Written Evidence Submitted by the Faculty of Pharmaceutical Medicine (FPM)

(C190091)

The Faculty of Pharmaceutical Medicine (FPM)

The Faculty of Pharmaceutical Medicine (FPM), founded in 1989, represents 1500 pharmaceutical physicians working in the UK and internationally. Our mission is to advance the science and practice of pharmaceutical medicine by working to develop and maintain physician competence, ethics, and integrity for the benefit of the public. Our response to the enquiry is based on our members' collective experience from involvement in COVID-19 activities.

Executive Summary

1. Vaccine development has embraced Pharmaceutical Industry, Academic and Government collaboration and focus on the whole supply chain in the case successful discovery of an effective one. There is a powerful case for international cooperation as the successful vaccines will be needed to ensure supply in both rich and poor countries. It is important that we build detailed safety follow up, especially if early population-based introduction is proposed. The example we can draw upon when planning for future pandemics is the collaborative efforts for new vaccines. It speaks to establishing a **National Framework** for development of not simply vaccines but also for medicines, both new and repurposed, and diagnostics for pandemic use. (**TOR item 2 &5**)
2. The UK national effort to undertake clinical trials of new and repurposed medicines was hampered by a having an opaque organisation which failed to communicate. Such organisations should have published terms of references with lists the membership and decisions that are communicated through meeting minutes. (**TOR item 2 & 6**)
3. Two areas of major concern were the selection of medicines for repurposing without adequate vetting of their pharmacology nor relationship to the published work on the disease. Secondly, the choice to study antiviral therapy in hospitalised patients delayed use until long after the peak of viral replication. Skills in clinical study design were limited. Future studies in the next wave of COVID-19 or a different viral pandemic requires that disease testing and case/contact tracing be linked to recruitment into clinical trials of vaccines and prophylactic treatments. Ideally these should be undertaken in the community. (**TOR item 2 & 6**)
4. There is a skills shortage for testing repurposed medicines approved for other diseases and development of new medicines that requires increased numbers of physicians experienced in early medicine development. These skills can be found among the FPM membership but need to be also developed in the NIHR and in the Pharma Industry. (**TOR item2 & 6**)
5. Effective innovation and flexibility were shown by the regulatory agencies, MHRA and HRA, they were exemplars. Individual hospital contracting requirements caused delays in starting studies for several months after approval. A centralised contracting process has long been needed in the UK to facilitate rapid clinical trial site start up. (**TOR 3**)
6. We see a **National Framework** for medicines and diagnostics to bringing together all parties to coordinate capacity for testing both for public health and for clinical care and research. For the coming winter it is essential that there is a rapid adoption of multiplexing RTC-PCR technology to provide detailed diagnosis for the many viruses that cause winter respiratory epidemics. (**TOR item 4**)

7. There is an immediate need to have an integrated clinical reporting system extending from general practise to hospital care. The availability of online anonymised general practice patient data in the CPRD has enabled some excellent work on factors associated with risk of severe COVID disease within the UK population. However, the lack of comparably detailed on-line linked hospital records hampers comparable research within a hospital setting. Interoperability is crucial to enable the patient pathway to be mapped from community to hospital including intensive care. Ideally this should operate "real-time" so that records are updated nightly. This is technically in our reach and could provide the methods to track hazards from use of vaccines/medicines. (**TOR item 5**)
8. Paucity of post-mortem information in the UK has hampered the early identification of disease mechanisms involved in the evolution of COVID19 disease. It is recommended that facilities for diagnostic autopsy with accompanying immunohistopathology and transcriptomics are expanded in the UK to enable earlier identification of disease pathology and facilitate early development of management strategies. (**TOR item 2 & 6**)
9. Continued support for host and viral genomic studies is essential for the future medicine development. (**TOR item 2 & 6**)

Clinical Medicines and Vaccines Development

Despite their training and expertise only a small number of our members were called to support the Government led research activities. Most of this research was selected and led by a limited number of medical academics and a smaller number of academic pharmacologists. In contrast our members contributed to the ~1200 global clinical trials of new medicines for COVID-19, many of which were first into COVID-19 patients or first into human (FIH) studies.

Consideration should be given to establishing a **National Framework** for the selection and vetting of repurposing of medicines along with introduction of new medicines that enables evidence-based decision to be made. Such a structure would draw upon the reassessment of dose response effects for patients with COVID-19 to determine the dose schedule for therapeutic success[1]. In addition, trials of medicines which are intended to mediate effects on respiratory viral disease by direct antiviral activity must focus on recruitment of patients during a narrow window of opportunity prior to peak viral load[2]. This would avoid the focused only on hospitalised patients when the peak viral load had already passed and impact on the disease reduced.

This new **National Framework** could work internationally to prevent misuse of the patient population, as occurred with the 237,000 volunteer patients involved in the global studies of HCQ (Source CLINTRIAL.GOV) despite lack of effect in animal models[3]. Such a structure could draw upon the considerable expertise in the development of antiviral medicines in the UK pharmaceutical industry. This expertise could be harnessed in the design and management of clinical studies. It could work to enable the technical capacity to undertake studies of anti-viral therapies to take advantage of the "track and trace" system to initiate treatment in the community prior to peak viral load, which occurs within 3-5 days of first symptom onset.

In contrast, pathology of the COVID-19 disease in hospitalised patients is predominantly driven by an exaggerated immune response accompanied by an extensive coagulopathy with disseminated intravascular coagulation and thrombosis. This knowledge has been acquired from histopathology performed in China, USA, and Italy with no contribution from the UK because of the low frequency of diagnostic postmortem investigation of patients dying from COVID19 early in the epidemic. Post-mortem investigations are critical in providing details histopathology of the effects of COVID-19 disease on organ systems. Development of new medicines and new devices for supporting breathing requires this understanding to be able to respond quickly. Worldwide there has been an enormous

effort to understand the pathology of the lung disease and its systemic effects, which has resulted in the recognition of endotheliitis[4], microvascular angiogenesis and intravascular thrombosis associated with dysregulation of the complement pathway[5,6], which, belatedly, is now being addressed therapeutically in hospitalised patients. There is an urgent need in the UK to upgrade the role of diagnostic autopsy to allow information and knowledge to be gained more quickly in future pandemics of novel diseases.

A truly **National Framework** to engage in selection for medicines for global pandemics would avoid the issues of poor communication and lack of transparency and could collaborate internationally to optimise global response. It would answer the criticisms that have been made about the current UK response[7]. It is proposed that the membership and working practices of all committees engaged in providing advice to Government should be made public, minutes of meetings published and reasons for decisions made transparently reported. This is a specific answer the item 6 of the terms of reference.

Disease tracking and testing

We would see a **National Framework** for medicines development extend to planning the development of diagnostics for this and future pandemics. This body could bring clarity and coordinate the provision to cover both Public Health (track and trace) and clinical medical needs (diagnosis, therapy decisions and research). It would avoid the initial handicap of limited provision of PHE and NHS clinical and regional genetics laboratory infrastructure where PCR-based testing is routine. Other countries with more diversified and innovative (often private) clinical laboratories were able to ramp up rates of testing much more quickly than the UK. A further limitation of the UK response to COVID-19 was compounded by the lack of availability of swabs, reagents and diagnostic platform equipment caused by supply problems associated with factory shutdowns in major manufacturing countries early in the evolution of the pandemic.

Although the DHSC rapidly scaled up testing capacity, the length of time taken, and the poor understanding of the infrastructure requirements for logging samples received, including confirmation of the identity of the person giving the sample, sample processing and reporting to relevant parties (including local public health services) has continued to limit efforts to track disease. As work progresses to get this service fully operational the key elements needed are to identify local outbreaks and for clinical trials it is essential to have fast return of results of the tests otherwise recruitment Is limited. A positive test is an absolute requirement for a patient to enter a COVID-19 study. These problems speak to a **National Framework** for diagnostics that integrates the technology and logistics infrastructure.

The UK has, through its vibrant diagnostics industry a tremendous capacity for addressing "the development of testing, diagnostic methods and technologies". Unfortunately, it seems almost none of this capability has been used. It is hoped that a legacy of the reaction to the pandemic might be the establishment of a robust testing infrastructure together with a diagnostics research & development management process combining academic, clinical and industry scientists to enable the future rapid development and deployment of any required novel tests.

The **National Framework** needs to consider urgently the provisions for the coming winter season. This will be complicated by the potential for influenza, RSV, and other respiratory virus outbreaks in addition to a resurgence of SARS CoV2. The testing system used in the winter must be capable of multiplex testing. Some companies can provide multiplex test kits enabling surveillance for influenza, RSV and SARS CoV2. The capacity for multiplex testing services needs to be urgently reviewed and

potentially expanded across all facilities including hospital services, PHE laboratories and the Lighthouse laboratories in advance of the coming winter.

Gaining Regulatory and Ethical Approval

The MHRA have produced a range of regulatory procedural innovations to guide applicants on management of non COVID and COVID trials, as well as to maintain medicines supply throughout the epidemic. In addition, innovations at the HRA have resulted in rapid assessments of clinical trial protocols[8]. Taken together these activities have reduced the time to gain regulatory and ethical approval for clinical trial protocols from ~6 weeks to 7-14 days. Both organisations might consider whether these innovations should be extended to future research activities for COVID and non COVID studies.

In contrast, contracting to set up a clinical trial in a hospital is frequently protracted and slow, notwithstanding previous agreement of standardised research agreements between the ABPI and the NHS. Based on the experience of our members it has commonly taken up to 12 weeks to open individual sites participating in COVID trials in the UK with the result that opportunities to recruit patients throughout the peak of the outbreak have been missed.

It is recommended that centrally approved standardised costing and contracting agreements are established to remove the requirement for individual site contractual arrangements that led delay in trial start up at site level in future.

Epidemiological Studies in Digitised Records

The Clinical Practice Research Datalink (CPRD) is a real-world research service supporting retrospective and prospective public health and clinical studies. CPRD collects de-identified patient data from a network of GP practices across the UK and links these to a range of other health related data to provide a longitudinal, representative UK population health dataset[9]. Research using CPRD data and services has informed clinical guidance and best practice, resulting in over 2,500 peer-reviewed publications investigating drug safety, use of medicines, effectiveness of health policy, health care delivery and disease risk factors for over 30 years.

Databases are updated monthly, which precludes 'real time' assessment of disease activity and contribution of patient factors to outcomes. The time taken to upload data should be reduced to a regular overnight activity. This would greatly facilitate timely research. Notwithstanding these delays the recent reported risks of dying from COVID-19 using a population base of 17 million patients greatly aid understanding and has led to a GP diagnostic tool to aid clinical management[10].

Currently there is no seamless link between the CPRD database and to the patients' hospital episode data. This further complicates the conduct of studies following patients from the community into hospital and back to the community. Improved linkage to and ideally standardising the structure of hospital clinical records would significantly enhance the quality of data available and improve the potential for conduct of 'virtual' clinical trials.

One immediate gain of such a development would be an ability for early detection of antibody enhanced disease or other complications of vaccines among vaccine recipients in future. A safety concern of future vaccines.

Genomic Studies

The UK has participated in an international effort on the contribution of host genetic factors to disease severity, comprising members of the Humanitas COVID-19 Task Force in Milan Italy and the members of the COVID-19 Host Genetics Initiative[11]. This effort has identified a 3p21.31 gene cluster as a genetic susceptibility locus in patients with respiratory failure due to COVID-19[12] and confirmed a potential involvement of the ABO blood-group system to disease severity risk. These findings offered considerable insight to potential mechanism of the disease. Support for human genome studies should be continued and enhanced via improved linkage of genomic data to CPRD held information. A National Framework could build and enhance the genomic response facilities to cope with future pandemics

In addition to studies of human genomic factors, sequencing of viral genomes using next generation sequencing protocols has established the phylogenetic tree of SARS CoV2 virus infection. This research has enabled identification of the geographic origin of the virus entering the UK population (predominantly from Spain, France and Italy in the 'ski' season[13]), as well as tracking of virus evolution during the outbreak which is relevant to potential match for and response to future vaccines.

This effort included identification of the D614G mutated strain, which is more readily transmitted than the original strain, in part explaining the higher incidence of disease in the EU and US, but which, fortunately, does not alter disease severity[14]. Subsequent investigation has documented that it is readily inhibited by antibodies generated by vaccine strains based on the original D614 variant[15]. Support for continued phylogenetic evaluation of SARS CoV2 is essential to track infections and assess the potential for vaccine escape mutants during clinical trials of candidate vaccines and following introduction of community vaccination programs in future.

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