. Although the situation gradually improved, lessons need to be learnt to prevent such occurrences in future pandemics. National ethical committees need to be more assertive in including value and scientific validity as part of the review process [7].

2.3 Deployment of Adaptive Clinical Trials

The deployment of multi-arm, multi-interventional adaptive trial designs as a means of assessing a multitude of therapeutic options was the game changer for drug development during the pandemic. The most scientifically comprehensive and regulatory compliant undertaking came from within the UK (RECOVERY trial) to investigate the repositioning of established treatments for hospitalized patients [8]. These included the repositioning of already approved medicines (e.g., dexamethasone, remdesivir, hydroxychloroquine, tocilizumab etc.) as well as new therapeutic options (e.g., convalescent plasma and monoclonal antibodies).

The RECOVERY trial led to the prompt approval of dexamethasone by the MHRA for critically ill patients, with a meaningful mortality benefit. The rapid delivery of a cheap and widely available medicine to treat a cohort of COVID-19 patients was a breakthrough event during the pandemic. Additional adaptive design trials included the global SOLIDARITY trial sponsored by the World Health Organization [9] and the ACTT-1 sponsored by the National Institute of Health in the USA [10].

Adaptive trial designs had previously played only limited roles in early clinical development programs [11] but have seldom been a core feature of confirmatory trials. The RECOVERY trial further highlighted the marginal benefit of remdesivir [12] and the inappropriate benefit–risk profiles of hydroxychloroquine [13], azithromycin [14], and convalescent plasma [15], confirming the folly of poor science, misinformation, and political interference during the pandemic.

2.4 Operational Excellence

Several operational innovations were also seen within the RECOVERY trial (and indeed in other trials in the UK and elsewhere). These included enhanced productivity through flexibility and simplification across various trial activities [6, 16], the optimal utilization of stretched healthcare resources, supplementation of patient data through digitized general practice (GP) and hospital databases, and flexible informed consent procedures with minimal inconvenience to seriously ill patients and their families.

The research ethics committees within the UK went into a pandemic mode with the launch of a rapid review for COVID trial protocols and enabling simplicity with two-paged informed consent forms and the use of alternative consent options as appropriate to the situation, including deferred consent, remote technology-based consent, and the judicious use of personal and professional legal representatives [17].
2.5 Regulatory Innovations

Several regulatory innovations were introduced by the MHRA and the UK Health Research Authority (HRA) to facilitate the development of novel therapeutics. The scaling up of ‘rolling regulatory reviews’ of trial data by the MHRA allowed modules of the electronic Common Technical Document dossier to be submitted as data was generated for pre-assessment rather than as part of a consolidated full dossier submission [18]. Rolling review was instrumental in the rapid dissemination of the various trial data from the RECOVERY and other key trials during the pandemic [19]. Additional guidance included measures to ease the conduct of clinical trials [20], ethics committee reviews [21] and fast track regulatory reviews [22].

3 Integrity of the Process: The RECOVERY Trial and Dexamethasone Approval as a Case Study

The question arises whether the innovative flexibilities and the urgency that were instituted could have resulted in compromises to the integrity of the scientific data and the regulatory review process. An assessment of the conduct of the RECOVERY trial and the approval of dexamethasone by the MHRA by most scientific commentators [23] conclude that both the conduct of the trial and the regulatory approval of the product were ethically and scientifically sound. The study had a robust power and patient data set (6425 patients), was well controlled with a 2:1 randomization (2104 patients to dexamethasone; 4321 patients to standard care), was assessed in multiple hospital centers (n = 176) across the UK with defined clinical entry criteria to recruit patients diagnosed with COVID-19 and a hard primary endpoint (mortality at 28 days).

4 Conclusions

Diminished R&D productivity in delivering new medicines has been extensively discussed in recent years as a concern by investors, payors, and the wider society. It has been suggested that the existing regulatory system is too cumbersome, stifles innovation and leads to long lead times in delivering novel therapies. The response of the drug development and regulatory process during the pandemic, exemplified by the approval of dexamethasone, has indicated that reducing bureaucracy and instituting flexibility within the existing system could contribute to enhancing R&D productivity without the need for any radical reorganization of the regulatory processes. We recognize that the innovations articulated in this paper would primarily be of relevance to the developed nations with similar, advanced regulatory systems. However, we also feel that learnings from the more advanced regulatory agencies during the pandemic would be of use to emerging nations in facilitating the development of simple, flexible and non-bureaucratic drug development and regulatory pathways.

These are lessons that could be applied judiciously and widely not only for future pandemics but also in select areas to enhance public health and improve access to medicines in low- and middle-income countries and for neglected or rare diseases. Examples could include incentives for the repositioning of existing medicines, better formalized academic and industry collaborations, capacity building of global regulatory systems and even cross-company collaborations in running confirmatory effectiveness trials using multi-arm, multi-interventional, adaptive designs. Although such trials may be problematic in the preapproval phase of newly developed medicines due to commercial and intellectual property conflicts of interest, they could be developed as valuable tools in the post-approval environment to facilitate the generation of evidence-based clinical guidelines by academic and professional bodies in disease areas of interest, including oncology and non-communicable diseases.

It is important to begin a conversation amongst the various stakeholders to assess the lessons learnt and apply them to the future development of medicinal products. Arriving at an appropriate balance across the maintenance of scientific standards, optimal regulations and commercial conflicts of interest will pose considerable challenges but what the COVID-19 pandemic has shown is that where there is will, there is always a way.

Declarations

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